

パラジウム触媒を用いたプロパルギル化合物と  
求核剤の連続的環化反応による  
高度置換複素環化合物の合成

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本文中、以下の用語及び反応剤は下記のように略記した。

Ac	acetyl
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
brsm	based on recovered starting material
Bu	butyl
cat.	catalytic amount <i>or</i> catalyzed
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DIAD	diisopropyl azodicarboxylate
DMAP	<i>N, N</i> -4-dimethylaminopyridine
DMF	<i>N, N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DPEphos	bis[2-(diphenylphosphino)phenyl] ether
dppb	1,4- bis(diphenylphosphino)butane
dppe	1,2- bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppm	1,1- bis(diphenylphosphino)methane
dppp	1,3- bis(diphenylphosphino)propane
dpppent	1,5- bis(diphenylphosphino)pentane
dr	diastereomer ratio
eq	equivalent
Et	ethyl
h	hour

HMBC	hetero-nuclear multiple quantum coherence
HRMS	high-resolution mass spectrum
<i>i</i> -	iso
IR	Infrared
L	ligand
LDA	lithium diisopropylamide
M	metal
Me	methyl
min	minute
mp	melting point
MS	mass spectrometry
<i>m/z</i>	mass to charge ratio
<i>n</i> -	normal
NMP	<i>N</i> -methylpyrrolidinone
NMR	nuclear magnetic resonance
Nu	nucleophile
Pd	palladium
Ph	phenyl
Pr	propyl
quant	quantitative yield
rt	room temperature
sp.	sponge
TBAF	tetra <i>n</i> -butylammonium fluoride
TBAT	tetra <i>n</i> -butylammonium difluorotriphenylsilicate

TBS	tertiarybutyldimethylsilyl
<i>tert-</i>	tertiary
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
tol	tolyl
Ts	<i>p</i> -toluenesulfonyl

## 総論

複素環化合物は医薬品、農薬、触媒、反応試薬、機能性材料等、人類の役に立つ化学物質の多くに基本骨格として含まれている (Figure S-1)。特に複雑な置換様式をもつ複素環は様々な生理活性物質に存在し、薬学的にも重要である。例えば *Amphimedon sponge* より単離された Nakadoramin A (S-1) は骨格内に縮合フランをもつマンザミンアルカロイドである<sup>1)</sup>。本化合物は細胞毒性、抗菌性、抗真菌性などの多様な生理活性が報告されていることから強い注目を浴びている化合物であるが *Amphimedon sp.* 1.0 kg 中 6.0 mg しか含まれておらず、単離量は少ない。そのため本化合物の構造と活性には強い興味をもたれ様々な全合成研究が行われている<sup>2)</sup>。また医薬品の Sunitinib (S-2) はチロシンキナーゼ阻害作用をもつ抗がん剤であり、構造上の特徴として四置換ピロールを母核にもつことが挙げられる<sup>3)</sup>。本化合物の合成では四置換ピロールの複雑な置換様式を位置選択的に導入するため、多段階を要している。

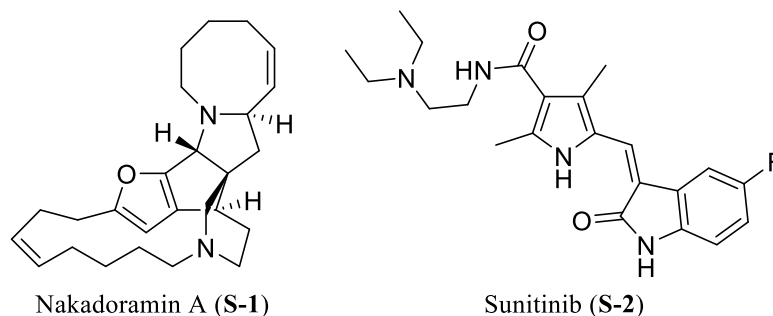
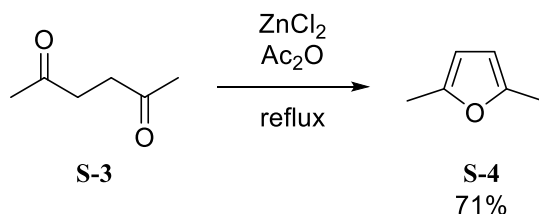


Figure S-1

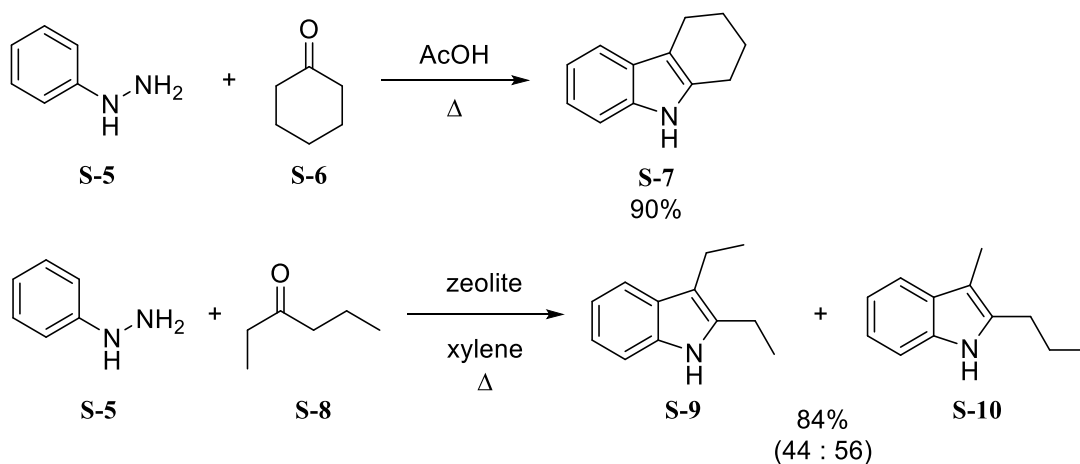
このように天然物や医薬品の複雑に置換された複素環骨格を構築することを目指し、複素環を選択的に合成する方法が古くから研究されている。例えば Paal-Knorr フラン合成では 1,4-ジケトン S-3 に対し酸を作用させると分子内脱水縮合

し、置換されたフラン **S-4** が得られる<sup>4)</sup>。本反応はフランを合成する最も基本的な反応であるが基質である 1,4-ジケトン化合物の合成法が限られており、多様な置換フランの合成が難しいという問題点がある<sup>4d)</sup> (Scheme S-1)。



**Scheme S-1**

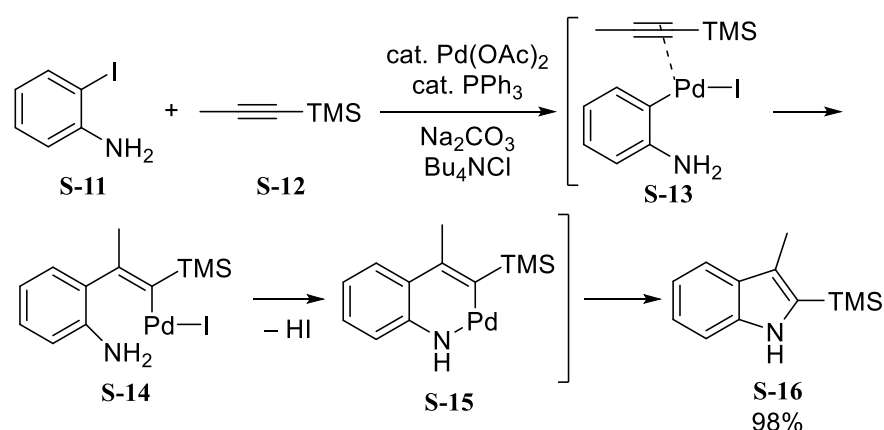
また Fischer インドール合成においてはフェニルヒドラジン **S-5** とケトン **S-6** に対し酸を作用させるとインドール **S-7** が生成する<sup>5)</sup> (Scheme S-2)。この方法は置換インドールの最も有名な合成法となっているが、非対称ケトンを基質に用いると二種類の位置異性体が生じやすいという問題がある。例えばフェニルヒドラジンに対しゼオライト存在下キシレン溶媒中加熱還流の条件下 3-hexanone (**S-8**)を用いると、2種類の位置異性体インドール **S-9**, **S-10** が得られる<sup>5d)</sup>。



**Scheme S-2**



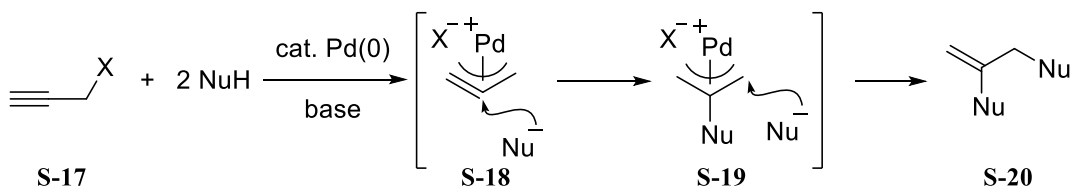
このように複素環化合物の合成は古くから研究されているが、多様な置換様式をもつ複素環を自由自在に作り上げる方法論の確立には未だ至っていないのが現状である。そのため現在においても新たな複素環構築法の開発は盛んに行われている。なかでも遷移金属触媒を用いる方法論の開発は最も精力的に研究されている分野の一つである。例えば Larock らはパラジウム触媒存在下、2-iodoaniline (**S-11**) と二置換アルキン **S-12** を塩基存在下作用させるとヨードアニリンのトランスメタル化により中間体 **S-13** が形成後、アルキンへの挿入、アニリン窒素原子のパラジウムへの配位、パラジウムの脱離によりインドール **S-16** が生じることを報告した<sup>6)</sup> (Scheme S-3)。本反応は位置選択的な置換インドールの合成法であり、Larock インドール合成と呼ばれ天然物や生理活性物質の合成に広く利用されている<sup>7)</sup>。



Scheme S-3

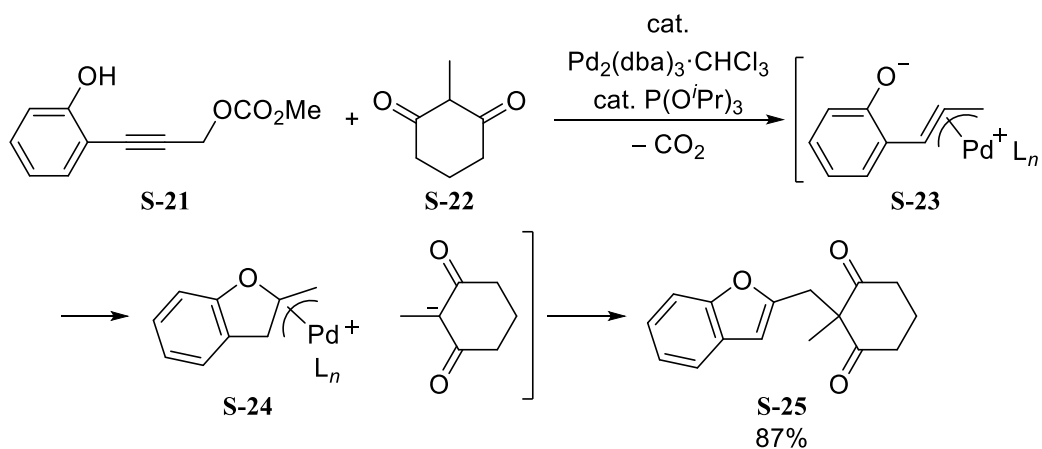
またプロパルギル化合物を反応基質に用いた複素環化合物の合成も精力的に行われている。脱離基を導入したプロパルギル化合物はパラジウム触媒存在下にて多様な反応性を示すことが知られており、例えばプロパルギル化合物 **S-17** に対しパラジウム触媒存在下ソフトな求核剤を用いると、二つの求核部位が導入された生成物 **S-20** を与える。反応機構としてははじめにプロパルギルエステルとパラジウム触媒が反応しπ-プロパルギルパラジウム錯体 **S-18** が生じた後、本錯体に対し求

核剤が付加し $\pi$ -アリルパラジウム錯体 **S-19** を形成する。その後更にもう一分子の求核剤が作用することで、化合物 **S-20** が生成する<sup>8)</sup> (Scheme S-4)。



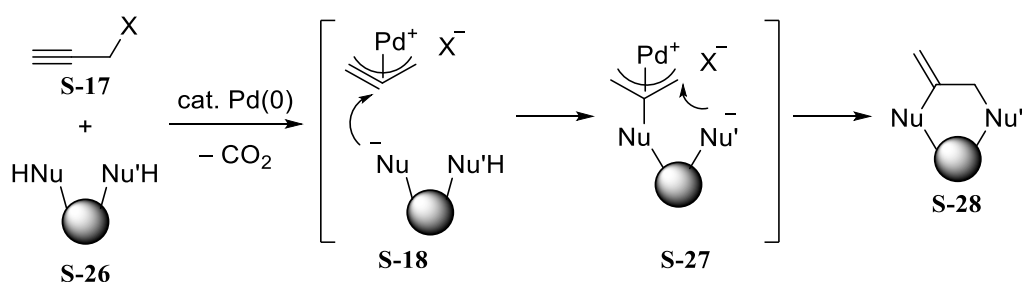
Scheme S-4

本反応性を活用した複素環の合成例として、当研究室の吉田らは分子内にフェノールを有する炭酸プロパルギルエステル **S-21** に対し 0 価パラジウム触媒とシクロヘキサジオン **S-22** を作用させると、求核部位が導入されたベンゾフラン **S-25** が得られることを見出している<sup>9)</sup>。本反応でははじめに炭酸プロパルギルエステルとパラジウムが反応し脱炭酸を伴って $\pi$ -プロパルギルパラジウム錯体 **S-23** となった後、同一分子内のフェノールからの求核付加が進行し $\pi$ -アリルパラジウム中間体 **S-24** へと変換される。その後シクロヘキサジオンからの求核攻撃が進行しベンゾフラン **S-25** が得られたものと考えられる (Scheme S-5)。



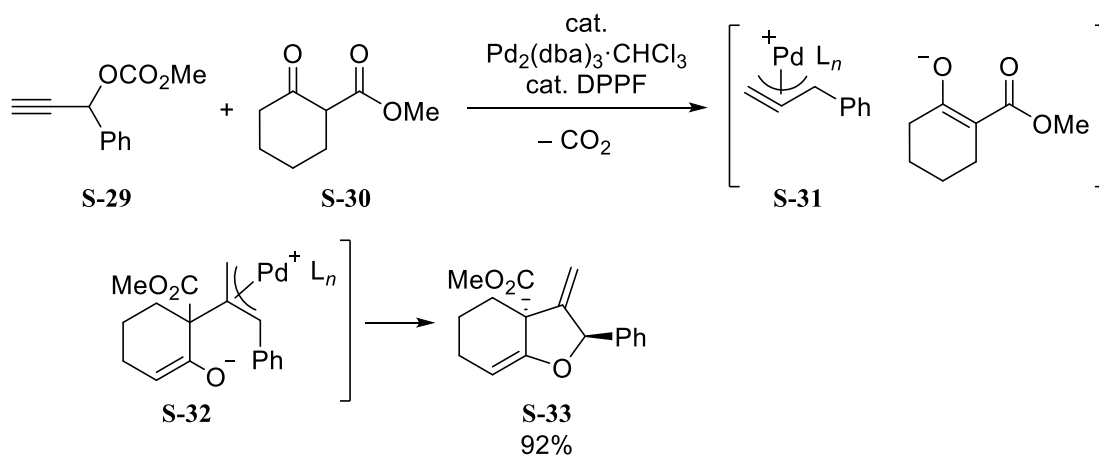
Scheme S-5

またパラジウム触媒存在下プロパルギル化合物 **S-17** に対し分子内に二つの求核部位をもつ化合物 **S-26** を反応させることで、環状化合物 **S-28** を構築する方法も報告されている<sup>10)</sup>。すなわちはじめにパラジウム触媒とプロパルギル化合物 **S-26** が反応し $\pi$ -プロパルギルパラジウム錯体 **S-18** が形成後、一つの求核部位と反応し $\pi$ -アリルパラジウム中間体 **S-27** となる。その後更にもう一つの求核部位が分子内で反応することで環化体 **S-28** が生成する (Scheme S-6)。本反応の特徴として、用いる反応基質 **S-26** を適切に分子デザインすることにより様々な複雑な環状化合物が一挙に構築可能であることが挙げられる。当研究室ではこれまで本反応性を活用した複素環化合物の合成に取り組んできた。



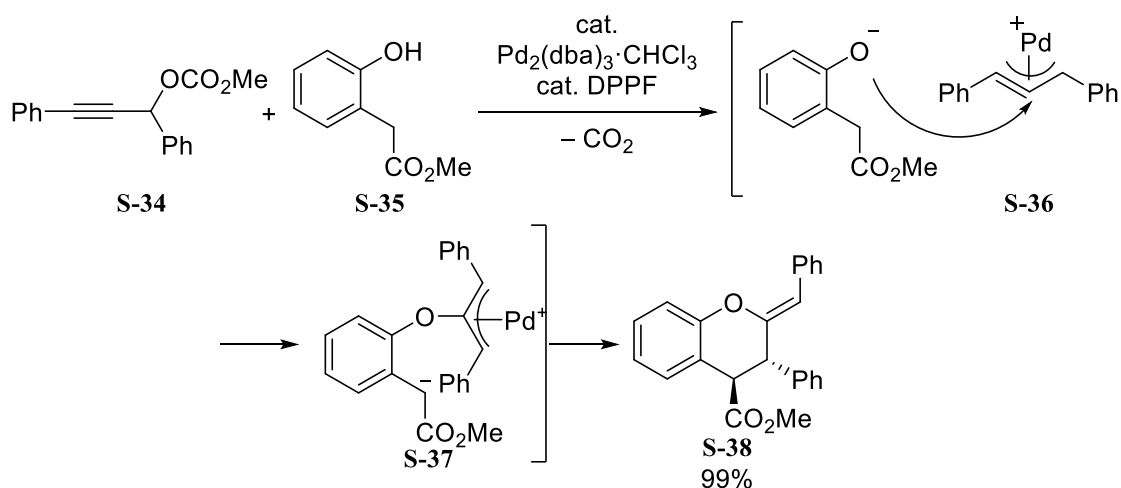
Scheme S-6

例えば炭酸プロパルギル化合物 **S-29** に対し $\beta$ -ケトエステル **S-30** を求核剤として用いると、 $\pi$ -プロパルギルパラジウム錯体 **S-31** に対する活性メチン炭素からの、続くケトン酸素からの連続的な環化反応が進行し、四級不斉炭素を有するテトラヒドロベンゾフラン **S-33** が立体選択的に得られることを見出している<sup>11)</sup> (Scheme S-7)。



**Scheme S-7**

また求核剤として2-ヒドロキシフェニル酢酸エステル **S-35** を作用させると、はじめに $\pi$ -プロパルギルパラジウム中間体 **S-36** に対するフェノール酸素原子の求核付加が進行し、その後エステル $\alpha$ 位の炭素からの環化付加が連続的に進行することで置換クロマン **S-38** が立体選択的に生成することを見出している<sup>12)</sup> (Scheme S-8)。



**Scheme S-8**

以上のようにこれまでパラジウム触媒を用いたプロパルギルエステルと求核剤の反応により、多様な複素環化合物が合成できることが報告されている。今回著者は本反応の更なる適応範囲拡大と効率化を目指し、連続的環化反応により高度に置換された複素環化合物を一挙に構築する新しい方法論の開発を試みることにした。

はじめに求核剤の適用範囲拡大について検討した。一般にプロパルギルエステルやアリルエステルに対し良好な求核性を示すものとして、 $\beta$ -ジカルボニルアニオン **S-39** やフェノキシド **S-40** 等のソフトな求核剤が知られている。その一方でモノケトンのような不安定エノラート **S-41** が生じる求核剤については反応性が低いとされている (Figure S-2)。

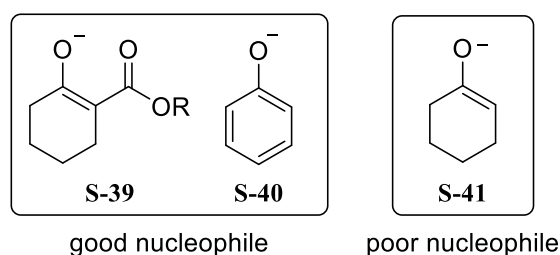
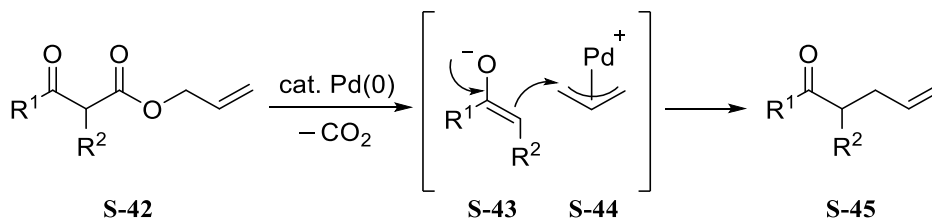


Figure S-2

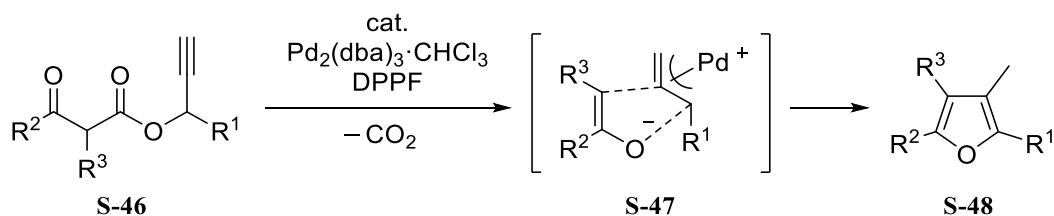
この問題を解決する一つの方法として、求核部位とアリル単位を連結したアリル $\beta$ -ケトエステルを反応基質に用いることが挙げられる<sup>13)</sup>。例えば三枝らはアリル $\beta$ -ケトエステル **S-42** に対しパラジウム触媒を用いると、脱炭酸を伴って不安定エノラート **S-43** と $\pi$ -アリルパラジウム **S-44** が系中にて生じた後、すみやかに求核付加が進行することでケトンの $\alpha$ 位がアリル化された生成物 **S-45** を与えることを見出した (Scheme S-9)。この反応は非常に温和な条件で進行することから、エ

ナンチオ選択的な反応への展開や天然物合成への応用等、幅広い活用例が報告されている<sup>14)</sup>。



Scheme S-9

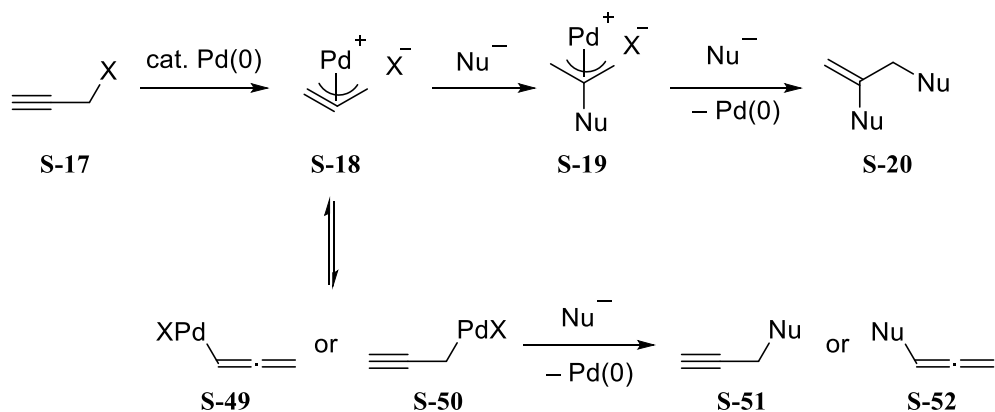
以上のような背景のもと、著者はパラジウム触媒存在下プロパルギル化合物に対し不安定エノラートを求核剤として作用させることを計画した。すなわちアリルβ-ケトエステルの例を参考にし、求核部位とプロパルギル単位を連結したプロパルギルβ-ケトエステル **S-46** を用いると、パラジウム触媒存在下プロパルギル化合物と不安定エノラートの連続的環化反応が進行するのではないかと考え検討を行った。その結果プロパルギルβ-ケトエステルに対しパラジウム触媒を作用させると、予期した通りプロパルギルパラジウム中間体とモノケトンエノラートの連続的な環化反応が進行し置換フラン **S-48** が一挙に得られることを見出した<sup>15)</sup> (Scheme S-10)。詳細については本論第一章で述べる。



Scheme S-10

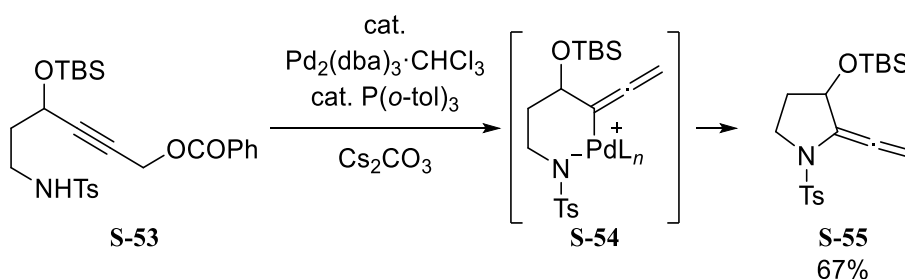
ところでプロパルギル化合物 **S-17** とパラジウムより生成するπ-プロパルギルパラジウム錯体はσ-アレニルパラジウム **S-49** およびσ-プロパルギルパラジウム

**S-50** との平衡関係にあることが知られている<sup>16)</sup>。これら $\sigma$ -錯体に対し求核剤が反応することでプロパルギル置換体 **S-51**、アレニル置換体 **S-52** が生成することも報告されている<sup>17)</sup> (Scheme S-11)。



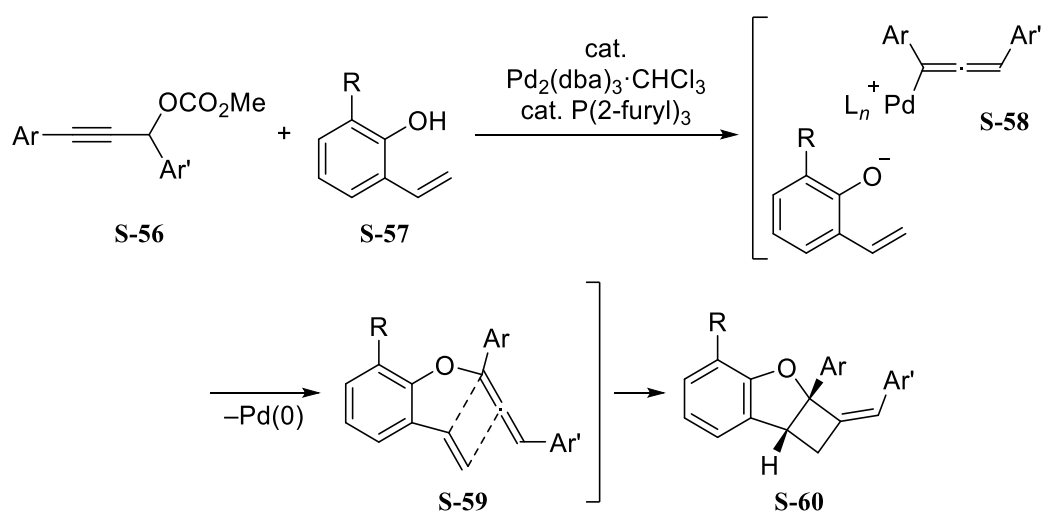
**Scheme S-11**

本反応例として森らは分子内にトシルアミド部位をもつプロパルギルエステル **S-53** に対し 0 価パラジウム触媒を作用させると、 $\sigma$ -アレニルパラジウム錯体 **S-54** が生成後、分子内環化が進行しピペリジンをもちアレン **S-55** が得られることを見いだしている<sup>17b)</sup> (Scheme S-12)。本反応は $\sigma$ -錯体に対しても求核置換反応が進行しうることを示している。しかしながらこれまで報告されている例はすべて分子内反応であり、分子間における反応例は報告されていなかった。



**Scheme S-12**

著者はプロパルギル化合物を用いるパラジウム触媒反応の検討過程において、アリール置換炭酸プロパルギルエステル **S-56** と 2-ビニルフェノール **S-57** を作用させると $\sigma$ -アレニルパラジウム中間体 **S-58** に対するフェノール酸素原子の分子間求核付加、続く[2+2]型環化付加が連続的に進行し4員環を有するベンゾフラン **S-60** が一挙に生成することを明らかにした<sup>18)</sup>(Scheme S-13)。詳細については本論第二章で述べる。



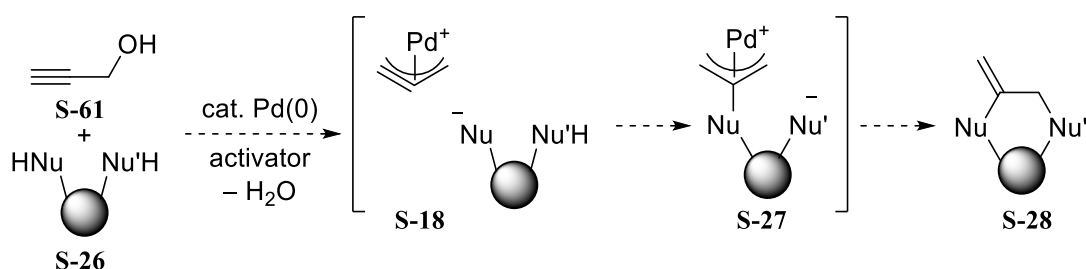
Scheme S-13

これまでに報告された反応はパラジウム触媒存在下プロパルギル化合物を求核剤と作用させ様々な環状化合物を構築できる優れた反応だが、プロパルギル位に脱離性の高いエステル、カーボネート、ハロゲンといった置換基を導入する必要があり、プロパルギルアルコールのような脱離能の低い基質を用いた例は報告されていなかった。そのため既存の反応では基質合成においてプロパルギルアルコールを合成後、炭酸エステルなどの脱離基に変換する工程が必要である。

そこでもし水酸基を脱離基として機能させることができればプロパルギルアルコールを官能基変換することなく基質として用いることが可能でありより原子効率の高い反応へと改良できる。著者らはこれらの反応の更なる応用と効率化を目

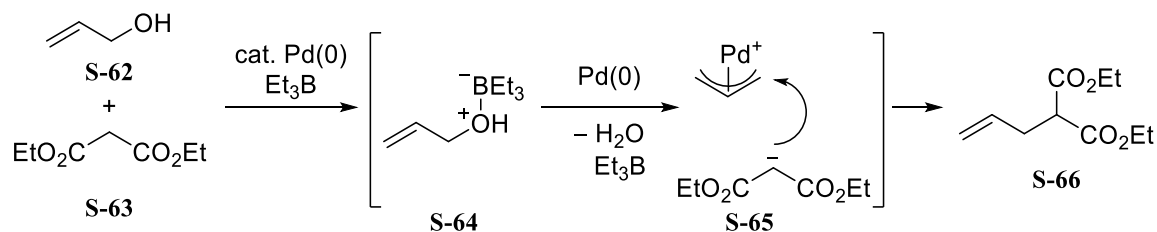


指し、プロパルギルアルコール **S-61** を基質に用いた求核剤との連続的環化反応を検討した。すなわちプロパルギルアルコールに対し水酸基を活性化させる反応剤存在下パラジウム触媒を作用させればプロパルギルパラジウム錯体 **S-18** が生成し、続く求核剤との連続的環化反応も進行するのではないかと考えた (Scheme S-14)。



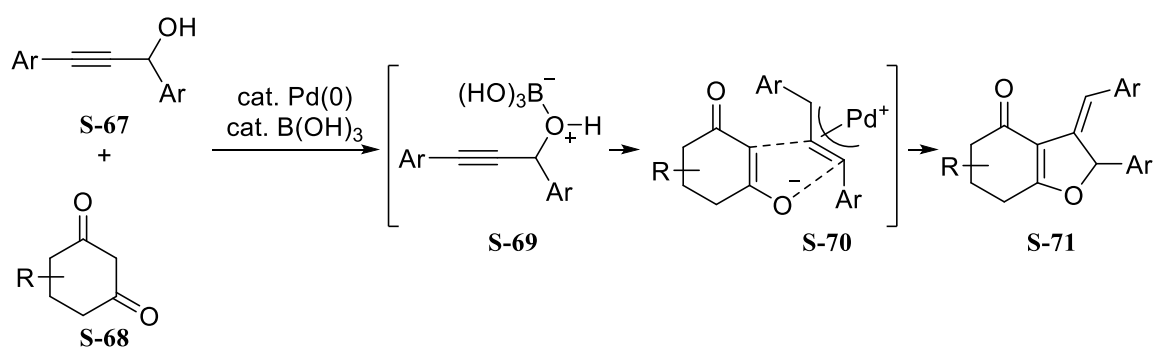
Scheme S-14

水酸基を活性化したパラジウム触媒反応として、アリルアルコールを基質に用いた例が以前報告されている<sup>19)</sup>。例えば木村らはアリルアルコール **S-62** に対しパラジウム触媒存在下トリエチルボランを加えると、 $\beta$ -ジエステル **S-63** との求核置換反応が進行し **S-66** が得られることを見出している。本反応ではルイス酸であるトリエチルボランが水酸基に配位することで直接的に活性化していると考えられる<sup>19a)</sup> (Scheme S-15)。



Scheme S-15

著者はこのアリルアルコールの例を参考にし、水酸基の活性化剤としてルイス酸を選択しプロパルギルアルコールと求核剤の連続的環化反応について検討した。その結果、パラジウム触媒存在下プロパルギルアルコール **S-67** と 1,3-ジケトン **S-68** に対しホウ酸を作用させると連続的環化反応が進行し、テトラヒドロベンゾフラン **S-71** が生成することを見出した (Scheme S-16)。詳細は本論第三章で述べる。

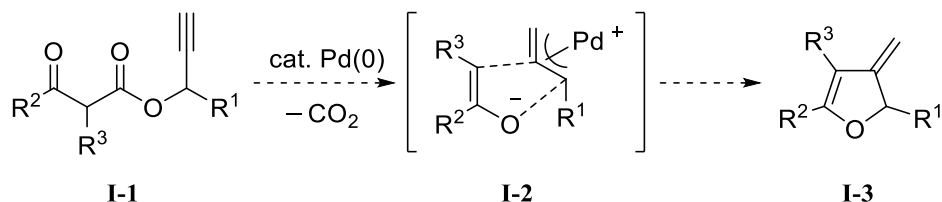


Scheme S-16

# 第一章

## パラジウム触媒を用いたプロパルギルβ- ケトエステルの連続反応による置換フランの合成

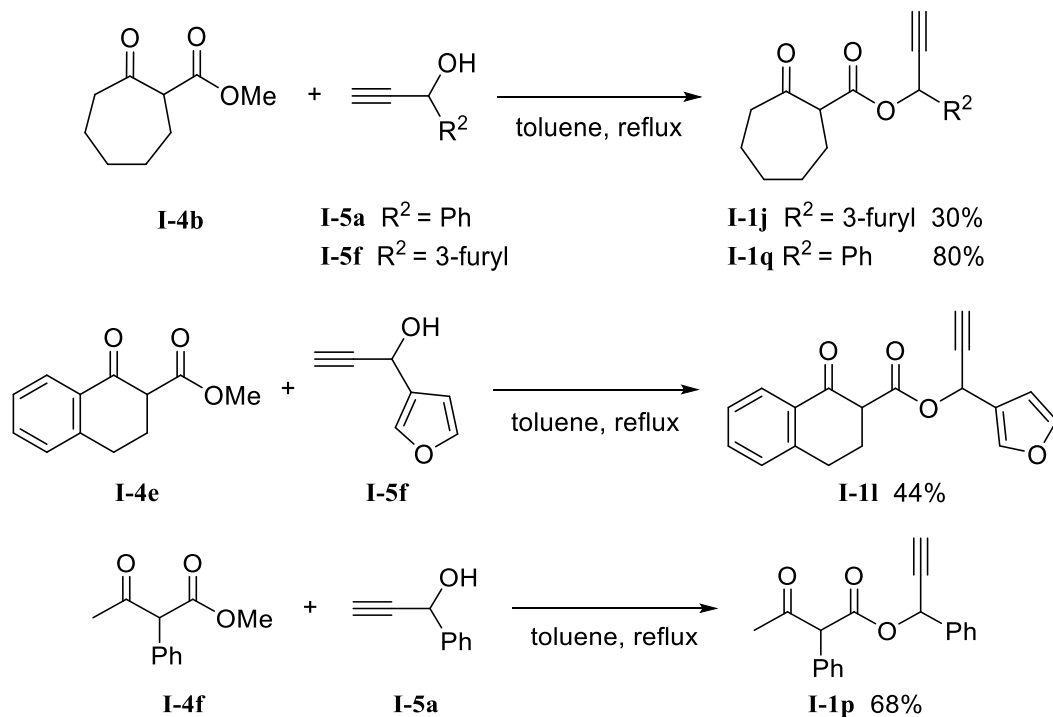
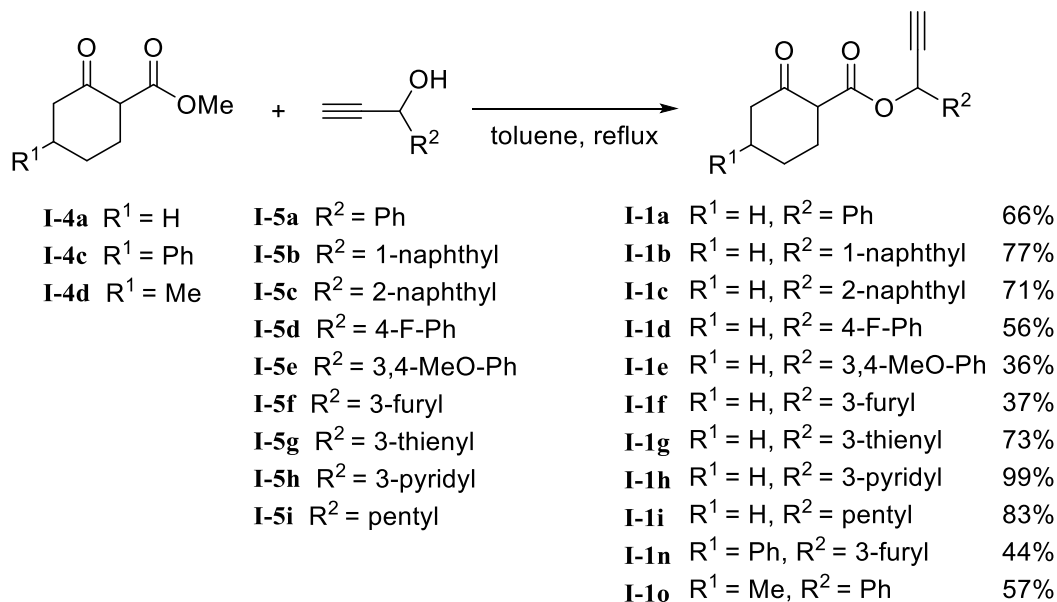
著者はπ-プロパルギルパラジウム中間体に対する連続的環化反応の展開として、新たにモノケトン由来の不安定エノラートを求核剤として作用させることを計画した。不安定エノラートを求核剤として用いる方法として、総論で述べたようにプロパルギル単位と不安定エノラート部位を連結したプロパルギルβ-ケトエステル **I-1** を基質に用いることを考案した。すなわち基質 **I-1** に対しパラジウム触媒を作用させると脱炭酸を伴いπ-プロパルギルパラジウム中間体とエノラート **I-2** が生成後、連続的な環化反応が進行し環化体 **I-3** が一挙に生成するものと考えた (Scheme I-1)。以下本連続反応の開発を行うべく研究に着手した。



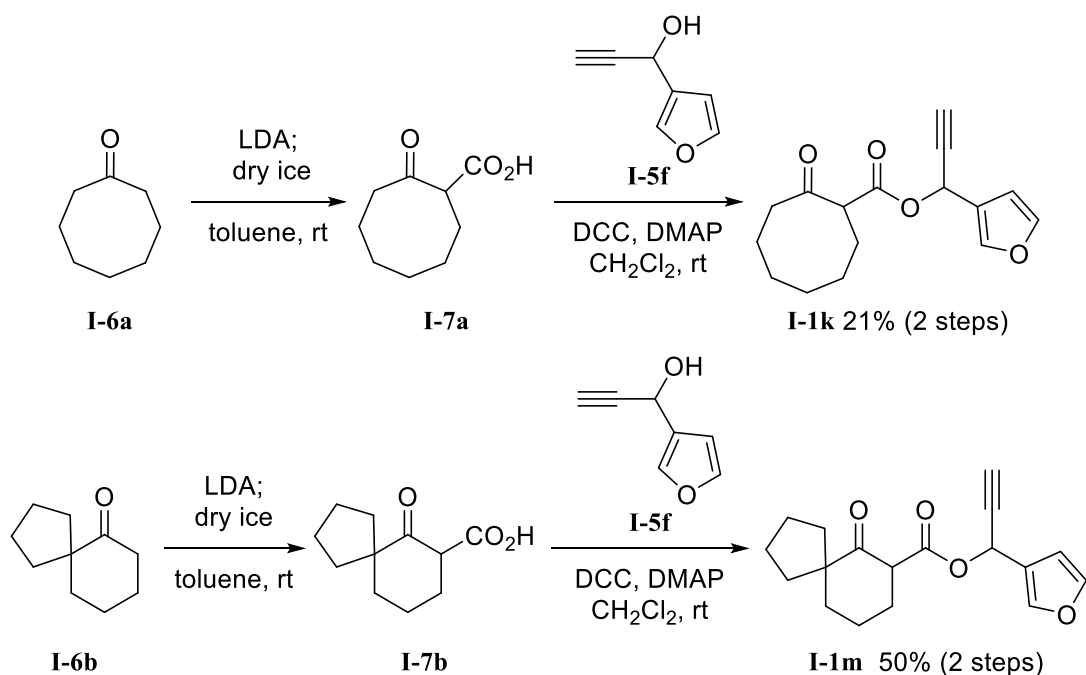
Scheme I-1

本反応に用いる基質は次のように合成した。文献既知のβ-ケトエステル **I-4a**、**I-4c**、**I-4d** に対しプロパルギルアルコール **I-5a**–**I-5i** をトルエン溶媒中加熱還流条件下作用させ、相当するプロパルギルβ-ケトエステル **I-1a**–**I-1i**、**I-1n**、**I-1o** を合成した<sup>20)</sup> (Scheme I-2)。同様の手法を用いβ-ケトエステル **I-4b**、**I-4e**、**I-4f** より **I-1j**、**I-1l**、**I-1p**、**I-1q** を構築した。またケトン **I-6a**、**I-6b** に対し各々LDA 存在下ドライアイスを用いて作用させることでβ-ケトカルボン酸 **I-7a**、**I-7b** とした後、DCC,

DMAP を用いプロパルギルアルコール **I-5f** と縮合することでプロパルギルβ-ケトエステル **I-1k**、**I-1m** を合成した<sup>21)</sup> (Scheme I-3)。

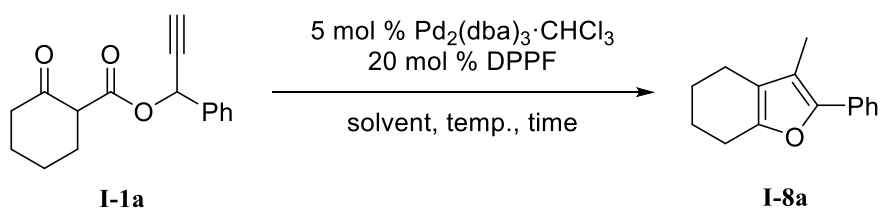


Scheme I-2



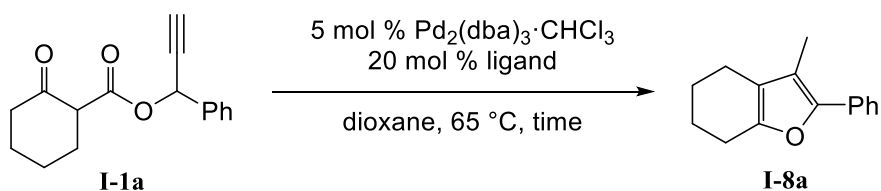
以上のようにして得られた基質を用いてパラジウム触媒を用いた連続的環化反応の検討を行った (Table I-1)。はじめにプロパルギル位にフェニル基を持つ基質 **I-1a** に対し、5 mol % の  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  及び 20 mol % の DPPF 存在下 DMSO 溶媒中 120 °C にて攪拌したところ予期した反応は進行し、更に二重結合の異性化した置換フラン **I-8a** が収率 35% で生成した (entry 1)。環化体 **I-8a** の更なる収率向上を目指し溶媒と温度の検討をしたところ (entries 2–9)、dioxane 溶媒中 65 °C にて反応を行うことで **I-8a** の収率は 75% まで向上した (entry 7)。また本反応はパラジウム触媒の量を 2.5 mol % に減じても同等の反応性を示し、収率 76% で生成物を与えることが明らかとなった (entry 10)。

続いて様々な配位子を用いて検討を行った (Table I-2)。その結果、entries 2–6 に示すような二座ホスフィン配位子を用いた場合に反応は進行したものの、いずれも DPPF を上回る結果は得られなかった。また  $\text{DPPent}$  や  $\text{PPh}_3$  を配位子として用いたときは反応が進行せず、原料が回収されるのみだった (entries 7 and 8)。

**Table I-1. Initial attempts using propargyl  $\beta$ -ketoester I-1a.**

entry	solvent	temp. [°C]	time [h]	yield [%]
1	DMSO	120	5 min	35
2	DMSO	80	2	40
3	DMF	80	1.5	19
4	NMP	80	1	45
5	dioxane	80	2	63
6	THF	65	2	70
7	dioxane	65	2.5	75
8	dioxane	50	5	52
9	dioxane	rt	8	64
10 <sup>[a]</sup>	dioxane	65	1	76

[a] 2.5 mol %  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  and 10 mol % DPPF were used.

**Table I-2. Effect of ligand.**

entry	ligand	time [h]	yield [%]
1	DPPF	2.5	75
2	DPPP	0.5	29
3	DPPB	4	24
4	DPPP	0.5	29
5	DPPE	3	9
6	BINAP	2	60
7	DPPent	16	no reaction
8	40 mol% $\text{PPh}_3$	2.5	no reaction

続いて得られた最適条件下 (Table I-1, entry 10) にて、本反応の一般性を見る目的でプロパルギル位に様々な置換基を導入した基質 **I-1b–I-1l** を用い検討を行った (Table I-3)。プロパルギル位にナフチル基、4-フルオロフェニル基、3,4-ジメトキシフェニル基のようなアリール基をもつ **I-1b–I-1e** に対し反応を行った場合も **I-1a** の場合と同様の反応は進行し、相当する置換フラン **I-8b–I-8e** が良好な収率で得られてきた (entries 1–4)。また、フリール基、チエニル基、ピリジル基のような複素環を持つ基質 **I-1f–1h** を用いても良い収率であった (entries 5–7)。一方ペンチル基を導入した基質 **I-1i** を用いると置換フラン **I-8i** が 43% と中程度の収率ではあるものの得られると同時に、ジエン **I-9i** が 38% の収率で副生成物として生成した (entry 8)。

次に様々なケトン部位を持つ基質 **I-1j–I-1p** に対し反応を行った (Table I-4)。その結果、7員環、8員環のケトン部位を持つ **I-1j**、**I-1k** を用いた場合も同様の反応が進行し、環化体 **I-8j**、**I-8k** がそれぞれ収率 70%、74% であった (entries 1 and 2)。続いてテトラロン部を持つ **I-1l** を基質に用い検討を行ったところ、置換フラン **I-8l** が収率 70% と良好な結果であった (entry 3)。分子内にスピロ環を持つ基質 **I-1m** を用いた場合も環化反応は進行し、62% の収率で **I-8m** を与えた (entry 4)。またケトンのβ位にフェニル基、メチル基を導入した **I-1n**、**I-1o** 用いた場合、環化体 **I-8n**、**I-8o** をそれぞれ収率 76%、57% でいずれも単一の生成物として得られることがわかった (entries 5 and 6)。一方、鎖状のβ-ケトエステル **I-1p** を用い反応の検討を行ったところ、環化反応は進行するものの **I-8p** は 21% と低収率に留まった (entry 7)。

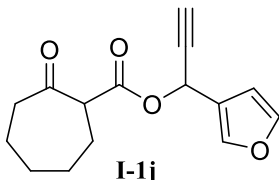
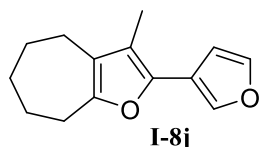
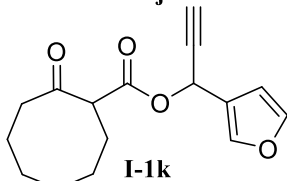
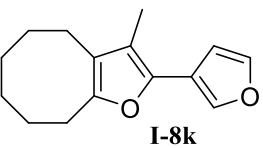
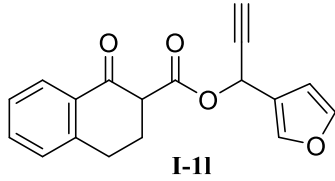
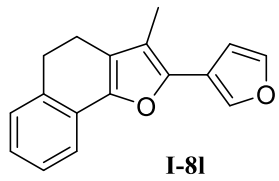
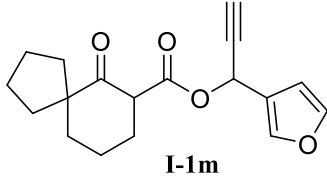
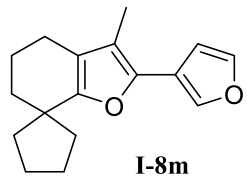
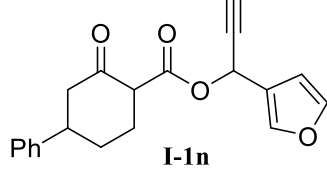
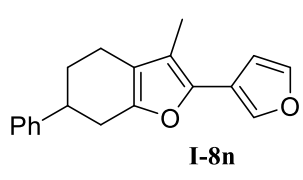
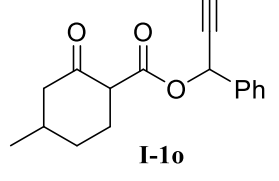
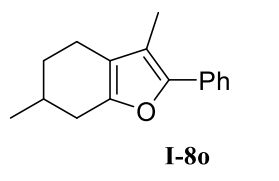
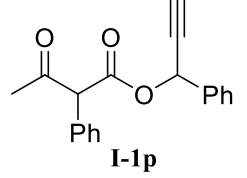
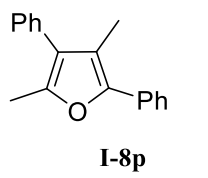
**Table I-3. Reactions using various propargyl  $\beta$ -ketoesters I-1b–I-1i.<sup>[a]</sup>**

entry	substrate I-1	product I-8	yield [%]
1	 <b>I-1b</b>	 <b>I-8b</b>	62
2	 <b>I-1c</b>	 <b>I-8c</b>	60
3	 <b>I-1d</b>	 <b>I-8d</b>	68
4	 <b>I-1e</b>	 <b>I-8e</b>	63
5	 <b>I-1f</b>	 <b>I-8f</b>	79
6	 <b>I-1g</b>	 <b>I-8g</b>	73
7	 <b>I-1h</b>	 <b>I-8h</b>	61
8	 <b>I-1i</b>	 <b>I-8i</b>	43 (I-9i: 38)
		 <b>I-9i</b> (1:1 mixture)	

[a] The reactions were carried out using I-1 in the presence of 2.5 mol% Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and 10 mol% DPPF in dioxane at 65 °C for 20-60 min



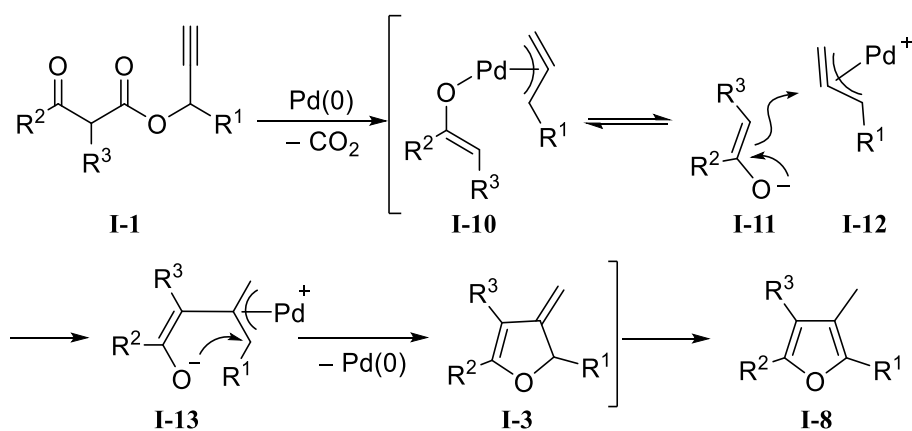
**Table I-4. Reactions using various propargyl  $\beta$ -ketoesters I-1j–I-1p.<sup>[a]</sup>**

entry	substrate I-1	product I-8	yield [%]
1	 <b>I-1j</b>	 <b>I-8j</b>	70
2	 <b>I-1k</b>	 <b>I-8k</b>	74
3	 <b>I-1l</b>	 <b>I-8l</b>	70
4	 <b>I-1m</b>	 <b>I-8m</b>	62
5	 <b>I-1n</b>	 <b>I-8n</b>	76
6	 <b>I-1o</b>	 <b>I-8o</b>	57
7 <sup>[b]</sup>	 <b>I-1p</b>	 <b>I-8p</b>	21

[a] The reactions were carried out using **I-1** in the presence of 2.5 mol% Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and 10 mol% DPPF in dioxane at 65 °C for 20-60 min  
 [b] The reaction was carried out at 100 °C.

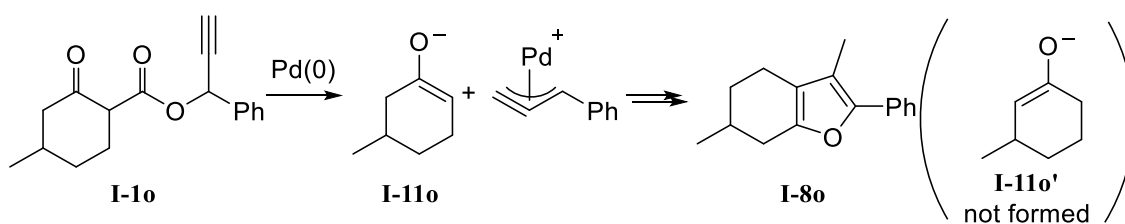
本反応の予想される反応機構を Scheme I-4 に示す。はじめにパラジウム触媒が炭酸プロパルギルエステル **I-1** と反応することにより脱炭酸が進行し、 $\pi$ -プロパ

ルギルパラジウムエノラート **I-10** が生成する。本中間体はエノラート **I-11** とπ-プロパルギルパラジウム **I-12** が分離したイオン対と平衡状態にあると考えられ、続いてπ-プロパルギルパラジウム **I-12** に対するエノラート **I-11** の求核付加しπ-アリルパラジウム中間体 **I-13** へと変換される。**I-13** よりエノラート酸素からの分子内求核攻撃が進行することで環化体 **I-3** が生成、その後熱力学的に安定なフラン **I-8** へと異性化したものと考えられる。



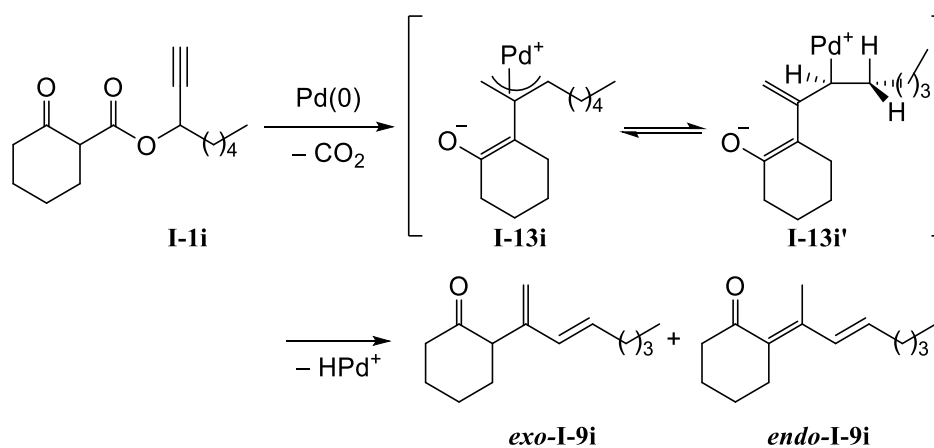
**Scheme I-4**

またケトンのβ位に置換基をもつ基質 **I-10** から単一の生成物 **I-8o** が生成したことから、本反応においてエノラート中間体 **I-11o** が位置選択的に生じて反応に関与しており、**I-11o** の位置異性体 **I-11o'** は反応系内で生成していないことが示唆された (Scheme I-5)。



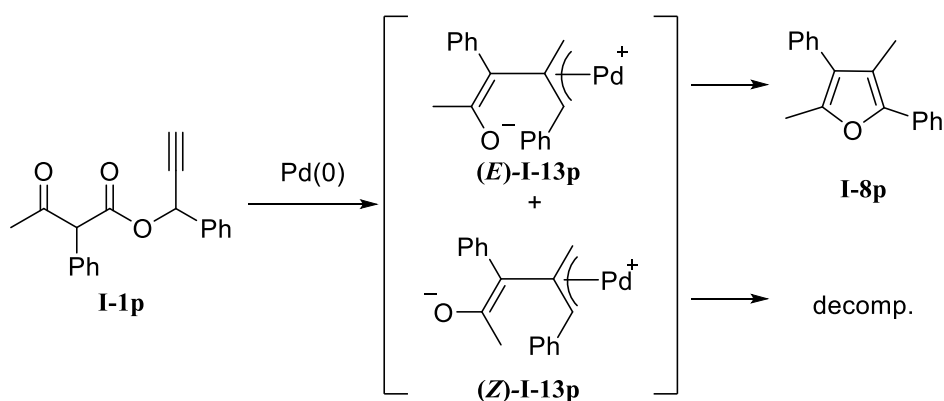
**Scheme I-5**

Table I-3 においてプロパルギル位にアルキル基が導入された基質 **I-1i** を用いたときジエン **I-9i** が副生した理由としては、相当する $\pi$ -アリルパラジウム **I-13i** 形成時隣接するアルキル基によりパラジウムの $\beta$ -ヒドリド脱離が同時に進行したためであると思われる (Scheme I-6)。



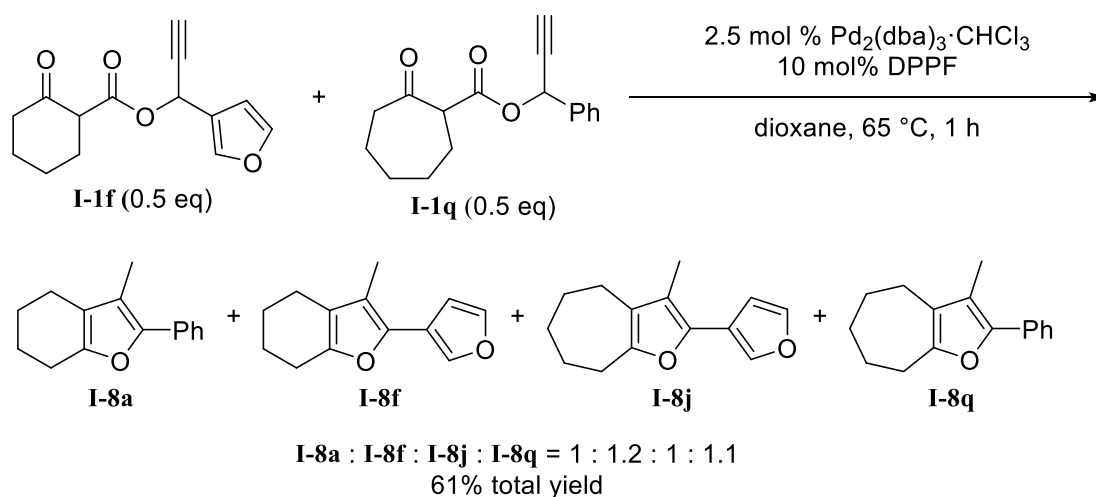
**Scheme I-6**

また Table I-4 において鎖状の基質 **I-1p** を用いた際に生成する環化体 **I-8p** が低収率であった原因として、 $\pi$ -アリルパラジウム中間体となったとき二つの幾何異性体(*E*)-及び(*Z*)-**I-13p** が生じ、(*E*)-**I-13p** は環化反応が進行し置換フラン **I-8p** を与えるものの(*Z*)-**I-13p** からは環化反応が進行しなかったためと考えられる (Scheme I-7)。

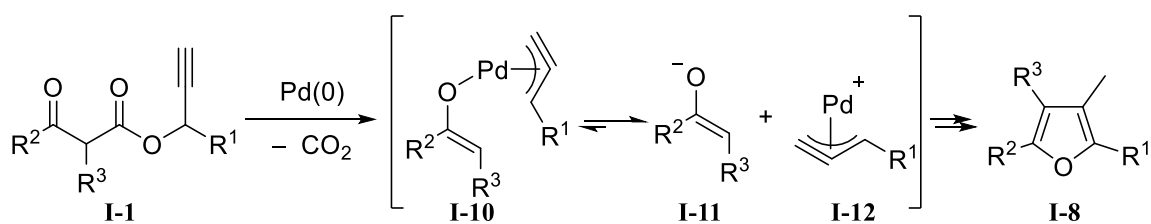


**Scheme I-7**

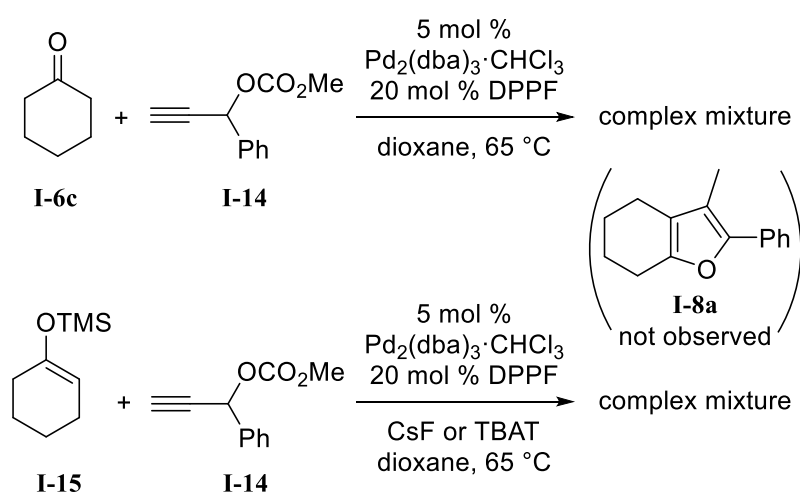
続いて更なる反応機構の解析のためクロスオーバー実験を行った。すなわち等量のプロパルギルβ-ケトエステル **I-1f** および **I-1q** 存在下にてパラジウム触媒を作用させたところ、4種の置換フラン **I-8a**、**I-8f**、**I-8j**、**I-8q** が 1 : 1.2 : 1 : 1.1 の生成比で得られた (Scheme I-8)。このことから本反応は脱炭酸が進行後、 $\pi$ -プロパルギルパラジウム錯体とエノラートが一度完全に分離した後求核付加が進行する分子間反応であることを強く支持している (Scheme I-9)。



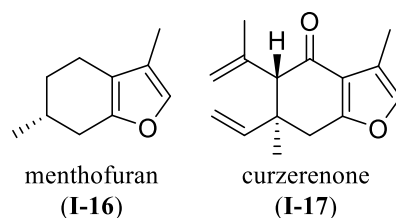
**Scheme I-8**



次にプロパルギルβ-ケトエステルを用いた本反応の有効性を確かめるべく、求核部位であるケトン部とプロパルギルエステル部が分離した「分子間」反応を行った。すなわちパラジウム触媒存在下 cyclohexanone (**I-6c**) に対し炭酸プロパルギルエステル **I-14** を作用させることで同様の連続的環化反応が進行するか検討を行った (Scheme I-10)。結果、複雑な混合物が得られるのみであり環化体 **I-8a** は生成しなかった。またシリルエノールエーテル **I-15** を求核剤として用い脱シリル化剤として CsF<sup>22)</sup> あるいは TBAT<sup>23)</sup> 存在下検討を行ったが、本条件においても連続的環化反応は進行せず複雑な混合物が得られるのみだった。以上の結果はケトン部とプロパルギルエステル部が連結したプロパルギルエステルでのみフランを生成する反応が進行しうることを示している。



以上をまとめると今回著者はパラジウム触媒を用いたプロパルギル $\pi$ -ケトエステルの連続的付加環化反応の検討を行い一般性の検討及び反応機構の考察を行った。本反応は置換フランの新たな合成方法であり、今後 Figure I-1 に示すようなフラン骨格を含む生理活性分子の合成等、様々な有機合成への応用が期待される。



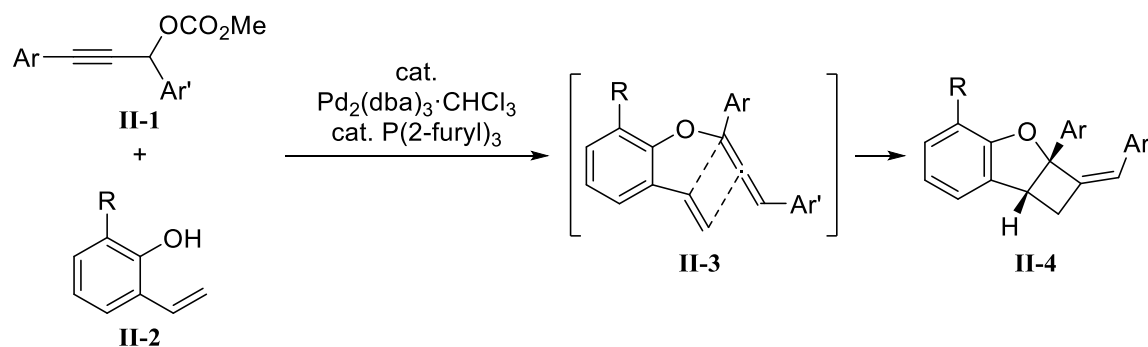
**Figure I-1**

## 第二章

### パラジウム触媒を用いた

### 炭酸プロパルギルエステルと 2-ビニルフェノールの 連続的求核置換-[2+2]環化付加反応

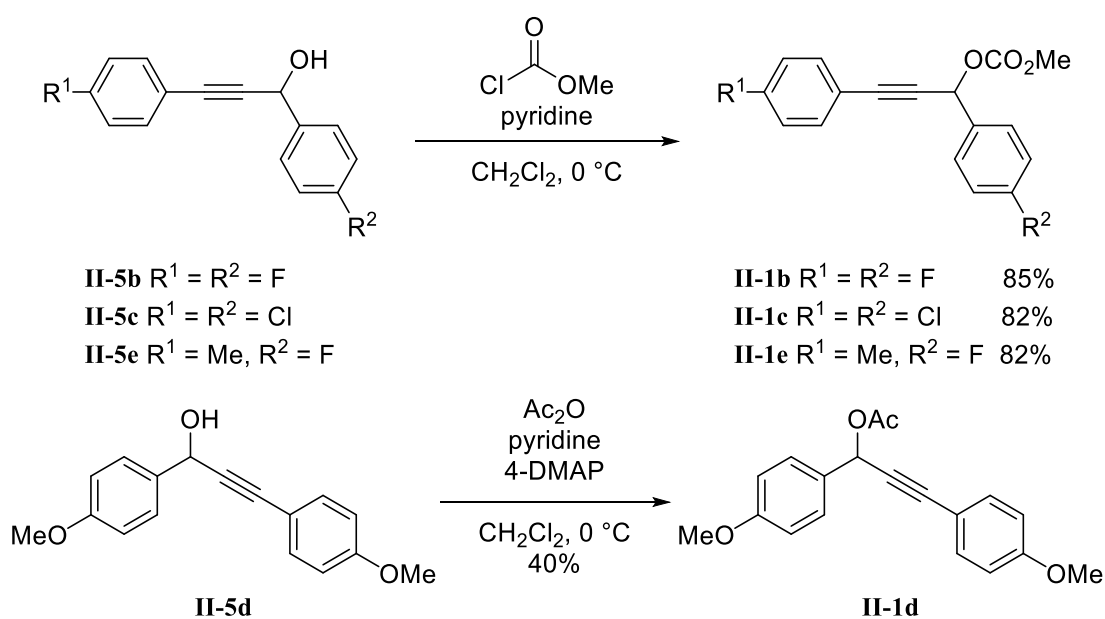
総論で述べたように $\pi$ -プロパルギルパラジウム錯体は $\sigma$ -アレニルパラジウムおよび $\sigma$ -プロパルギルパラジウム錯体と平衡関係にあることが知られている。一方でこれら $\sigma$ 錯体に対しソフトな求核剤が分子間で反応する例は報告されていなかった。著者はプロパルギルエステル **II-1** を用いたパラジウム触媒反応の検討過程において求核剤としてオルト置換ビニルフェノール **II-2** を用いると末端炭素に求核付加が進行しフェノキシアレン **II-3** が生成後[2+2]型環化付加反応が連続して進行し、四員環を含む三環性化合物 **II-4** が得られることを予期せず見出した<sup>18)</sup> (Scheme II-1)。本反応の詳細について以下に述べる。



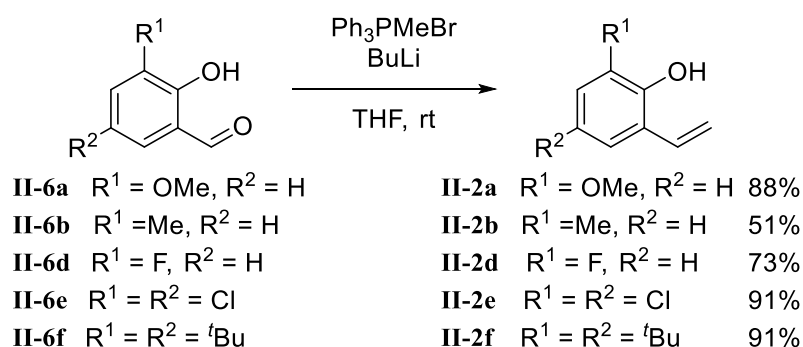
Scheme II-1

反応基質は以下のように合成した。プロパルギルアルコール **II-5b**、**II-5c**、**II-5e** に対しクロロ炭酸メチルを作用させることで炭酸プロパルギルエステル **II-1b**、**II-1c**、**II-1e** を得た<sup>24)</sup> (Scheme II-2)。また *p*-メトキシフェニル基を導入したプロパル

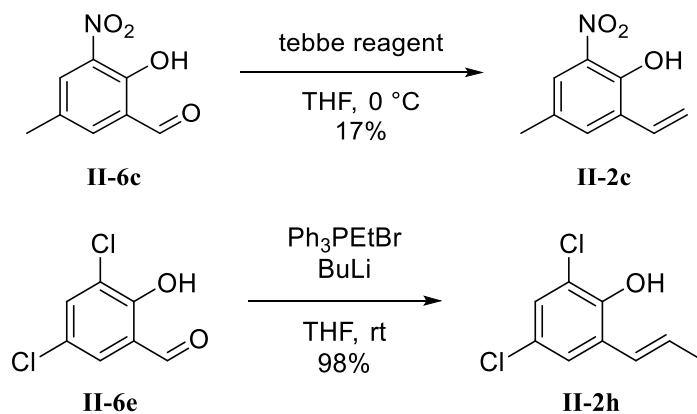
ギルアルコール **II-5d** に対し無水酢酸を用いることでプロパルギルエステル **II-1d** とした。続いてサリシルアルデヒド **II-6a**、**II-6b**、**II-6d–II-6f** に対し Wittig 反応を行うことで、2-ビニルフェノール **II-2a**、**II-2b**、**II-2d–II-2f** を得た<sup>25)</sup> (Scheme II-3)。また 3-Nitro-5-methylsalicylaldehyde (**II-6c**) に対し Tebbe 試薬を作用させることでビニルフェノール **II-2c** を合成した。更に 3,5-Dichlorosalicylaldehyde (**II-6e**) に対し Wittig 反応を行いプロペニルフェノール **II-2h** を得た。



Scheme II-2



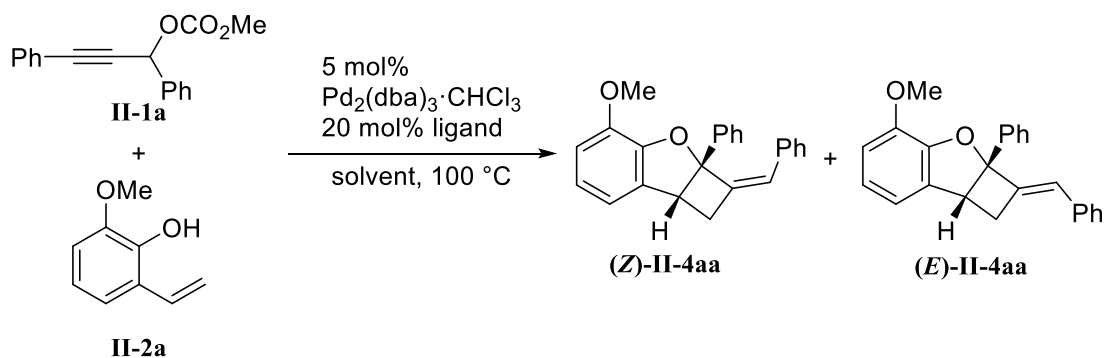




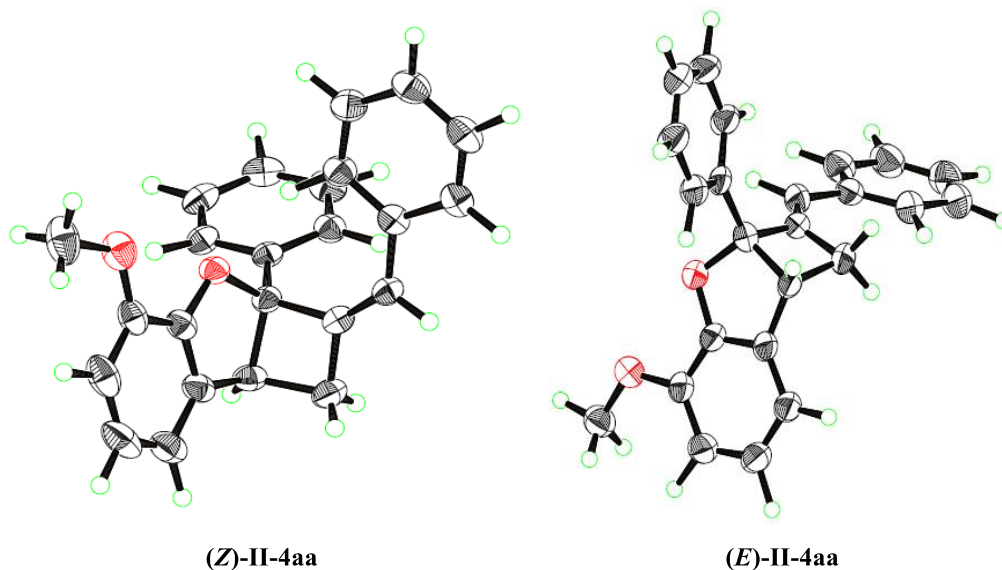
**Scheme II-3**

以上のように合成した基質に対しパラジウム触媒を作用させて反応の検討を行った (TableII-1)。はじめにジフェニル置換炭酸プロパルギルエステル **II-1a** と *o*-メトキシビニルフェノール **II-2a** に対し、5 mol%の  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  及び 20 mol%の DPPF 存在下 DMSO 溶媒中 100 °Cにて攪拌したところ、四員環を含む三環性化合物(**Z**)-**II-4aa** およびその幾何異性体(**E**)-**II-4aa** が 4.5:1 の比率、収率 59%で生成した (entry 1)。得られた両環化体の化学構造は X 線結晶構造解析を行うことにより決定した (Figure II-1)。続いて環化体 **II-4aa** の更なる収率向上を目指し、配位子を変えて検討を行った (entries 2–5)。その結果配位子を二座配位子から単座配位子に変えることで改善が見られ、 $\text{P}(2\text{-furyl})_3$  が最も良い収率であった (entry 5)。次に溶媒の検討を行ったところ (entries 6 and 7)、dioxane 溶媒中作用させると環化体の収率は 85%まで向上することが明らかとなった (entry 7)。

**Table II-1. Initial attempts for the reaction of II-1a with II-2a.**



entry	ligand	solvent	Z/E	yield [%]
1	DPPF	DMSO	4.5:1	59
2	DPPB	DMSO	5.5:1	35
3	$\text{PPh}_3$	DMSO	2.9:1	62
4	P( <i>o</i> -tolyl)	DMSO	5.5:1	64
5	P(2-furyl)	DMSO	5.5:1	69
6	P(2-furyl)	toluene	3.4:1	67
7	P(2-furyl)	dioxane	3.5:1	85



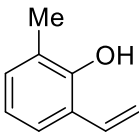
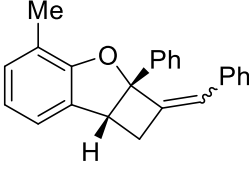
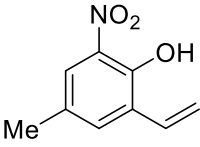
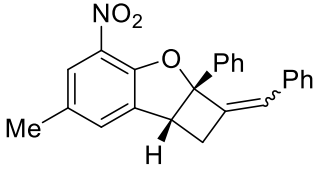
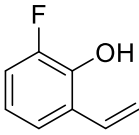
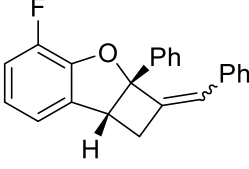
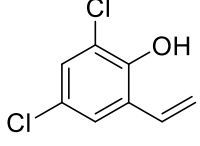
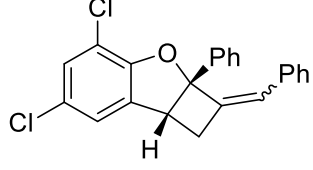
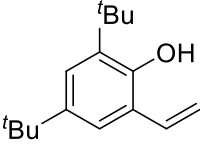
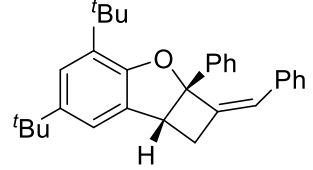
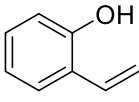
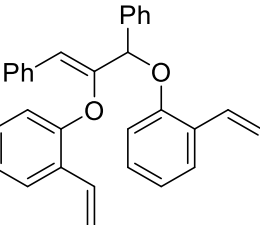
**Figure II-1**

次に炭酸プロパルギルエステル **II-1a** に対してオルト位に様々な置換基をもつ 2-ビニルフェノール **II-2b-II-g** を用いた反応を試みた (Table II-2)。その結果、オルト位にメチル基、ニトロ基、ハロゲンをもつ **II-2b-II-2e** を用いても同様の反

応が進行し、それぞれ相当する三環性化合物 **II-4ab–II-4ae** が 82%、78%、70%、92% と良好な収率でジアステレオ優先的に得られた (entries 1–4)。またかさ高い <sup>t</sup>Bu 基をもつ基質 **II-2f** を用いた場合には環化体(**Z**)-**II-4af** が定量的かつ選択的に生成することが明らかとなった (entry 5)。一方オルト位に置換基を持たない **II-2g** を用いると、二つの求核剤が導入されたアリル化合物 **II-7** が生じるのみであった (entry 6)。なお得られた環化体 **II-4ab–II-4af** の立体化学に関しては(**Z**)-**II-4aa** との <sup>1</sup>H-NMR スペクトルの類似性からいずれも(**Z**)-体が主生成物であると推定した。

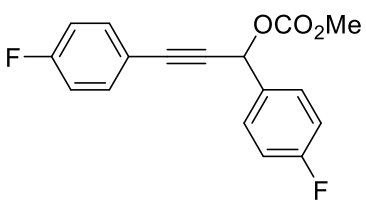
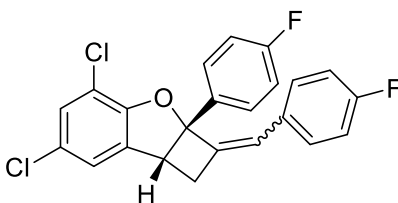
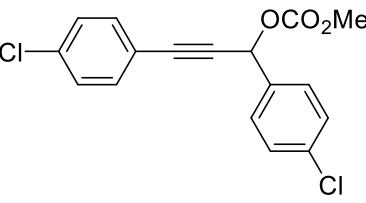
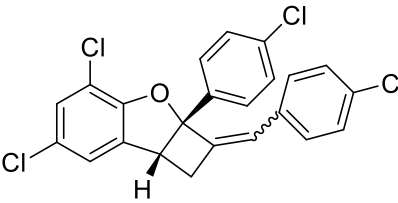
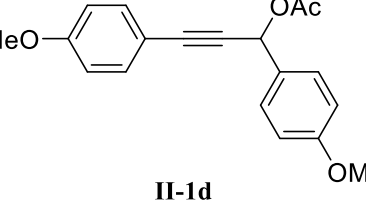
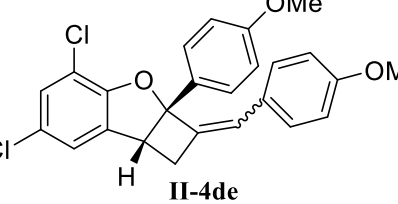
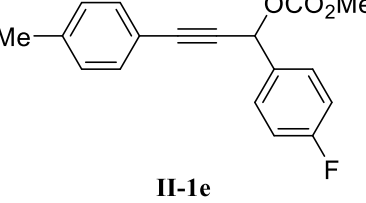
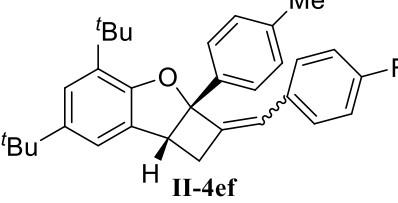
続いて様々な置換基を持つ炭酸プロパルギルエステルを基質に用い反応を行った (Table II-3)。すなわち合成したプロパルギルエステル **II-1b–II-1d** に対しビニルフェノール **II-2e** を作用させた。その結果本反応はプロパルギルエステルのアリール基上にフッ素、塩素、メトキシ基をパラ位に導入した基質においても円滑に進行し、相当する環化体 **II-4be–II-4de** を 88%、89%、72% で与えることが明らかとなった (entries 1–3)。次にプロパルギル位側に *p*-フロロフェニル基、アルキン末端に *p*-トリル基を導入した炭酸プロパルギルエステル **II-1e** を用いビニルフェノール **II-2f** との反応を検討した。その結果アルキン末端のトリル基とフェノール由来の酸素原子が同じ炭素に置換された環化体 **II-4ef** を位置選択的かつ定量的に与えることが分かった (entry 4)。なお **II-4ef** の構造は X 線結晶構造解析により決定した (Figure II-2)。

**Table II-2. Substrate scope of the reactions using various substituted vinylphenols II-2b–II-2g with II-1a.** [a]

entry	substrate II-2	product II-4	yield [%] Z/E
1	 <b>II-2b</b>	 <b>II-4ab</b>	82 4.5:1
2	 <b>II-2c</b>	 <b>II-4ac</b>	70 4:1
3 <sup>[b]</sup>	 <b>II-2d</b>	 <b>II-4ad</b>	78 4.5:1
4	 <b>II-2e</b>	 <b>II-4ae</b>	92 4.4:1
5	 <b>II-2f</b>	 <b>II-4af</b>	99 >20:1
6	 <b>II-2g</b>	 <b>II-7</b>	99

[a] The reactions were carried out using **II-1a** and **II-2** in the presence of 5 mol% Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and 20 mol% P(2-furyl)<sub>3</sub> in dioxane at 100 °C for 1 h.  
 [b] P(*o*-tolyl)<sub>3</sub> was used as the ligand.

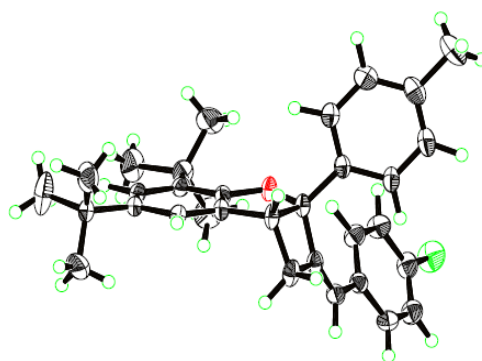
**Table II-3. Reactions using various propargylic esters II-1b–II-1e with II-2e.** [a]

entry	propargylic ester II-1	product II-4	yield [%] Z/E
1	 <p style="text-align: center;"><b>II-1b</b></p>	 <p style="text-align: center;"><b>II-4be</b></p>	88 4.7:1
2	 <p style="text-align: center;"><b>II-1c</b></p>	 <p style="text-align: center;"><b>II-4ce</b></p>	89 5.9:1
3 <sup>[b]</sup>	 <p style="text-align: center;"><b>II-1d</b></p>	 <p style="text-align: center;"><b>II-4de</b></p>	72 10:1
4 <sup>[c]</sup>	 <p style="text-align: center;"><b>II-1e</b></p>	 <p style="text-align: center;"><b>II-4ef</b></p>	99 4.8:1

[a] The reactions were carried out using **II-1** and **II-2e** in the presence of 5 mol% Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and 20 mol% P(2-furyl)<sub>3</sub> in dioxane at 100 °C for 1 h.

[b] K<sub>3</sub>PO<sub>4</sub> was added as the base.

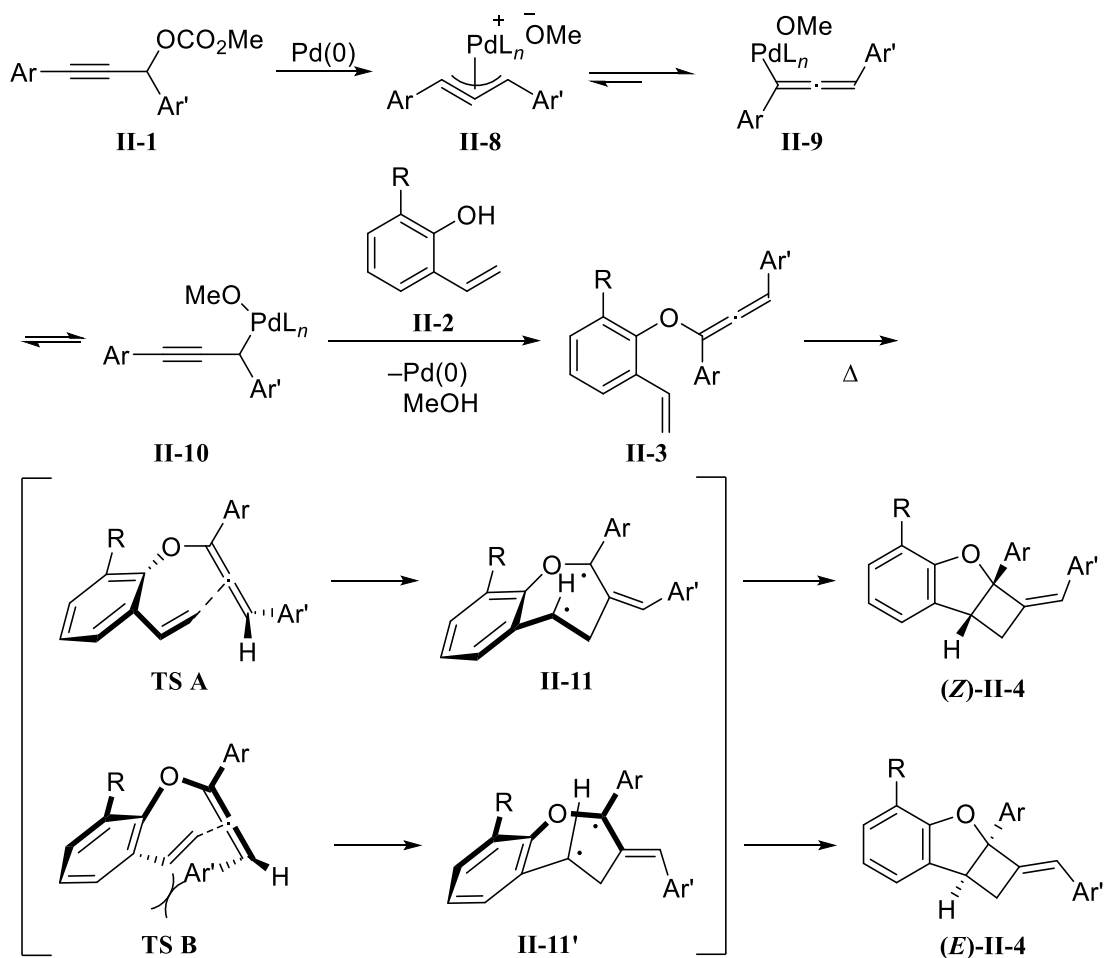
[c] Vinylphenol **II-2f** was used as the substrate.



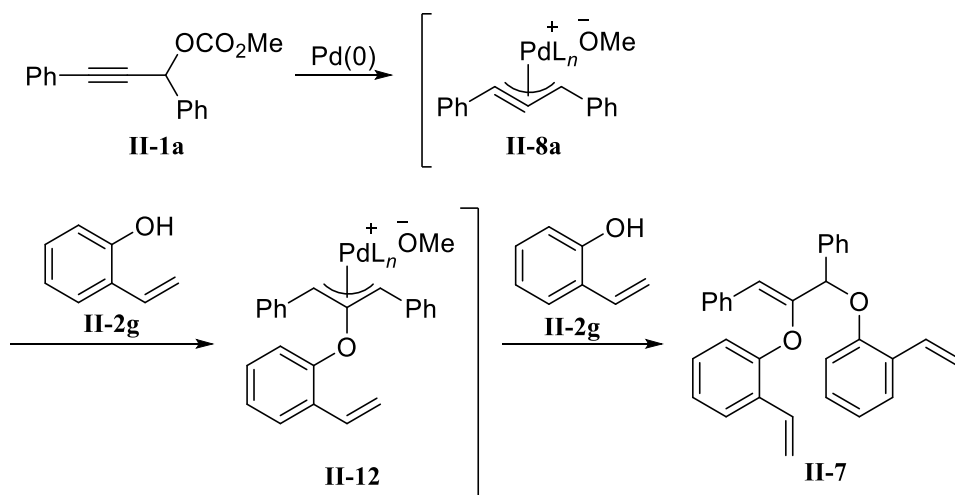
(Z)-II-4ef

**Figure II-2**

本反応の予想される機構を Scheme II-4 に示す。はじめにパラジウム触媒が炭酸プロパルギルエステル **II-1** と反応することにより脱炭酸が進行し、 $\pi$ -プロパルギルパラジウム錯体 **II-8** が生成する。本錯体は $\sigma$ -アレニル錯体 **II-9** もしくは $\sigma$ -プロパルギル錯体 **II-10** と平衡状態であり、続いて本錯体に対するビニルフェノール **II-2** の求核的置換反応が進行し、ビニルアレン **II-3** となる。本化合物は更に加熱条件下にてジラジカル中間体の生成を経る段階的な[2+2]型環化付加反応を引き起こし<sup>26)</sup>、三環性化合物 **II-4** を与えたものと推定される。また本反応において **(Z)-II-4** がジアステレオ優先的に生成した理由としては、環化の際に遷移状態 **TS A** を経る反応が優先的に進行したことが考えられる。**TS A** の形ではビニル基とアレン末端のアリール基の立体反発を避けて進行し、反応中間体 **II-11** を経由して **(Z)-II-4** が得られる。一方 **(E)-II-4** が生じる **TS B** の遷移状態では Ar' とビニル基の立体反発が生じるため **TS A** に比べ高いエネルギーを持つ。遷移状態 **TS A** と **TS B** のエネルギー差から **(Z)-II-4** は **(E)-II-4** よりも優先的に得られたと予想される。また Table II-1 において二座配位子よりも単座配位子が良い結果を与えたのは、配位子の効果により **II-8**、**II-9**、**II-10** の平衡が $\sigma$ -錯体側に偏り反応が促進されたためと思われる<sup>17c)27)</sup>。Table II-2、entry 7 においてビニルフェノール **II-2g** を用いると二つの求核剤が導入されたアリル化合物 **II-7** が得られた理由として、**II-2g** はオルト位に置換基を持たないためフェノールの求核性が高くなり、 $\pi$ -プロパルギルパラジウム **II-8** の中心炭素への求核付加が優先したためと考えられる (Scheme II-5)。

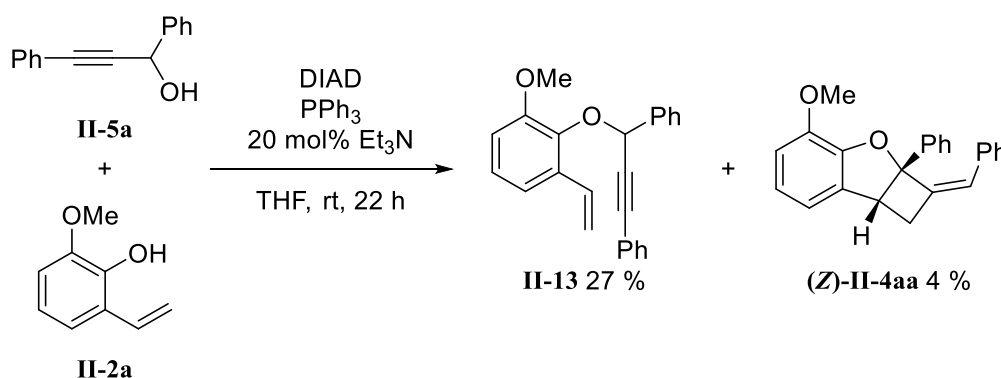


Scheme II-4



Scheme II-5

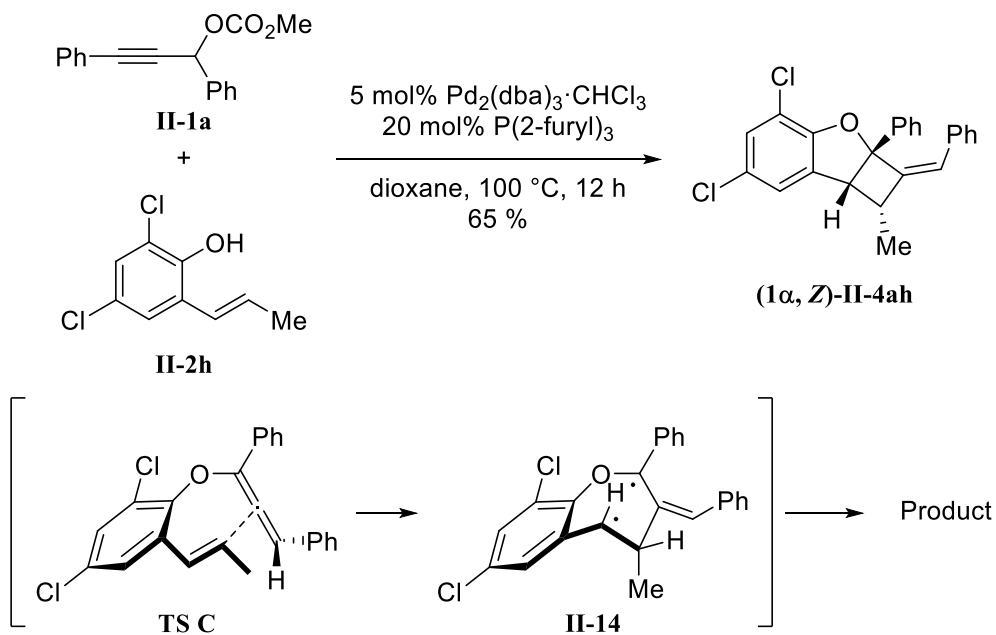
フェノキシアレン **II-3** が反応中間体として生じていることを確かめるため、次にプロパルギルアルコール **II-5a** にビニルフェノール **II-2a** を光延反応の条件にて作用させて検討を行った (Scheme II-6)。 **II-2a** と **II-5a** に対し DIAD と PPh<sub>3</sub> を作用させたところ、パラジウム触媒を用いた環化反応と同じ三環性フラン **II-4aa** が収率 4% でプロパルギルフェノール **II-13** と共に生成することが分かった。 **II-4aa** は **II-5a** に対し **II-2a** が S<sub>N</sub>2'形式で求核付加しアレン **II-3** を形成後、[2+2]型の環化付加が進行することで生成したと予想される。この結果は求核付加後[2+2]型環化が連続して進行する Scheme II-4 の機構を支持するものである。



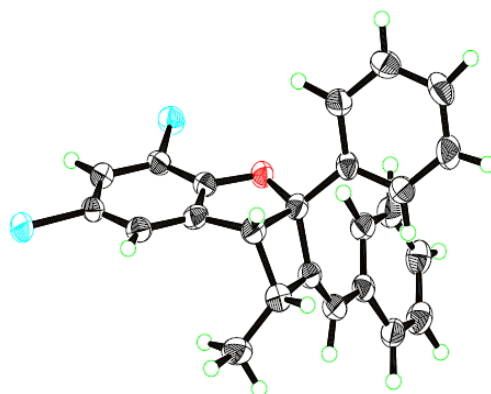
Scheme II-6

続いて(*E*)-プロペニル基をもつフェノール **II-2h** に対し炭酸プロパルギルエステル **II-1a** を用い検討した (Scheme II-7)。その結果連続的環化反応は進行し、1位のメチル基がα側に配向した三環性化合物(**1α**, **Z**)-**II-4ah** が単一の生成物として得られた。生成物の立体化学から本反応では遷移状態 **TS C** の形をとりジラジカル中間体 **II-14** を形成後、プロペニル基の立体反転を伴う形で環化が進行していると予想される。本結果は[2+2]型環化付加が協奏的ではなくジラジカル中間体の生成を経る段階的な経路で進行することを示唆している。なお本化合物の立体化学はX線結晶構造解析を行うことにより決定している (Figure II-3)。





Scheme II-7

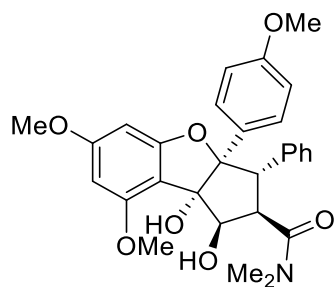


(1α, Z)-II-4ah

Figure II-3

以上をまとめると今回著者はパラジウム触媒を用いたプロパルギルエステルの新たな反応として、求核剤として2-ビニルフェノールを用いると四員環を含む三環性化合物が得られることを見出した。本反応ではフェノキシアレン中間体の生成、続く[2+2]型環化付加が連続的に進行しており、本反応は求核剤がσ-プロパルギル/アレニルパラジウム錯体に対し分子間求核付加した初の例である。本反応は

用いる基質に制限があるものの、高度に官能基化された環化体を一挙に得られることから、Figure II-4 に示すようなベンゾフラン骨格をもつ天然物の全合成などといった有機合成への応用が期待される。



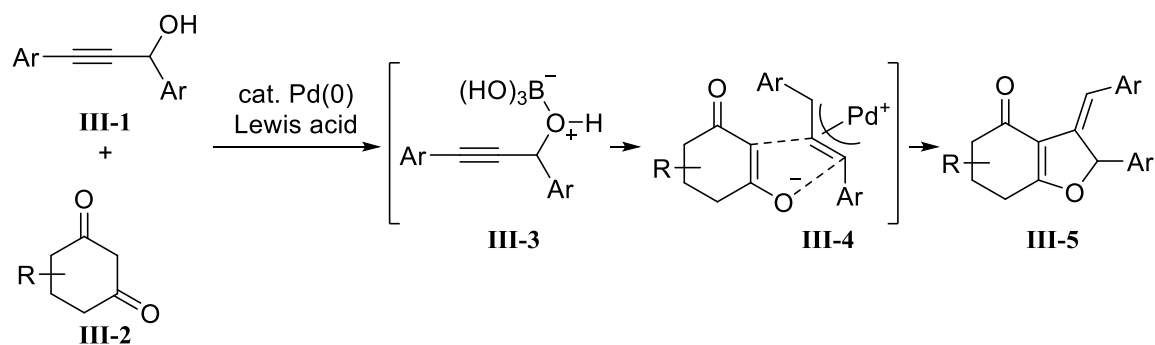
Rocaglamide (II-15)

Figure II-4

### 第三章

## パラジウム触媒を用いたプロパルギルアルコールと 求核剤の連続的環化反応

著者はプロパルギル化合物を用いるパラジウム触媒と求核剤の連続的環化反応の更なる応用と効率化を目指し、新たにプロパルギルアルコールを反応基質に用いた反応を考案した。すなわち総論で述べたようにルイス酸を活性化剤として用いることで水酸基の脱離性が向上し、求核剤との連続的環化反応が進行するものと考えた。反応基質としてプロパルギルアルコール **III-1** とβ-ジカルボニル化合物 **III-2** を選択し、ルイス酸存在下連続的環化反応が進行するか検討を行った (Scheme III-1)。



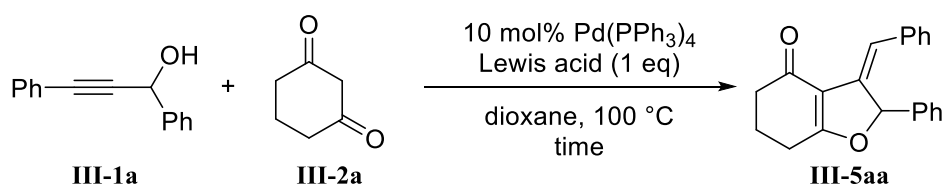
Scheme III-1

はじめにジフェニル置換プロパルギルアルコール **III-1a** と 1,3-cyclohexanedione (**III-2a**) に対し dioxane 溶媒中 10 mol% の Pd(PPh<sub>3</sub>)<sub>4</sub> 存在下様々なルイス酸を作用させた (Table III-1)。その結果 1 当量の B(OH)<sub>3</sub> を作用させると予期した反応が進行し、二環性化合物 **III-5aa** が 45% の収率で単一の生成物として得られた (entry 1)。一方で BF<sub>3</sub>·OEt<sub>2</sub> を作用させた際は基質の分解に留まり (entry 2)、触媒量の

Sc(OTf)<sub>3</sub> 存在下では反応は進行するものの低収率に留まった (entry 3)。そこで環化体 **III-5aa** の更なる収率の向上を目指し活性化剤にホウ素化合物を用いた検討を中心に行った (entries 4–10)。はじめに種々のアルキルボロン酸を検討したがいずれも低収率であった (entries 4–7)。続いて様々なホウ酸エステルを検討したところ (entries 8–10)、B(O<sup>i</sup>Pr)<sub>3</sub> を用いた場合環化体の収率は 52%まで向上することが分かった (entry 9)。

**Table III-1. Lewis acid mediated Pd(0) catalyzed cyclization using propargyl alcohol**

**III-1a and cyclohexanedione III-2a.**

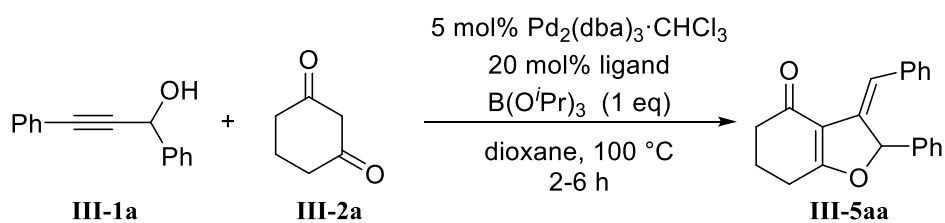


entry	Lewis acid	time [h]	yield [%]
1	B(OH) <sub>3</sub>	3	45
2	BF <sub>3</sub> ·OEt <sub>2</sub>	1	decomp.
3	5mol% Sc(OTf) <sub>3</sub>	5	10
4	Et <sub>2</sub> B(OMe)	5	7
5	MeB(OH) <sub>2</sub>	2.5	12
6	EtB(OH) <sub>2</sub>	3.5	31
7	<sup>n</sup> BuB(OH) <sub>2</sub>	5.5	19
8	B(OMe) <sub>3</sub>	6	12
9	B(O <sup>i</sup> Pr) <sub>3</sub>	3	52
10	B(OTMS) <sub>3</sub>	9	30

次に反応条件の最適化を目指し配位子を変えて検討した (Table III-2)。すなわち 5 mol% の Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> と 1 当量の B(O<sup>i</sup>Pr)<sub>3</sub> 存在下、様々なリン配位子を作用させた。DPPM を配位子として用いると反応は進行しなかったものの (entry 1)、他の二座配位子を作用させると反応が進行した (entries 2–8)。なかでも BINAP を用いた際に **III-5aa** が 76% と最も良い収率で得られた (entry 8)。また entry 8 の条件

において、 $B(OH)_3$  をルイス酸として作用させると若干の収率向上が見られ、80%で環化体 **III-5aa** が得られることが分かった (entry 9)。

**Table III-2. Effect of ligand.**

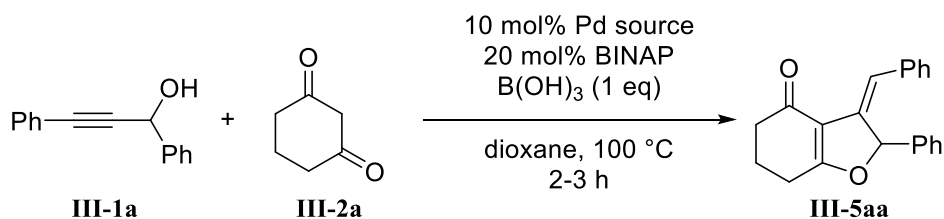


entry	ligand	yield [%]
1	DPPM	no reaction
2	DPPE	34
3	DPPP	67
4	DPPB	71
5	DPPPent	55
6	DPPF	48
7	DPEphos	32
8	BINAP	76
9 <sup>[a]</sup>	BINAP	80

[a]  $B(OH)_3$  was used instead of  $B(O^iPr)_3$ .

更に用いるパラジウム触媒を変えて検討を行った (Table III-3)。20 mol%のBINAP及び1当量の $(OH)_3$ を選択し、様々な購入可能な二価パラジウム錯体を用いたところ (entries 2–5)、 $Pd(OAc)_2$ を用いると87%と最高の収率で目的物が得られた (entry 4)。加えて本反応では $B(OH)_3$ を20 mol%と触媒量に減じても同等の反応性を示し84%で生成物を与えることが明らかとなった (entry 6)。一方、 $B(OH)_3$ を加えない条件では反応性の大幅な低下が見られ環化体の収率は20%まで減少した (entry 7)。

**Table III-3. Effect of palladium source.**



entry	Pd source	yield [%]
1	$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$	80
2	$\text{PdCl}_2$	no reaction
3	$\text{PdCl}_2(\text{MeCN})_2$	no reaction
4	$\text{Pd}(\text{OAc})_2$	87
5	$\text{Pd}(\text{OCOCF}_3)_2$	46
6 <sup>[a]</sup>	$\text{Pd}(\text{OAc})_2$	84
7 <sup>[b]</sup>	$\text{Pd}(\text{OAc})_2$	20

[a] 20 mol%  $\text{B}(\text{OH})_3$  was used.

[b]  $\text{B}(\text{OH})_3$  was not used.

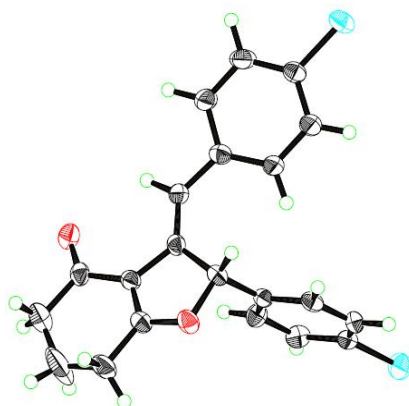
続いて得られた最適条件 (Table III-3、entry 6) にて、様々な置換様式をもつプロパルギルアルコール **III-1b–III-1e** を用い連続的環化反応を行った (Table III-4)。すなわち基質のベンゼン環上にメチル基やハロゲンを導入したプロパルギルアルコール **III-1b–III-1e** に対しシクロヘキサンジオン **III-2a** を作用させる反応を検討した (entries 1–4)。その結果いずれも **III-1a** の場合と同様の反応が進行し、相当するテトラヒドロベンゾフラン **III-5ba–III-5ea** が中程度から良好な収率で生成した。なお得られた環化体のオレフィン部の幾何異性は **III-5ea** に対し X 線結晶構造解析を行うことで Z 型であると決定し (Figure III-1)、他の環化体のオレフィンの相対配置に関しては **III-5ea** との  $^1\text{H-NMR}$  スペクトルの類似性から (Z)-オレフィンをもつと推定した。

**Table III-4. Reactions using various propargyl esters III-1b–III-1e with III-2a.** [a]

10 mol% Pd(OAc)<sub>2</sub>  
20 mol% BINAP  
20 mol% B(OH)<sub>3</sub>  
dioxane, 100 °C

entry	propargylic alcohol III-1	product III-5	yield [%]
1	 <b>III-1b</b>	 <b>III-5ba</b>	81
2	 <b>III-1c</b>	 <b>III-5ca</b>	85
3	 <b>III-1d</b>	 <b>III-5da</b>	62
4	 <b>III-1e</b>	 <b>III-5ea</b>	84

[a] The reactions were carried out using **III-1** and **III-2a** in the presence of 10 mol% Pd(OAc)<sub>2</sub>, 20 mol% BINAP and 20 ml% B(OH)<sub>3</sub> in dioxane at 100 °C for 2-4 h.



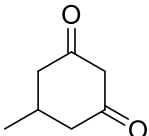
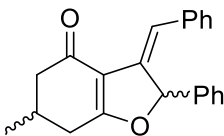
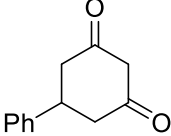
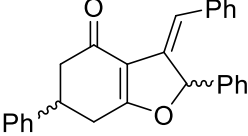
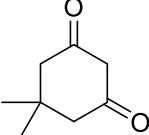
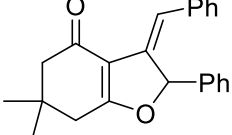
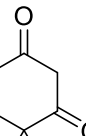
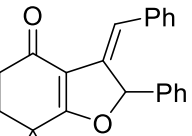
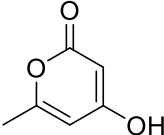
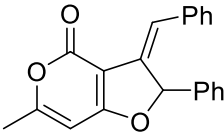
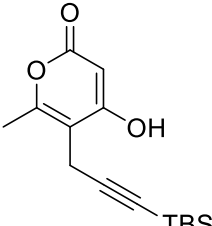
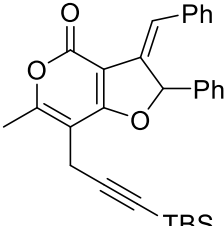
III-5ea

Figure III-1

次にプロパルギルアルコール **III-1a** に対して様々な $\beta$ -ジカルボニル化合物 **III-2b–III-2g** を用いた反応を試みた (Table III-5)。その結果本反応はシクロヘキサンジオン上の 5 位にメチル基、フェニル基を導入した **III-2b**、**III-2c** を用いても円滑に連続的環化反応が進行し、相当する環化体 **III-5ab**、**III-5ac** が 1:1 のジアステレオマー混合物として得られた (entries 1 and 2)。また 5-ジメチル基を導入した **III-2d** 作用させても環化体 **III-5ad** は良好な収率で得られた (entry 3)。更に 4 位にジメチル基をもつ **III-2e** を用いると、7 位にジメチル基を有する生成物 **III-5ae** が位置選択的に得られることが分かった (entry 4)。なお **III-5ae** の化学構造は HMBC の観測により決定した (Figure III-2)<sup>28</sup>。また、ピロン **III-2f**、**III-2g** を求核剤として用いても反応は円滑に進行し環化体 **III-5af**、**III-5ag** を良好な収率で与えることを見出した。

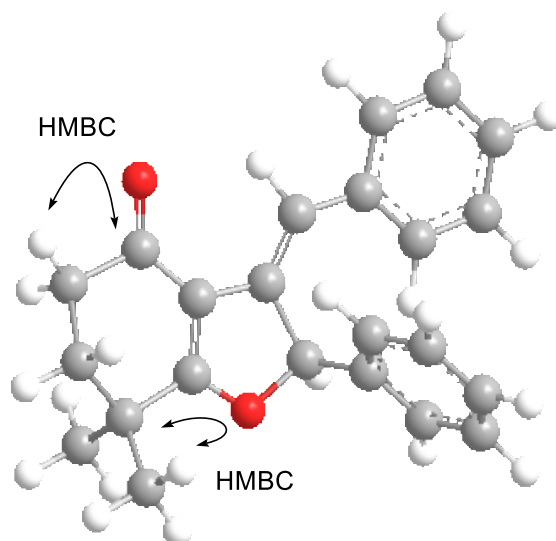


**Table III-5. Reactions using various nucleophiles III-2b–III-2g with III-1a.** <sup>[a]</sup>

entry	substrate <b>III-2</b>	product <b>III-5</b>	yield [%]
1 <sup>[b]</sup>	 <b>III-2b</b>	 <b>III-5ab</b>	82 (dr 1 : 1)
2	 <b>III-2c</b>	 <b>III-5ac</b>	80 (dr 1 : 1)
3	 <b>III-2d</b>	 <b>III-5ad</b>	77
4 <sup>[b]</sup>	 <b>III-2e</b>	 <b>III-5ae</b>	53 (brsm)
5	 <b>III-2f</b>	 <b>III-5af</b>	62
6	 <b>III-2g</b>	 <b>III-5ag</b>	72

[a] The reactions were carried out using **III-1a** and **III-2** in the presence of 10 mol% Pd(OAc)<sub>2</sub>, 20 mol% BINAP and 20 ml% B(OH)<sub>3</sub> in dioxane at 100 °C for 2-4 h.

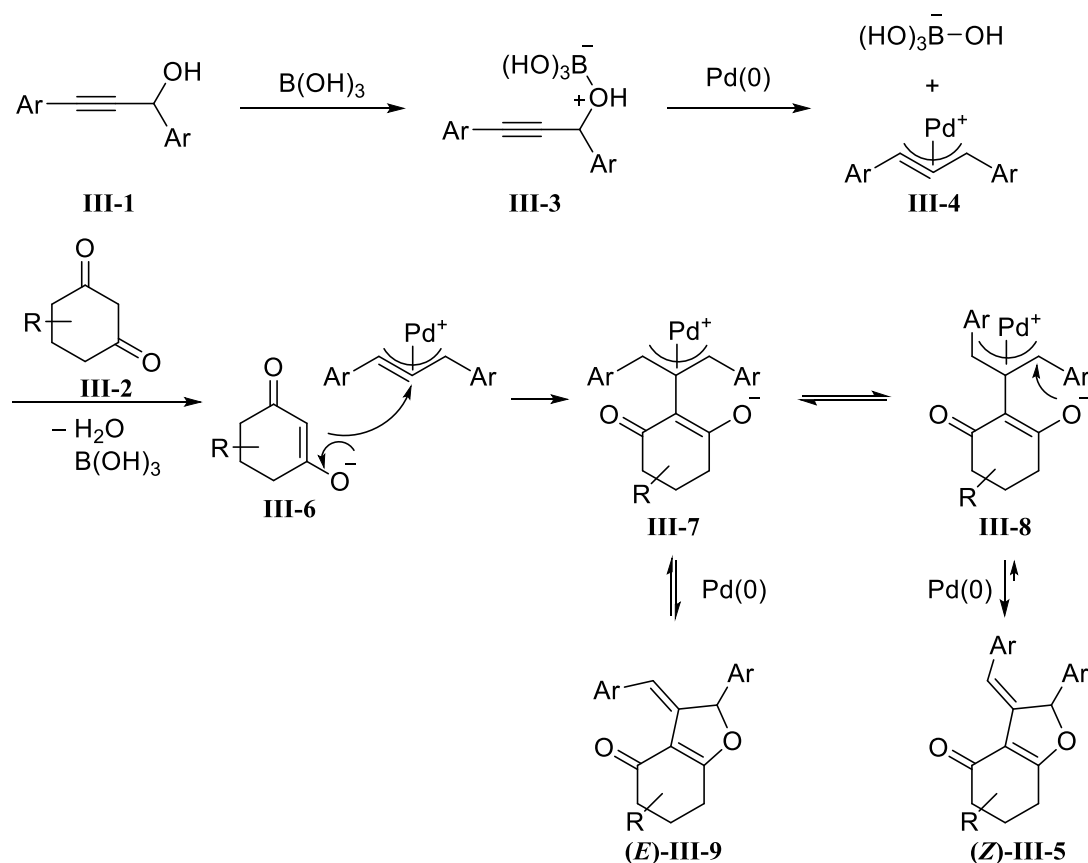
[b] 3 eq β-dicarbonyl compound **III-2** was used.



**Figure III-2.** HMBC correlation of **III-5ae**

本反応の予想される反応機構を次に示す (Scheme III-2)。はじめにホウ酸がプロパルギルアルコール **III-1** の水酸基に配位することで **III-3** を形成し水酸基の脱離能を高める。続いて活性化された **III-3** に対するパラジウムの求核付加が進行し  $\pi$ -プロパルギルパラジウム錯体 **III-4** の生成後、 $\beta$ -ジカルボニル化合物 **III-2** より生じた $\beta$ -ケトエノラート **III-6** が $\pi$ -プロパルギルパラジウム **III-4** へ求核付加し、 $\pi$ -アリルパラジウム錯体 **III-7**、**III-8** に変換される。その後 **III-7**、**III-8** はそれぞれケトエノラート酸素からの分子内求核付加が進行することで環化体(*E*)-**III-5**、(*Z*)-**III-5** が生成したと思われる。本連続的環化反応において(*Z*)-オレフィンをもつ環化体が選択的に得られた理由として、 $\pi$ -アリルパラジウム錯体 **III-7** と **III-8** および生成物(*E*)-**III-5**、(*Z*)-**III-5**の間には $\pi$ - $\sigma$ - $\pi$ の平衡が存在し、熱力学的に安定な生成物(*Z*)-**III-5**に収束したことが考えられる<sup>29)</sup>。以前までに報告された $\pi$ -アリルパラジウム中間体に対する求核付加は高温条件下では熱力学的に安定な生成物が得られることが知られており<sup>30)</sup>、本反応においても同様の傾向を示したと思われる。また Table III-3、entry 7において環化体の収率が大幅に低下したことは、ホウ酸によって水酸基の脱離能が高まり環化反応を円滑に進行させたとする本機

構を支持している。Table III-4、entry 4 において 7 位にジメチル基を持つ環化体 **III-5ae** が位置選択的に得られた理由として、熱力学的に安定な生成物に収束したことが考えられる<sup>31)</sup>。



Scheme III-2

以上のように著者はパラジウム触媒を用いたプロパルギルアルコールと $\beta$ -ジカルボニル化合物の連続的な環化反応により環状化合物が得られることを見出した。既存のパラジウム触媒反応では基質合成においてプロパルギルアルコールを合成後、炭酸エステルなどの脱離基に変換する工程が必要であった。本反応は触媒量のルイス酸によって水酸基を直接活性化し脱離能を高めることで、プロパルギルアルコールを官能基変換することなく基質として用いることができることから、原子効率の高いパラジウム触媒連続的環化反応であるといえる。

## 結論

著者はパラジウム触媒を用いたプロパルギル化合物と求核剤の連続的環化反応に着目し、本反応を様々な基質に対し適用することで適応範囲の拡大と効率化を試みた。

まず、プロパルギル部位とモノケトン部位を連結したプロパルギル $\beta$ -ケトエステルを基質に用いたパラジウム触媒反応の開発を行った。その結果[3+2]型の連続的な環化反応が進行し、置換フランを与えることを見出した。本反応はプロパルギル $\beta$ -ケトエステルを基質として用いることで効果的にモノケトンエノラートが生成し、プロパルギルパラジウムに対し求核剤として機能する初の例である。

次に炭酸プロパルギルエステルに対し 2-ビニルフェノールを求核剤に用いるパラジウム触媒反応を検討した。その結果、フェノキシレン中間体を形成後[2+2]型環化付加が連続し高度に官能基化された三環性ベンゾフランが生成することを明らかにした。本反応は $\sigma$ -プロパルギル/アレニルパラジウム錯体に対しソフトな求核剤が分子間で反応する初の例である。

またパラジウムおよびホウ酸触媒存在下にてプロパルギルアルコールと $\beta$ -ジカルボニル化合物の連続的環化反応が進行することを明らかにした。本反応はプロパルギルアルコールを基質に用いた初の連続的環化反応である。

以上のように著者は様々な求核剤、プロパルギル化合物を用いるパラジウム触媒を用いた連続的環化反応を見出した。

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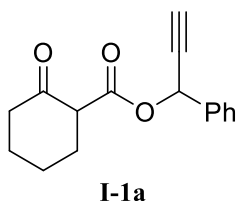
## Experimental Section

**General.** All nonaqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to standard protocol. Ketone **I-4b**<sup>32)</sup>, silyl enol ether **I-15**<sup>33)</sup>, propargyl alcohol **II-5e**<sup>34)</sup>, propargyl carbonates **II-1a**, **II-1b**, **II-1d**<sup>12)</sup>, phenols **II-2a**, **II-2b**, **II-2e**, **II-2h**<sup>25)</sup> and pyrone **III-2g**<sup>35)</sup> were prepared according to the procedures described in the literature. The phrase ‘residue upon workup’ refers to the residue obtained when the organic layer was separated and dried over anhydrous MgSO<sub>4</sub> and the solvent was evaporated under reduced pressure. Column chromatography was performed on silica gel 60N (Kanto, spherical neutral, 63-210 μm), and flash column chromatography was performed on Silica Gel 60N (Kanto, spherical neutral, 40-50 μm) using the indicated solvent. IR spectra were recorded on JAS.CO FT/IR-410 spectrometer. <sup>1</sup>H NMR were measured in CDCl<sub>3</sub> solution and referenced to TMS (0.00 ppm) using JEOL GSX400 (400 MHz) and JNM-AL300 (300 MHz) spectrometers. <sup>13</sup>C NMR were measured in CDCl<sub>3</sub> solution and referenced to CDCl<sub>3</sub> (77.0 ppm) using JEOL GSX400 (100 MHz) and JNM-AL300 (75 MHz) spectrometers. Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broadened. Mass spectra were recorded on Waters MICRO MASS LCT-Premier spectrometers. All melting points were measured with Yanaco MP-500D melting point apparatus and Büchi melting point M-565.

## Experiments in Chapter I

### General procedure for preparations of propargyl $\beta$ -ketoesters <sup>20)</sup>

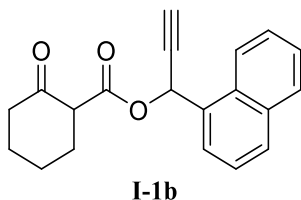
**Synthesis of I-1a (Scheme I-2).** To a stirred mixture of the  $\beta$ -keto ester **I-4a** (708 mg, 4.53 mmol) in toluene (20 mL) was added 1-phenyl-2-propyn-1-ol (**I-5a**) (898 mg, 5.44 mmol) at rt, stirring was continued for 122 h under refluxing condition. After cooling to rt, the reaction mixture was directly concentrated. The residue was chromatographed on silica gel with hexane-AcOEt (96:4 v/v) as eluent to give the propargyl  $\beta$ -ketoester **I-1a** (770 mg, 66%) as a colorless oil.



### 2-Oxocyclohexanecarboxylic acid 1-phenyl-2-propynyl ester (**I-1a**)

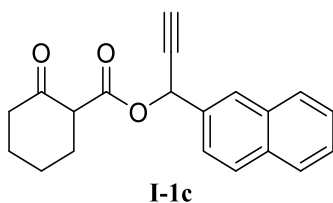
Yield 66%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3289, 2940, 2126, 1748, 1715, 1652, 1618  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 3:1 mixture of tautomers:  $\delta$  1.56–1.75 (3H, m), 1.76–2.10 (1H, m), 2.15–2.40 (3.5H, m), 2.40–2.50 (0.5H, m), 2.66 (0.75H, d,  $J = 2.4$  Hz), 2.67 (0.25H, d,  $J = 2.4$  Hz), 3.36–3.50 (0.25H, m), 6.52 (0.75H, d,  $J = 2.4$  Hz), 6.54 (0.25H, d,  $J = 2.4$  Hz), 7.34–7.45 (3H, m), 7.45–7.55 (2H, m), 11.98 (0.75H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  21.5 ( $\text{CH}_2$ ), 22.00 ( $\text{CH}_2$ ), 22.05 ( $\text{CH}_2$ ), 22.9 ( $\text{CH}_2$ ), 23.1 ( $\text{CH}_2$ ), 26.80 ( $\text{CH}_2$ ), 26.84 ( $\text{CH}_2$ ), 29.0 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_2$ ), 41.2 ( $\text{CH}_2$ ), 41.3 ( $\text{CH}_2$ ), 56.7 (CH), 56.8 (CH), 64.6 (CH), 65.55 (CH), 65.61 (CH), 75.4 (Cq), 75.70 (Cq), 75.72 (Cq), 79.56 (CH), 79.65 (CH), 80.2 (CH), 97.1 (Cq), 127.2 (CH), 127.37 (CH), 127.43 (CH), 128.35 (CH), 128.42 (Cq), 128.7 (CH), 128.76 (CH), 128.82 (CH), 135.7 (Cq), 136.0 (Cq), 136.4 (Cq), 168.5 (Cq),

168.6 (Cq), 171.0 (Cq), 173.2 (Cq), 205.1 (Cq), 205.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{16}H_{16}NaO_3$   $[M+Na]^+$  279.0997, found 279.0994.



### 2-Oxocyclohexanecarboxylic acid 1-naphthalen-1-yl-2-propynyl ester (I-1b)

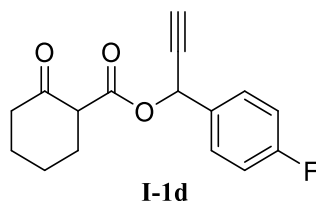
Yield 77%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3290, 2939, 1654, 1606  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ ) for 2:1 mixture of tautomers:  $\delta$  1.57–1.75 (3H, m), 1.75–2.00 (1H, m), 2.05–2.32 (4H, m), 2.70 (0.67H, d,  $J = 2.0$  Hz), 2.73 (0.33H, d,  $J = 2.0$  Hz), 3.39–3.50 (0.33H, m), 7.10 (0.67H, d,  $J = 2.0$  Hz), 7.11 (0.33H, d,  $J = 2.0$  Hz), 7.46–7.52 (3H, m), 7.80–8.00 (3H, m), 8.12–8.24 (1H, m), 12.00 (0.67H, s);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ ) for mixture of tautomers and diastereomers:  $\delta$  21.9 ( $CH_2$ ), 22.35 ( $CH_2$ ), 22.42 ( $CH_2$ ), 23.3 ( $CH_2$ ), 23.4 ( $CH_2$ ), 27.1 ( $CH_2$ ), 29.4 ( $CH_2$ ), 30.10 ( $CH_2$ ), 30.12 ( $CH_2$ ), 41.57 ( $CH_2$ ), 41.63 ( $CH_2$ ), 57.15 (CH), 57.21 (CH), 63.8 (CH), 64.49 (CH), 64.58 (CH), 76.2 (Cq), 76.7 (Cq), 77.5 (Cq), 79.9 (CH), 80.0 (CH), 80.6 (CH), 97.6 (Cq), 123.8 (CH), 124.0 (CH), 125.1 (CH), 125.27 (CH), 125.33 (CH), 126.0 (CH), 126.19 (CH), 126.24 (CH), 126.6 (CH), 126.81 (CH), 126.86 (CH), 126.9 (CH), 127.1 (CH), 128.9 (CH), 129.0 (CH), 130.2 (CH), 130.3 (Cq), 130.6 (Cq), 131.3 (Cq), 131.6 (Cq), 132.1 (Cq), 134.07 (Cq), 134.14 (Cq), 134.2 (Cq), 169.0 (Cq), 169.1 (Cq), 171.4 (Cq), 173.7 (Cq), 205.4 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{20}H_{19}O_3$   $[M+H]^+$  307.1334, found 307.1339.





### 2-Oxocyclohexanecarboxylic acid 1-naphthalen-2-yl-2-propynyl ester (I-1c)

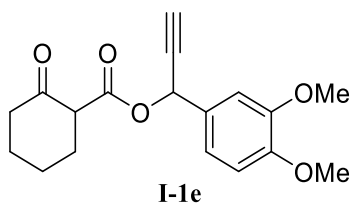
Yield 71%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3290, 2938, 1653, 1606  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 3:1 mixture of tautomers:  $\delta$  1.54–1.72 (3.5H, m), 1.82–2.00 (0.5H, m), 2.13–2.38 (4H, m), 2.71 (0.75H, d,  $J = 2.4$  Hz), 2.74 (0.25H, d,  $J = 2.4$  Hz), 3.47 (0.25H, t,  $J = 8.2$  Hz), 6.69 (0.75H, d,  $J = 2.4$  Hz), 6.70 (0.25H, d,  $J = 2.4$  Hz), 7.45–7.54 (2H, m), 7.60–7.69 (1H, m), 7.78–7.90 (3H, m), 8.00–8.06 (1H, m), 12.00 (0.75H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  21.6 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 26.9 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 29.9 ( $\text{CH}_2$ ), 39.9 ( $\text{CH}_2$ ), 41.5 ( $\text{CH}_2$ ), 56.9 (CH), 57.0 (CH), 64.9 (CH), 65.9 (CH), 66.0 (CH), 75.7 (Cq), 76.1 (Cq), 76.7 (Cq), 79.7 (CH), 79.8 (CH), 80.4 (CH), 97.3 (Cq), 123.3 (CH), 124.7 (CH), 124.8 (CH), 124.9 (CH), 126.3 (CH), 126.4 (CH), 126.5 (CH), 126.60 (CH), 126.65 (CH), 126.8 (CH), 126.95 (CH), 126.99 (CH), 127.1 (CH), 127.6 (CH), 127.9 (CH), 128.17 (CH), 128.21 (CH), 128.25 (Cq), 128.4 (CH), 128.5 (CH), 128.6 (CH), 132.87 (Cq), 132.90 (Cq), 133.1 (Cq), 133.3 (Cq), 133.4 (Cq), 133.8 (Cq), 133.9 (Cq), 135.4 (Cq), 140.9 (Cq), 168.9 (Cq), 171.2 (Cq), 173.4 (Cq), 205.36 (Cq), 205.42 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{19}\text{O}_3$   $[\text{M}+\text{H}]^+$  307.1334, found 307.1339.



### 2-Oxocyclohexanecarboxylic acid 1-(4-fluorophenyl)-2-propynyl ester (I-1d)

Yield 56%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3296, 2941, 1748, 1715, 1654, 1607, 1214  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 2:1 mixture of tautomers:  $\delta$  1.55–1.71 (3H, m), 1.71–2.04 (1H, m), 2.05–2.55 (4H, m), 2.66 (0.67H, d,  $J = 2.4$  Hz), 2.68 (0.33H, d,  $J = 2.4$  Hz), 3.42 (0.33H, t,  $J = 6.0$  Hz), 6.51 (0.67H, d,  $J = 2.0$

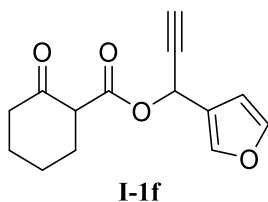
Hz), 6.52 (0.33H, d,  $J = 2.0$  Hz), 7.06 (0.67H, t,  $J = 8.4$  Hz), 7.07 (1.33H, t,  $J = 8.4$  Hz), 7.53 (1.33H, dd,  $J = 5.6$  and  $8.4$  Hz), 7.55 (0.67H, dd,  $J = 5.6$  and  $8.4$  Hz), 11.94 (0.67H, s);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  21.6 ( $\text{CH}_2$ ), 22.07 ( $\text{CH}_2$ ), 22.11 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 23.1 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 26.88 ( $\text{CH}_2$ ), 26.94 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 41.4 ( $\text{CH}_2$ ), 41.5 ( $\text{CH}_2$ ), 56.8 (CH), 57.0 (CH), 64.0 (CH), 64.95 (CH), 65.02 (CH), 75.6 (Cq), 75.95 (Cq), 75.97 (Cq), 79.4 (CH), 79.5 (CH), 80.1 (CH), 97.1 (Cq), 115.4 (CH, d,  $J = 21.5$  Hz), 115.5 (CH, d,  $J = 21.5$  Hz), 129.4 (CH, d,  $J = 8.2$  Hz), 129.5 (CH, d,  $J = 8.2$  Hz), 129.6 (CH, d,  $J = 8.2$  Hz), 131.8 (Cq, d,  $J = 3.5$  Hz), 132.0 (Cq, d,  $J = 3.5$  Hz), 132.4 (Cq, d,  $J = 3.5$  Hz), 162.81 (Cq, d,  $J = 246$  Hz), 162.86 (Cq, d,  $J = 246$  Hz), 168.6 (Cq), 168.7 (Cq), 171.0 (Cq), 173.5 (Cq), 205.3 (Cq), 205.5 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{15}\text{FNaO}_3$   $[\text{M}+\text{Na}]^+$  297.0903 found 297.0906.



### 2-Oxocyclohexanecarboxylic acid 1-(3,4-dimethoxyphenyl)-2-propynyl ester (I-1e)

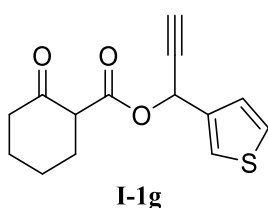
Yield 36%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3282, 2939, 1746, 1714, 1653, 1607  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ) for 2:1 mixture of tautomers:  $\delta$  1.51–2.55 (8H, m), 2.67 (0.67H, d,  $J = 2.0$  Hz), 2.69 (0.33H, d,  $J = 2.0$  Hz), 3.43 (0.33H, t,  $J = 6.4$  Hz), 3.88 (3H, s), 3.91 (3H, s), 6.48 (0.67H, d,  $J = 2.0$  Hz), 6.52 (0.33H, d,  $J = 2.0$  Hz), 6.80–6.90 (1H, m), 7.05–7.20 (2H, m), 12.0 (0.67H, s);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  21.7 ( $\text{CH}_2$ ), 22.2 ( $\text{CH}_2$ ), 22.3 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 23.3 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 29.9 ( $\text{CH}_2$ ), 41.4 ( $\text{CH}_2$ ), 41.6 ( $\text{CH}_2$ ), 55.89 ( $\text{CH}_3$ ), 55.91 ( $\text{CH}_3$ ), 57.0 (CH), 57.1 (CH), 64.8 (CH), 65.7 (CH), 65.8 (CH), 75.2 (Cq), 75.58 (Cq), 75.62 (Cq), 79.8 (CH), 79.9 (CH), 80.6 (CH), 97.4 (Cq),

110.8 (CH), 110.9 (CH), 111.0 (CH), 120.2 (CH), 120.3 (CH), 120.5 (CH), 128.4 (Cq), 128.6 (Cq), 129.1 (Cq), 149.0 (Cq), 149.6 (Cq), 168.8 (Cq), 168.9 (Cq), 171.2 (Cq), 173.3 (Cq), 205.4 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{18}H_{20}NaO_5$   $[M+Na]^+$  339.1208 found 339.1202.



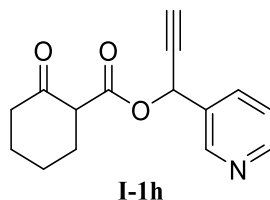
### 2-Oxocyclohexanecarboxylic acid 1-furan-3-yl-2-propynyl ester (I-1f)

Yield 37%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3293, 2941, 2129, 1747, 1652, 1608  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ ) for 3:1 mixture of tautomers:  $\delta$  1.50–1.73 (3.5H, m), 1.77–2.10 (0.5H, m), 2.11–2.39 (3.5H, m), 2.40–2.55 (0.5H, m), 2.60 (0.75H, d,  $J = 2.0$  Hz), 2.62 (0.25H, d,  $J = 2.0$  Hz), 3.41 (0.25H, m), 6.46–6.55 (2H, m), 7.40 (1H, m), 7.59 (1H, m), 11.97 (0.75H, s);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ ) for mixture of tautomers and diastereomers:  $\delta$  21.7 ( $CH_2$ ), 22.2 ( $CH_2$ ), 23.2 ( $CH_2$ ), 23.3 ( $CH_2$ ), 26.97 ( $CH_2$ ), 27.04 ( $CH_2$ ), 29.2 ( $CH_2$ ), 29.8 ( $CH_2$ ), 29.9 ( $CH_2$ ), 41.4 ( $CH_2$ ), 41.6 ( $CH_2$ ), 56.9 (CH), 57.1 (CH), 57.7 (CH), 58.5 (CH), 58.6 (CH), 74.0 (Cq), 74.2 (Cq), 74.3 (Cq), 79.1 (CH), 79.2 (CH), 79.7 (CH), 97.3 (Cq), 109.47 (CH), 109.53 (CH), 122.0 (Cq), 122.3 (Cq), 141.6 (CH), 141.7 (CH), 141.8 (CH), 143.5 (CH), 143.6 (CH), 168.7 (Cq), 168.8 (Cq), 171.2 (Cq), 173.4 (Cq), 205.3 (Cq), 205.4 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{14}H_{14}NaO_4$   $[M+Na]^+$  269.0790, found 269.0798.



## 2-Oxocyclohexanecarboxylic acid 1-thiophen-3-yl-2-propynyl ester (I-1g)

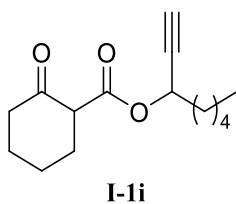
Yield 73%; colorless plates (AcOEt–hexane, mp.85.5–88.5 °C); IR (neat) 3291, 2938, 1653, 1607  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.53–1.71 (4H, m), 2.15–2.35 (4H, m), 2.64 (1H, d,  $J = 2.4$  Hz), 6.59 (1H, d,  $J = 2.4$  Hz), 7.19 (1H, dd,  $J = 5.2$  and 1.2 Hz), 7.32 (1H, dd,  $J = 5.2$  and 3.2 Hz), 7.48 (1H, dd,  $J = 3.2$  and 1.2 Hz), 11.97 (1H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.8 ( $\text{CH}_2$ ), 22.27 ( $\text{CH}_2$ ), 22.30 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 60.6 (CH), 74.6 (Cq), 80.2 (CH), 97.3 (Cq), 124.5 (CH), 126.5 (CH), 126.6 (CH), 137.4 (Cq), 171.2 (Cq), 173.5 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{14}\text{NaO}_3\text{S}$   $[\text{M}+\text{Na}]^+$  285.0561, found 285.0557.



## 2-Oxocyclohexanecarboxylic acid 1-pyridin-3-yl-2-propynyl ester (I-1h)

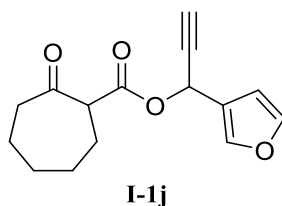
Yield 99%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3289, 2940, 1749, 1714, 1654, 1607  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 2:1 mixture of tautomers:  $\delta$  1.56–2.55 (8H, m), 2.75 (0.67H, d,  $J = 2.0$  Hz), 2.77 (0.33H, d,  $J = 2.0$  Hz), 3.46 (0.33H, m), 6.57 (0.67H, d,  $J = 2.0$  Hz), 6.58 (0.33H, d,  $J = 2.0$  Hz), 7.30–7.50 (1H, m), 7.87–8.00 (1H, m), 8.45–9.15 (2H, br), 11.91 (0.67H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  21.6 ( $\text{CH}_2$ ), 22.07 ( $\text{CH}_2$ ), 22.10 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 23.3 ( $\text{CH}_2$ ), 26.90 ( $\text{CH}_2$ ), 26.95 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 29.7 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 41.4 ( $\text{CH}_2$ ), 41.6 ( $\text{CH}_2$ ), 56.8 (CH), 57.0 (CH), 62.6 (CH), 63.56 ( $\text{CH}_2$ ), 63.63 ( $\text{CH}_2$ ), 76.2 (Cq), 76.6 (Cq), 78.6 (CH), 78.7 (CH), 79.3 (CH), 97.0 (Cq), 123.3 (CH), 123.4 (CH), 131.7 (Cq), 131.9 (Cq), 132.3 (Cq), 135.0 (CH), 135.1 (CH), 135.2 (CH), 148.9 (CH), 149.0 (CH), 150.09 (CH), 150.15 (CH), 150.2 (CH), 168.5 (Cq), 168.7 (Cq), 170.8 (Cq), 173.9 (Cq), 205.1 (Cq), 205.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{15}\text{NNaO}_3$   $[\text{M}+\text{Na}]^+$  280.0950, found

280.0944.



### 2-Oxocyclohexanecarboxylic acid 1-ethynylhexyl ester (I-1i)

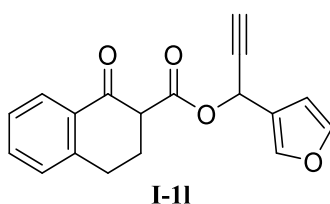
Yield 83%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3295, 2935, 1748, 1717, 1655, 1612  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 2:1 mixture of tautomers:  $\delta$  0.90 (2H, t,  $J = 7.2$  Hz), 0.91 (1H, t,  $J = 7.2$  Hz), 1.26–1.34 (4H, m), 1.44–1.50 (2H, m), 1.57–1.72 (4H, m), 1.76–1.86 (2H, m), 2.10–2.30 (4H, m), 2.45 (0.67H, d,  $J = 2.0$  Hz), 2.46 (0.33H, d,  $J = 2.0$  Hz), 3.41 (0.33H, t,  $J = 7.2$  Hz), 5.40 (0.67H, dt,  $J = 2.0$  and 6.6 Hz), 5.44 (0.33H, dt,  $J = 2.0$  and 6.6 Hz), 12.05 (0.67H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  13.8 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_2$ ), 22.20 ( $\text{CH}_2$ ), 22.23 ( $\text{CH}_2$ ), 22.3 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 24.3 ( $\text{CH}_2$ ), 24.36 ( $\text{CH}_2$ ), 24.44 ( $\text{CH}_2$ ), 26.96 ( $\text{CH}_2$ ), 27.04 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 29.9 ( $\text{CH}_2$ ), 31.10 ( $\text{CH}_2$ ), 31.15 ( $\text{CH}_2$ ), 34.3 ( $\text{CH}_2$ ), 34.43 ( $\text{CH}_2$ ), 34.47 ( $\text{CH}_2$ ), 56.9 ( $\text{CH}_2$ ), 57.0 ( $\text{CH}_2$ ), 63.4 (CH), 64.3 (CH), 64.4 (CH), 73.3 (Cq), 73.5 (Cq), 73.6 (Cq), 80.8 (CH), 81.0 (CH), 81.4 (CH), 97.3 (Cq), 168.8 (Cq), 168.9 (Cq), 171.4 (Cq), 172.9 (Cq), 205.5 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{22}\text{NaO}_3$   $[\text{M}+\text{Na}]^+$  273.1467, found 273.1463.



### 2-Oxocycloheptanecarboxylic acid 1-furan-3-yl-2-propynyl ester (I-1j)

Yield 30%; yellow oil; 1:1 mixture of diastereomers; IR (neat) 3288, 2933, 2129, 1747,

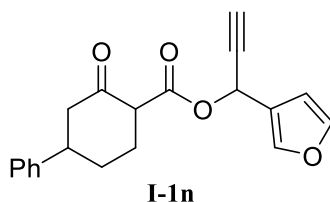
1704, 1637, 1600  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 1:1 mixture of diastereomers:  $\delta$  1.36–1.60 (4H, m), 1.62–2.16 (4H, m), 2.55–2.63 (3H, m), 3.59 (0.5H, dd,  $J = 10.2$  and 3.2 Hz), 3.63 (0.5H, dd,  $J = 9.8$  and 3.6 Hz), 6.43–6.52 (2H, m.), 7.35–7.61 (2H, m);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of diastereomers:  $\delta$  23.9 ( $\text{CH}_2$ ), 24.0 ( $\text{CH}_2$ ), 24.1 ( $\text{CH}_2$ ), 27.3 ( $\text{CH}_2$ ), 27.4 ( $\text{CH}_2$ ), 27.9 ( $\text{CH}_2$ ), 28.0 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 43.0 ( $\text{CH}_2$ ), 58.3 (CH), 58.5 (CH), 74.2 (Cq), 74.3 (Cq), 78.9 (CH), 79.2 (CH), 109.41 (CH), 109.42 (CH), 121.9 (Cq), 122.0 (Cq), 141.6 (CH), 141.7 (CH), 143.5 (CH), 169.2 (Cq), 169.4 (Cq), 208.0 (Cq), 208.1 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{16}\text{NaO}_4$   $[\text{M}+\text{Na}]^+$  283.0946, found 283.0956.



**1-Oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid 1-furan-3-yl-2-propynyl ester (I-11)**

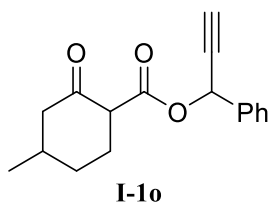
Yield 44%; yellow oil; mixture of tautomers and diastereomers; IR (neat) 3291, 2942, 2128, 1746, 1683, 1651  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 1:1 mixture of tautomers:  $\delta$  2.30–2.67 (3H, m), 2.77–3.07 (2H, m), 3.61–3.70 (0.5H, m) 6.51–6.56 (2H, m), 7.15–8.06 (6H, m), 12.22 (0.5H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  20.4 ( $\text{CH}_2$ ), 26.2 ( $\text{CH}_2$ ), 26.3 ( $\text{CH}_2$ ), 27.57 ( $\text{CH}_2$ ), 27.60 ( $\text{CH}_2$ ), 54.3 (CH), 54.5 (CH), 58.0 (CH), 58.7 (CH), 58.9 (CH), 74.2 (Cq), 74.36 (Cq), 74.41 (Cq), 79.1 (Cq), 79.2 (CH), 79.7 (Cq), 96.4 (Cq), 109.47 (CH), 109.51 (CH), 109.54 (CH), 122.0 (Cq), 122.3 (Cq), 124.4 (CH), 126.5 (CH), 126.9 (CH), 127.4 (CH), 127.7 (CH), 128.7 (CH), 128.8 (CH), 129.7 (CH), 130.8 (Cq), 131.6 (Cq), 133.86 (CH), 133.88 (CH), 139.5 (Cqx3), 141.7 (CH), 141.8 (CH), 143.43 (CH), 143.47 (CH), 143.57 (CH), 143.61 (CH), 166.1 (Cq), 169.0

(Cq), 169.1 (Cq), 171.3 (Cq), 192.4 (Cq), 192.5 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{18}H_{14}NaO_4$   $[M+Na]^+$  317.0790, found 317.0800.



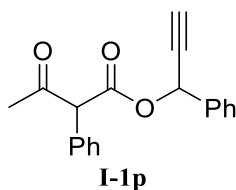
### **2-Oxo-4-phenylcyclohexanecarboxylic acid 1-furan-3-yl-2-propynyl ester (I-1n)**

Yield 44%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3291, 2936, 1747, 1715, 1654, 1613  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ ) for 3:2 mixture of tautomers:  $\delta$  1.60–3.10 (8H, m), 3.49–3.55 (0.4H, m), 6.49–6.60 (2H, m), 7.10–7.41 (6H, m), 7.60–7.65 (1H, m), 11.99 (0.6H, s);  $^{13}C$ -NMR (75 MHz,  $CDCl_3$ ) for mixture of tautomers and diastereomers:  $\delta$  22.3 ( $CH_2$ ), 28.0 ( $CH_2$ ), 28.1 ( $CH_2$ ), 28.46 ( $CH_2$ ), 28.54 ( $CH_2$ ), 29.3 ( $CH_2$ ), 29.4 ( $CH_2$ ), 29.6 ( $CH_2$ ), 31.51 ( $CH_2$ ), 36.55 ( $CH_2$ ), 36.5 ( $CH_2$ ), 39.2 (CH), 44.2 (CH), 44.4 (CH), 44.8 (CH), 44.9 (CH), 47.1( $CH_2$ ), 47.3 ( $CH_2$ ), 48.7 ( $CH_2$ ), 48.8 ( $CH_2$ ), 55.19 (CH), 55.23 (CH), 56.5 (CH), 56.8 (CH), 57.8 (CH), 58.5 (CH), 58.6 (CH), 58.89 (CH), 58.93 (CH), 74.2 (Cq), 74.3 (Cq), 74.4 (Cq), 74.7 (Cq), 75.5 (Cq), 78.76 (CH), 78.81 (CH), 79.1 (CH), 79.3 (CH), 79.6 (CH), 96.9 (Cq), 109.3 (CH), 109.4 (CH), 109.5 (CH), 109.56 (CH), 109.58 (CH), 122.0 (Cq), 122.1 (Cq), 122.18 (Cq), 122.20 (Cq), 126.3 (CH), 126.4 (CH), 126.5 (CH), 126.6 (CH), 126.73 (CH), 126.74 (CH), 126.9 (CH), 128.5 (CH), 128.60 (CH), 128.62 (CH), 128.7 (CH), 141.64 (CH), 141.65 (CH), 141.8 (CH), 141.9 (CH), 143.30 (CH), 143.32 (CH), 143.55 (CH), 143.57 (CH), 143.62 (Cq), 143.68 (Cq), 143.72 (Cq), 143.8 (Cq), 144.7 (Cq), 168.57 (Cq), 168.62 (Cq), 168.65 (Cq), 168.7 (Cq), 171.0 (Cq), 172.6 (Cq), 204.1 (Cq), 204.3 (Cq), 204.9 (Cq), 205.0 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{20}H_{19}O_4$   $[M+H]^+$  322.1283, found 322.1281.



#### 4-Methyl-2-oxocyclohexanecarboxylic acid 1-phenyl-2-propynyl ester (I-10)

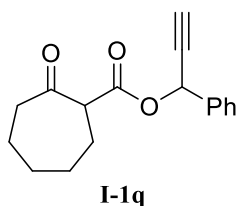
Yield 57%; colorless oil; mixture of tautomers and diastereomers; IR (neat) 3292, 2926, 1655, 1610  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 3:1 mixture of tautomers:  $\delta$  0.98 (2.25H, d,  $J = 2.8$  Hz), 1.01 (0.75H, d,  $J = 2.8$  Hz), 1.10–1.28 (1H, m), 1.70–2.50 (6H, m), 2.65 (0.75H, d,  $J = 2.0$  Hz), 2.68 (0.25H, d,  $J = 2.0$  Hz), 3.37 (0.25H, t,  $J = 8.4$  Hz), 6.53 (0.75H, d,  $J = 2.0$  Hz), 6.55 (0.25H, d,  $J = 2.0$  Hz), 7.30–7.43 (3H, m), 7.51–7.57 (2H, m), 11.92 (0.75H, s);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  14.0 ( $\text{CH}_3$ ), 17.5 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ), 21.1 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_2$ ), 21.8 ( $\text{CH}_2$ ), 21.87 ( $\text{CH}_2$ ), 21.94 ( $\text{CH}_2$ ), 27.6 ( $\text{CH}$ ), 27.9 ( $\text{CH}$ ), 28.3 ( $\text{CH}$ ), 28.4 ( $\text{CH}$ ), 29.6 ( $\text{CH}$ ), 30.2 ( $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 32.1 ( $\text{CH}_2$ ), 30.4 ( $\text{CH}_2$ ), 34.5 ( $\text{CH}_2$ ), 37.1 ( $\text{CH}_2$ ), 48.3 ( $\text{CH}_2$ ), 48.4 ( $\text{CH}_2$ ), 49.6 ( $\text{CH}_2$ ), 49.7 ( $\text{CH}_2$ ), 55.33 ( $\text{CH}$ ), 55.35 ( $\text{CH}$ ), 56.3 ( $\text{CH}$ ), 56.6 ( $\text{CH}$ ), 60.2 ( $\text{CH}$ ), 64.7 ( $\text{CH}$ ), 65.52 ( $\text{CH}$ ), 65.58 ( $\text{CH}$ ), 65.9 ( $\text{CH}$ ), 75.4 ( $\text{Cq}$ ), 75.6 ( $\text{Cq}$ ), 75.7 ( $\text{Cq}$ ), 75.8 ( $\text{Cq}$ ), 75.9 ( $\text{Cq}$ ), 79.5 ( $\text{CH}$ ), 79.7 ( $\text{CH}$ ), 79.8 ( $\text{CH}$ ), 80.28 ( $\text{CH}$ ), 80.31 ( $\text{CH}$ ), 96.5 ( $\text{Cq}$ ), 127.27 ( $\text{CH}$ ), 127.29 ( $\text{CH}$ ), 127.41 ( $\text{CH}$ ), 127.43 ( $\text{CH}$ ), 127.46 ( $\text{CH}$ ), 127.55 ( $\text{CH}$ ), 128.4 ( $\text{CH}$ ), 128.45 ( $\text{CH}$ ), 128.49 ( $\text{CH}$ ), 128.50 ( $\text{CH}$ ), 128.52 ( $\text{CH}$ ), 128.76 ( $\text{CH}$ ), 128.77 ( $\text{CH}$ ), 128.85 ( $\text{CH}$ ), 129.0 ( $\text{CH}$ ), 135.7 ( $\text{Cq}$ ), 135.8 ( $\text{Cq}$ ), 136.0 ( $\text{Cq}$ ), 136.1 ( $\text{Cq}$ ), 136.5 ( $\text{Cq}$ ), 168.5 ( $\text{Cq}$ ), 168.6 ( $\text{Cq}$ ), 168.7 ( $\text{Cq}$ ), 168.8 ( $\text{Cq}$ ), 171.0 ( $\text{Cq}$ ), 172.8 ( $\text{Cq}$ ), 204.7 ( $\text{Cq}$ ), 204.8 ( $\text{Cq}$ ), 205.3 ( $\text{Cq}$ ), 205.4 ( $\text{Cq}$ ); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{18}\text{NaO}_3$   $[\text{M}+\text{Na}]^+$  293.1154, found 293.1145.





### 3-Oxo-2-phenylbutyric acid 1-phenyl-2-propynyl ester (I-1p)

Yield 68%; colorless solid; 10:1 mixture of diastereomers; IR (neat) 3283, 2126, 1753, 1718  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 10:1 mixture of diastereomers:  $\delta$  2.12 (2.7H, s), 2.16 (0.3H, s), 2.66 (0.9H, d,  $J = 2.0$  Hz), 2.69 (0.1H, d,  $J = 2.0$  Hz), 4.72 (0.1H, s), 4.74 (0.9H, s), 6.51 (0.1H, d,  $J = 2.0$  Hz), 6.53 (0.9H, d,  $J = 2.0$  Hz), 7.32–7.41 (8H, m), 7.50–7.55 (2H, m);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of diastereomers:  $\delta$  28.5 ( $\text{CH}_3$ ), 29.1 ( $\text{CH}_3$ ), 50.9 (CH), 52.5 (CH), 65.4 (CH), 66.4 (CH), 75.3 (CH), 76.1 (CH), 79.5 (Cq), 126.9 (CH), 127.0 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 129.1 (CH), 129.2 (CH), 129.3 (CH), 130.1 (Cq), 131.2 (Cq), 132.1 (Cq), 135.7 (Cq), 167.3 (Cq), 168.9 (Cq), 200.8 (Cq), 206.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{16}\text{NaO}_3$   $[\text{M}+\text{Na}]^+$  315.0997, found 315.1011.



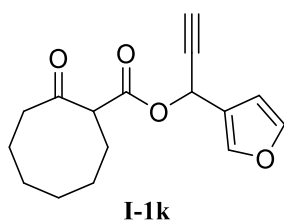
### 2-Oxocycloheptanecarboxylic acid 1-phenyl-2-propynyl ester (I-1q)

Yield 80%; colorless solid; 1:1 mixture of diastereomers; IR (neat) 3283, 2932, 1746, 1703  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 1:1 mixture of diastereomers:  $\delta$  1.41–2.15 (8H, m), 2.54–2.64 (2H, m), 2.67 (0.5H, d,  $J = 2.4$  Hz), 2.68 (0.5H, d,  $J = 2.4$  Hz), 3.58 (0.5H, dd,  $J = 4.0$  and 10.2 Hz), 3.63 (0.5H, dd,  $J = 4.0$  and 10.2 Hz), 6.49 (0.5H, d,  $J = 2.4$  Hz), 6.50 (0.5H, d,  $J = 2.4$  Hz), 7.35–7.55 (5H, m);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of diastereomers:  $\delta$  24.07 ( $\text{CH}_2$ ), 24.15 ( $\text{CH}_2$ ), 27.4 ( $\text{CH}_2$ ), 27.5 ( $\text{CH}_2$ ), 27.9 ( $\text{CH}_2$ ), 28.0 ( $\text{CH}_2$ ), 29.45 ( $\text{CH}_2$ ), 29.50 ( $\text{CH}_2$ ), 43.1 ( $\text{CH}_2$ ), 58.6 (CH), 58.8 (CH), 65.8 (CH), 65.9 (CH), 75.77 (Cq), 75.79 (Cq), 79.6 (CH), 79.8 (CH), 127.57 (CH), 127.63 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 129.1 (CH), 135.9 (Cq), 136.1 (Cq), 169.3 (Cq), 169.5 (Cq), 208.2

(Cq); HRMS (ESI)  $m/z$  calcd for  $C_{17}H_{19}O_3$   $[M+H]^+$  271.1334, found 271.1342.

### General procedure for preparations of propargyl $\beta$ -ketoesters <sup>21)</sup>

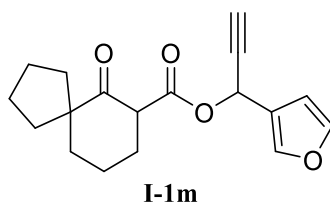
**Synthesis of I-1k (Scheme I-3).** To a stirring solution of diisopropylamine (0.33 mL, 2.38 mmol) in toluene (10 mL) were added *n*-BuLi (1.62 M in hexane, 1.47 mL) at 0 °C, and stirring continued for 15 min at the same temperature. After the reaction mixture was cooled to -78 °C, cyclooctanone (**I-6a**) (217 mg, 1.72 mmol) in toluene (20 mL) was added dropwise, and stirring was continued for 15 min at the same temperature. The resultant solution was allowed to warm up to rt and then added an excess amount of dry ice. After further stirring was continued until all dry ice disappeared, the reaction was then worked up by adding water and extracting with ether. The basic aqueous layer was acidified with dilute HCl and reextracted with ether. The organic layer was dried over  $MgSO_4$ , filtered and concentrated to give carboxylic acid **I-7a** (133 mg) as a colorless oil, which was used to the next reaction without further purification. To a stirred solution of crude in  $CH_2Cl_2$  (7.8 mL) was added propargyl alcohol **I-5f** (191 mg, 1.6 mmol), DCC (242 mg, 1.2 mmol), and DMAP (9.6 mg, 78  $\mu$ mol) at 0 °C. After stirring was continued for 1h at rt, the resultant mixture was filtered and concentrated. The residue was chromatographed on silica gel with hexane-AcOEt (96:4 v/v) as eluent to give the propargyl  $\beta$ -ketoester **I-1k** (100 mg, 2 steps 21%) as a colorless oil.



### 2-Oxocyclooctanecarboxylic acid 1-furan-3-ylprop-2-ynyl ester (**I-1k**)

Yield 21% (2 steps); colorless oil; mixture of tautomers and diastereomers; IR (neat) 3292,

2928, 2856, 1750, 1706, 1644, 1606, 1226  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 1:1 mixture of tautomers:  $\delta$  1.20–2.65 (13H, m), 3.57–3.71 (0.5H, m), 6.38–6.52 (2H, m), 7.35–7.42 (1H, m), 7.51–7.60 (1H, m), 12.34 (0.5H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  23.7 ( $\text{CH}_2$ ), 24.5 ( $\text{CH}_2$ ), 24.76 ( $\text{CH}_2$ ), 24.80 ( $\text{CH}_2$ ), 25.0 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_2$ ), 25.9 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 27.2 ( $\text{CH}_2$ ), 28.7 ( $\text{CH}_2$ ), 29.0 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 29.8 ( $\text{CH}_2$ ), 32.4 ( $\text{CH}_2$ ), 41.7 ( $\text{CH}_2$ ), 42.1 ( $\text{CH}_2$ ), 56.3 (CH), 56.7 (CH), 57.7 (CH), 58.58 (CH), 38.61 (CH), 73.9 (Cq), 74.3 (Cq), 74.4 (Cq), 78.9 (CH), 79.2 (CH), 79.8 (CH), 98.7 (Cq), 109.3 (CH), 109.37 (CH), 109.41 (CH), 121.88 (CH), 121.95 (CH), 122.4 (Cq), 141.4 (CH), 141.6 (CH), 141.8 (CH), 143.57 (Cq), 143.61 (Cq), 143.64 (Cq), 168.85 (Cq), 168.88 (Cq), 171.4 (Cq), 177.6 (Cq), 211.1 (Cq), 211.3 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{18}\text{NaO}_4$   $[\text{M}+\text{Na}]^+$  297.1103, found 297.1102.



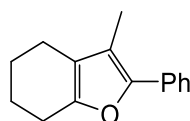
### **6-Oxospiro[4.5]decane-7-carboxylic acid 1-furan-3-ylprop-2-ynyl ester (I-1m)**

Yield 50% (2 steps); colorless oil; mixture of tautomers and diastereomers; IR (neat) 3294, 2939, 2864, 1747, 1706, 1648, 1602  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 1:1 mixture of tautomers:  $\delta$  1.20–2.50 (14H, m), 2.59 (0.5H, d,  $J = 2.4$  Hz), 2.61 (0.5H, d,  $J = 2.4$  Hz), 3.51–3.66 (0.5H, m), 6.47 (1H, d,  $J = 2.4$  Hz), 6.46 (0.5H, d,  $J = 0.8$  Hz), 6.51 (0.5H, d,  $J = 0.8$  Hz), 7.40 (1H, d,  $J = 2.0$  Hz), 7.60 (1H, dd,  $J = 2.0$  and 0.8 Hz), 12.23 (0.5H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of tautomers and diastereomers:  $\delta$  19.8 ( $\text{CH}_2$ ), 21.3 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ), 24.9 ( $\text{CH}_2$ ), 25.30 ( $\text{CH}_2$ ), 25.32 ( $\text{CH}_2$ ), 26.3 ( $\text{CH}_2$ ), 29.88 ( $\text{CH}_2$ ), 29.92 ( $\text{CH}_2$ ), 34.1 ( $\text{CH}_2$ ), 34.2 ( $\text{CH}_2$ ), 36.1 ( $\text{CH}_2$ ), 36.3 ( $\text{CH}_2$ ), 36.6 ( $\text{CH}_2$ ), 38.52 ( $\text{CH}_2$ ), 38.55 ( $\text{CH}_2$ ), 39.60 ( $\text{CH}_2$ ), 39.64 ( $\text{CH}_2$ ), 47.0 (Cq), 54.6 (CH), 54.9 (CH), 57.18

(Cq), 57.23 (Cq), 57.7 (CH), 58.46 (CH), 58.54 (CH), 74.0 (Cq), 74.1 (Cq), 74.2 (Cq), 79.3 (CH), 79.5 (CH), 79.9 (CH), 96.4 (Cq), 109.5 (CH), 109.66 (CH), 109.72 (CH), 122.23 (Cq), 122.25 (Cq), 122.4 (Cq), 141.61 (CH), 141.64 (CH), 141.8 (CH), 143.5 (CH<sub>3</sub>), 169.3 (Cq), 169.4 (Cq), 171.6 (Cq), 179.5 (Cq), 207.9 (Cq), 208.0 (Cq); HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>20</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup> 323.1259, found 323.1261.

### General procedure for palladium-catalyzed reactions using propargyl β-ketoesters

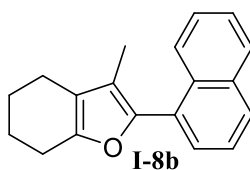
**Synthesis of I-8a (Table I-1, entry 10).** To a stirred solution of propargyl β-ketoester **I-1a** (58.0 mg, 226 μmol) in dioxane (2.3 mL) were added Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (5.9 mg, 5.6 μmol) and DPPF (12.5 mg, 22.6 μmol) at rt, and stirring was continued for 1h at 65 °C. The reaction mixture was filtered through a small amount of silica gel, and then concentrated. The residue was chromatographed on silica gel with hexane-AcOEt (99:1 v/v) as eluent to give the tetrahydrobenzofuran **I-8a** (36.7 mg, 173 μmol, 76%) as a colorless oil.



**I-8a**

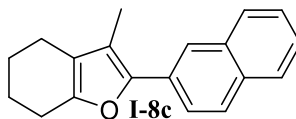
### 3-Methyl-2-phenyl-4,5,6,7-tetrahydrobenzofuran (I-8a)

Yield 76%; colorless oil; IR (neat) 2931, 1603, 1493 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 1.73–1.81 (2H, m), 1.81–1.90 (2H, m), 2.16 (3H, s), 2.37 (2H, t, *J* = 6.4 Hz), 2.63 (2H, t, *J* = 6.4 Hz), 7.20 (1H, t, *J* = 7.6 Hz), 7.37 (2H, t, *J* = 7.6 Hz), 7.59 (2H, dd, *J* = 7.2 and 1.6 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 9.71 (CH<sub>3</sub>), 20.7 (CH<sub>2</sub>), 23.0 (CH<sub>2</sub>), 23.1 (CH<sub>2</sub>), 23.2 (CH<sub>2</sub>), 116.1 (Cq), 120.1 (Cq), 125.0 (CH), 125.9 (CH), 128.4 (CH), 132.4 (Cq), 146.5 (Cq), 149.6 (Cq); HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>16</sub>NaO [M+Na]<sup>+</sup> 235.1099, found 235.1106.



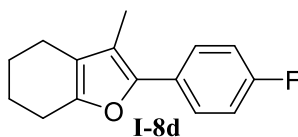
### 3-Methyl-2-naphthalen-1-yl-4,5,6,7-tetrahydrobenzofuran (I-8b)

Yield 62%; colorless oil; IR (neat) 2929, 1591, 1443  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.78–1.87 (2H, m), 1.87–1.94 (2H, m), 1.97 (3H, s), 2.45 (2H, t,  $J = 6.0$  Hz), 2.69 (2H, t,  $J = 6.0$  Hz), 7.45–7.51 (4H, m), 7.80–7.89 (2H, m), 8.05 (1H, dd,  $J = 6.4$  and 3.6 Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  9.30 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 23.1 ( $\text{CH}_2$ ), 23.4 ( $\text{CH}_2$ ), 117.8 (Cq), 119.3 (Cq), 125.2 (CH), 125.8 (CH), 126.0 (CH), 126.5 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 129.4 (Cq), 132.0 (Cq), 134.0 (Cq), 146.5 (Cq), 150.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{18}\text{NaO}$   $[\text{M}+\text{Na}]^+$  285.1255, found 285.1255.



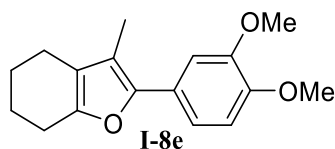
### 3-Methyl-2-naphthalen-2-yl-4,5,6,7-tetrahydrobenzofuran (I-8c)

Yield 60%; yellow plates (AcOEt–hexane, mp. 104.6–105.2  $^\circ\text{C}$ ); IR (neat) 2934, 1633, 1599, 1562  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.76–1.84 (2H, m), 1.84–1.91 (2H, m), 2.26 (3H, s), 2.41 (2H, t,  $J = 6.0$  Hz), 2.68 (2H, t,  $J = 6.0$  Hz), 7.39–7.49 (2H, m), 7.76–7.86 (4H, m), 8.00 (1H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  9.92 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 23.1 ( $\text{CH}_2$ ), 23.3 ( $\text{CH}_2$ ), 116.8 (Cq), 120.4 (Cq), 123.0 (CH), 123.7 (CH), 125.4 (CH), 126.1 (CH), 127.6 (CH), 128.0 (CH), 128.0 (CH), 129.9 (Cq), 131.9 (Cq), 133.6 (Cq), 146.6 (Cq), 149.9 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{18}\text{NaO}$   $[\text{M}+\text{Na}]^+$  285.1255, found 285.1254.



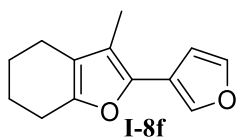
**2-(4-Fluorophenyl)-3-methyl-4,5,6,7-tetrahydrobenzofuran (I-8d)**

Yield 68%; colorless oil; IR (neat) 2934, 1504 1231, 834  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.71–1.80 (2H, m), 1.80–1.90 (2H, m), 2.12 (3H, s), 2.36 (2H, t,  $J = 6.0$  Hz), 2.61 (2H, t,  $J = 6.0$  Hz), 7.06 (2H, t,  $J = 8.8$  Hz), 7.53 (2H, dd,  $J = 8.8$  and 5.2 Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  9.59 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_2$ ), 23.98 ( $\text{CH}_2$ ), 23.05 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 115.4 ( $\text{CH}$ , d,  $J = 21.5$  Hz), 115.7 (Cq), 120.1 (Cq), 126.6 ( $\text{CH}$ , d,  $J = 7.4$  Hz), 128.7 (Cq, d,  $J = 2.5$  Hz), 145.8 (Cq), 149.5 (Cq), 161.3 (Cq, d,  $J = 243.7$  Hz); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{15}\text{OFNa}$   $[\text{M}+\text{Na}]^+$  253.1005, found 253.1005.



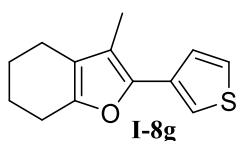
**2-(3,4-Dimethoxyphenyl)-3-methyl-4,5,6,7-tetrahydrobenzofuran (I-8e)**

Yield 63%; colorless needles (hexane, mp. 87.2–87.5  $^{\circ}\text{C}$ ); IR (neat) 2932, 1567 1511  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.73–1.81 (2H, m), 1.81–1.89 (2H, m), 2.13 (3H, s), 2.37 (2H, t,  $J = 6.0$  Hz), 2.63 (2H, t,  $J = 6.0$  Hz), 3.90 (3H, s), 3.93 (3H, s), 6.90 (1H, d,  $J = 7.6$  Hz), 7.11 (1H, d,  $J = 7.6$  Hz), 7.15 (1H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  9.62 ( $\text{CH}_3$ ), 20.7 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 23.1 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 55.9 ( $\text{CH}_3$ ), 55.9 ( $\text{CH}_3$ ), 108.7 ( $\text{CH}$ ), 111.3 ( $\text{CH}$ ), 114.8 (Cq), 117.8 ( $\text{CH}$ ), 120.0 (Cq), 125.7 (Cq), 146.5 (Cq), 147.6 (Cq), 147.6 (Cq), 149.0 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{21}\text{O}_3$   $[\text{M}+\text{H}]^+$  273.1491, found 273.1492.



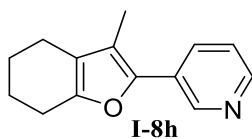
**2-Furan-3-yl-3-methyl-4,5,6,7-tetrahydrobenzofuran (I-8f)**

Yield 79%; yellow oil; IR (neat) 2932, 1770, 1444  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.71–1.79 (2H, m), 1.79–1.87 (2H, m), 2.03 (3H, s), 2.35 (2H, t,  $J = 6.0$  Hz), 2.59 (2H, t,  $J = 6.0$  Hz), 6.67 (1H, t,  $J = 2.0$  Hz), 7.43 (1H, t,  $J = 2.0$  Hz), 7.61 (1H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  8.83 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 23.1 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 108.1 (CH), 115.2 (Cq), 118.3 (Cq), 119.5 (Cq), 137.4 (CH), 140.8 (Cq), 142.9 (CH), 149.0 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{15}\text{O}_2$   $[\text{M}+\text{H}]^+$  203.1072, found 203.1078.



### 3-Methyl-2-thiophen-3-yl-4,5,6,7-tetrahydrobenzofuran (I-8g)

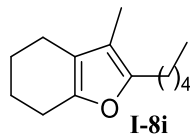
Yield 73%; colorless oil; IR (neat) 2931, 2845, 1642, 1444  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.70–1.79 (2H, m), 1.79–1.90 (2H, m), 2.10 (3H, s), 2.35 (2H, t,  $J = 6.0$  Hz), 2.60 (2H, t,  $J = 6.0$  Hz), 7.29–7.35 (2H, m), 7.36 (1H, d,  $J = 4.4$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  9.27 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 23.0 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 115.1 (Cq), 117.9 (CH), 119.6 (Cq), 125.2 (CH), 125.3 (CH), 133.5 (Cq), 144.1 (Cq), 148.9 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{14}\text{ONaS}$   $[\text{M}+\text{Na}]^+$  241.0663, found 241.0661.



### 3-Methyl-2-pyridin-3-yl-4,5,6,7-tetrahydrobenzofuran (I-8h)

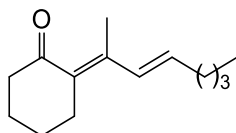
Yield 61%; colorless oil; IR (neat) 2933, 1674, 1590  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.74–1.82 (2H, m), 1.82–1.90 (2H, m), 2.18 (3H, s), 2.38 (2H, t,  $J = 6.0$  Hz), 2.64 (2H, t,  $J = 6.0$  Hz), 7.29 (1H, dd,  $J = 8.0$  and  $5.0$  Hz), 7.87 (1H, dt  $J = 8.0$  and  $2.0$  Hz), 8.43 (1H, dt,  $J = 5.0$  and  $2.0$  Hz), 8.86 (1H, t,  $J = 2.0$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  9.61 ( $\text{CH}_3$ ), 20.5 ( $\text{CH}_2$ ), 22.8 ( $\text{CH}_2$ ), 22.9 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ), 117.9 (Cq), 120.4 (Cq), 123.3 (CH), 128.4

(Cq), 131.5 (CH), 143.6 (Cq), 146.1 (Cq), 146.7 (Cq), 146.7 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{14}H_{16}NO$   $[M+H]^+$  214.1232, found 214.1234.



### 3-Methyl-2-pentyl-4,5,6,7-tetrahydrobenzofuran (I-8i)

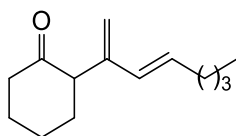
Yield 43%; colorless oil; IR (neat) 2930, 1599, 1444  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  0.89 (3H, t,  $J = 6.8$  Hz), 1.27–1.36 (5H, m), 1.55–1.61 (1H, m), 1.66–1.82 (4H, m), 1.83 (3H, s), 2.26–2.32 (2H, m), 2.48–2.60 (4H, m);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  7.97 ( $CH_3$ ), 14.0 ( $CH_3$ ), 20.8 ( $CH_2$ ), 22.5 ( $CH_2$ ), 23.1 ( $CH_2$ ), 23.1 ( $CH_2$ ), 23.2 ( $CH_2$ ), 26.1 ( $CH_2$ ), 28.6 ( $CH_2$ ), 31.5 ( $CH_2$ ), 113.2 (Cq), 118.0 (Cq), 147.7 (Cq), 149.0 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{14}H_{22}NaO$   $[M+Na]^+$  229.1568, found 225.1563.



### 2-(1-Methylhept-2-enylidene)-cyclohexanone (*endo*-I-9i)

Colorless oil; IR (neat) 2928, 1681, 1446  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  0.91 (3H, t,  $J = 6.8$  Hz), 1.25–1.45 (4H, m), 1.70–1.80 (2H, m), 1.84–1.93 (2H, m), 2.01 (3H, s), 2.19 (2H, q,  $J = 6.8$  Hz), 2.44 (2H, t,  $J = 6.8$  Hz), 2.64 (2H, t,  $J = 6.0$  Hz), 6.06 (1H, dt,  $J = 15.6$  and 6.8 Hz), 6.43 (1H, d,  $J = 15.6$  Hz);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  13.9 ( $CH_3$ ), 16.4 ( $CH_3$ ), 22.3 ( $CH_2$ ), 24.8 ( $CH_2$ ), 29.5 ( $CH_2$ ), 31.5 ( $CH_2$ ), 33.4 ( $CH_2$ ), 43.1 ( $CH_2 \times 2$ ), 128.4 (CH), 133.7 (Cq), 137.5 (CH), 137.8 (Cq), 205.9 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{14}H_{22}NaO$   $[M+Na]^+$  229.1568, found 229.1562.

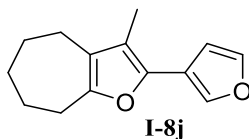




*exo*-I-9i

**2-(1-Methylenehept-2-enyl)-cyclohexanone (*exo*-I-9i)**

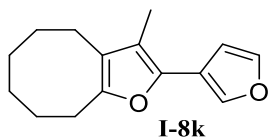
Colorless oil; IR (neat) 2930, 1714, 1449  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.89 (3H, t,  $J = 6.8$  Hz), 1.20–1.40 (4H, m), 1.71–1.77 (2H, m), 1.77–2.01 (2H, m), 2.01–2.16 (4H, m), 2.36–2.51 (2H, m), 3.33 (1H, dd,  $J = 12.0$  and 5.2 Hz), 4.89 (1H, s), 5.17 (1H, s), 5.49 (1H, dt,  $J = 15.6$  and 6.8 Hz), 6.07 (1H, d,  $J = 15.6$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9 ( $\text{CH}_3$ ), 22.3 ( $\text{CH}_2$ ), 25.4 ( $\text{CH}_2$ ), 28.0 ( $\text{CH}_2$ ), 31.4 ( $\text{CH}_2$ ), 32.5 ( $\text{CH}_2$ ), 33.0 ( $\text{CH}_2$ ), 42.4 ( $\text{CH}_2$ ), 53.7 (CH), 114.4 ( $\text{CH}_2$ ), 130.5 (CH), 131.4 (CH), 144.0 (Cq), 210.3 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{23}\text{O}$   $[\text{M}+\text{H}]^+$  207.1749, found 207.1756.



I-8j

**2-Furan-3-yl-3-methyl-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan (I-8j)**

Yield 70%; yellow oil; IR (neat) 2923, 1444  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.60–1.75 (4H, m), 1.75–1.80 (2H, m), 2.02 (3H, s), 2.39 (2H, t,  $J = 5.6$  Hz), 2.76 (2H, t,  $J = 6.0$  Hz), 6.66 (1H, s), 7.41 (1H, s), 7.60 (1H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  9.07 ( $\text{CH}_3$ ), 23.6 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 28.5 ( $\text{CH}_2$ ), 28.9 ( $\text{CH}_2$ ), 30.8 ( $\text{CH}_2$ ), 108.1 (CH), 116.6 (Cq), 118.2 (Cq), 122.6 (Cq), 137.4 (CH), 139.4 (Cq), 142.8 (CH), 151.7 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{17}\text{O}_2$   $[\text{M}+\text{H}]^+$  217.1229, found 217.1227.

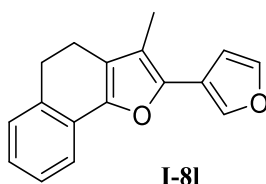


I-8k

**2-Furan-3-yl-3-methyl-4,5,6,7,8,9-hexahydrocycloocta[b]furan (I-8k)**

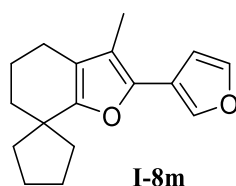
Yield 74%; colorless oil; IR (neat) 2927, 2852, 1452  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )

$\delta$  1.41–1.52 (4H, m), 1.61–1.78 (4H, m), 2.03 (3H, s), 2.49 (2H, t,  $J = 6.0$  Hz), 2.77 (2H, t,  $J = 6.0$  Hz), 6.68 (1H, s), 7.43 (1H, s), 7.61 (1H, s);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  8.89 ( $\text{CH}_3$ ), 21.5 ( $\text{CH}_2$ ), 25.6 ( $\text{CH}_2$ ), 25.9 ( $\text{CH}_2$ ), 26.1 ( $\text{CH}_2$ ), 27.9 ( $\text{CH}_2$ ), 28.2 ( $\text{CH}_2$ ), 108.1 (CH), 116.2 (Cq), 118.3 (Cq), 120.3 (Cq), 137.3 (CH), 140.0 (Cq), 142.8 (CH), 150.0 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{18}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$  217.1229, found 217.1227.



### 2-(Furan-3-yl)-3-methyl-4,5-dihydro-1H-naphtho[1,2-*b*]furan (I-8l)

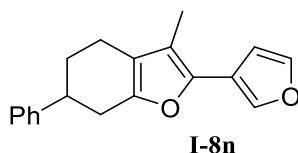
Yield 70%; yellow oil; IR (neat) 2929, 1496, 1170  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.12 (3H, s), 2.67 (2H, t,  $J = 7.6$  Hz), 2.98 (2H, t,  $J = 7.6$  Hz), 6.77 (1H, dd,  $J = 1.2$  and 0.8 Hz), 7.09 (1H, dd,  $J = 7.6$  and 1.2 Hz), 7.18 (1H, dd,  $J = 7.6$  and 1.2 Hz), 7.22 (1H, dt,  $J = 7.6$  and 1.2 Hz), 7.45–7.50 (2H, m), 7.72 (1H, s);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  9.02 ( $\text{CH}_3$ ), 19.4 ( $\text{CH}_2$ ), 28.9 ( $\text{CH}_2$ ), 108.1 (CH), 115.9 (Cq), 118.1 (Cq), 119.0 (CH), 122.0 (Cq), 126.1 (CH), 126.7 (CH), 127.8 (CH), 128.1 (Cq), 134.4 (Cq), 138.0 (CH), 143.0 (Cq), 143.1 (CH), 148.0 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$  273.0891, found 273.0896.



### 2-(Furan-3-yl)-3-methyl-5,6-dihydro-4H-spiro[benzofuran-7,1'-cyclopentane] (I-8m)

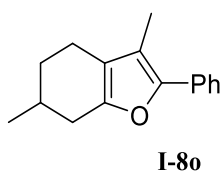
Yield 62%; colorless oil; IR (neat) 2930, 2862, 1444, 1169  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.52–1.60 (2H, m), 1.62–1.79 (7H, m), 1.79–1.84 (1H, m), 1.87–2.05 (2H, m), 2.02 (3H, s), 2.33 (2H, t,  $J = 6.0$  Hz), 6.66 (1H, t,  $J = 2.0$  Hz), 7.42 (1H, t,  $J = 2.0$  Hz), 7.60 (1H, s);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  8.94 ( $\text{CH}_3$ ), 21.0 ( $\text{CH}_2$ ), 21.3 ( $\text{CH}_2$ ), 25.1 ( $\text{CH}_2$ ),

37.2 (CH<sub>2</sub>), 38.3 (CH<sub>2</sub>), 43.4 (Cq), 108.1 (CH), 114.9 (Cq), 118.4 (Cq), 118.4 (Cq), 137.4 (CH), 140.6 (Cq), 142.8 (CH), 155.1 (Cq); HRMS (ESI) *m/z* calcd for C<sub>17</sub>H<sub>20</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 279.1361, found 279.1369.



### 2-Furan-3-yl-3-methyl-6-phenyl-4,5,6,7-tetrahydrobenzofuran (I-8n)

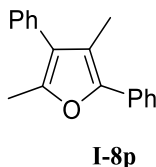
Yield 76%; yellow oil; IR (neat) 2920, 1746, 1453 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 1.83–1.94 (2H, m), 2.06 (3H, s), 2.47 (2H, dd, *J* = 4.4 and 1.6 Hz), 2.74 (1H, dd, *J* = 16.0 and 10.8 Hz), 2.92 (1H, dd, *J* = 16.0 and 5.2 Hz), 3.04 (1H, ddt, *J* = 5.2, 2.8 and 10.8 Hz), 6.68 (1H, dd, *J* = 2.0 and 0.8 Hz), 7.20–7.29 (3H, m), 7.29–7.37 (2H, m), 7.43 (1H, t, *J* = 2.0 Hz), 7.63 (1H, s); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 8.92 (CH<sub>3</sub>), 20.5 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 31.0 (CH<sub>2</sub>), 41.0 (CH), 108.1 (CH), 115.1 (Cq), 118.2 (Cq), 119.3 (Cq), 126.4 (CH), 126.9 (CH), 128.5 (CH), 137.5 (CH), 141.3 (Cq), 143.0 (CH), 145.8 (Cq), 148.6 (Cq); HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>19</sub>O<sub>2</sub> [M+H]<sup>+</sup> 279.1385, found 279.1385.



### 3,6-Dimethyl-2-phenyl-4,5,6,7-tetrahydrobenzofuran (I-8o)

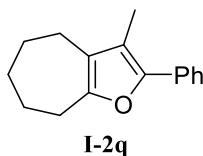
Yield 61%; colorless oil; IR (neat) 2923, 1603, 1493 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 1.10 (3H, d, *J* = 6.4 Hz), 1.33–1.45 (1H, m), 1.82–1.90 (1H, m), 1.90–2.20 (1H, m), 2.16 (3H, s), 2.19–2.30 (1H, m), 2.30–2.45 (2H, m), 2.73 (1H, dd, *J* = 16.2 and 5.2 Hz), 7.20 (1H, t, *J* = 7.2 Hz), 7.37 (2H, t, *J* = 7.2 Hz), 7.58 (2H, d, *J* = 7.2 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 9.77 (CH<sub>3</sub>), 20.1 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>), 29.7 (CH), 31.3 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 116.0

(Cq), 120.0 (Cq), 125.0 (CH), 126.0 (CH), 128.4 (CH), 132.5 (Cq), 146.7 (Cq), 149.4 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{16}H_{18}NaO$   $[M+Na]^+$  249.1255, found 249.1266.



### 2,4-Dimethyl-3,5-diphenylfuran (I-8p)<sup>36)</sup>

Yield 21%; colorless oil; IR (neat) 2923, 1732, 1597, 1498  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.20 (3H, s), 2.36 (3H, s), 7.23–7.34 (4H, m), 7.39–7.45 (4H, m), 7.64–7.66 (2H, m);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  10.8 (CH<sub>3</sub>), 12.4 (CH<sub>3</sub>), 116.4 (Cq), 124.8 (Cq), 125.3 (CH), 126.4 (CH), 126.7 (CH), 128.4 (CH), 128.5 (CH), 129.7 (CH), 132.0 (Cq), 132.7 (Cq), 146.9 (Cq), 147.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{18}H_{16}NaO$   $[M+Na]^+$  271.1099, found 271.1109.



### 3-Methyl-2-phenyl-5,6,7,8-tetrahydro-4H-cyclohepta[b]furan (I-8q)<sup>37)</sup>

Yield 66%; colorless oil; IR (neat) 2923, 1602, 1492, 1444  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.68–1.82 (6H, m), 2.15 (3H, s), 2.43 (2H, t,  $J = 6.0$  Hz), 2.81 (2H, t,  $J = 6.0$  Hz), 7.20 (1H, t,  $J = 7.6$  Hz), 7.37 (2H, t,  $J = 7.6$  Hz), 7.60 (2H, d,  $J = 7.6$  Hz);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  9.84 (CH<sub>3</sub>), 23.7 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 117.3 (Cq), 123.3 (Cq), 125.1 (CH), 126.0 (CH), 128.4 (CH), 132.3 (Cq), 145.2 (Cq), 152.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{16}H_{18}NaO$   $[M+Na]^+$  249.1255, found 249.1251.

### Procedure for the crossover reaction of propargyl $\beta$ -ketoesters using palladium

**catalyst (Scheme I-8).** To a stirred solution of 2-Oxocyclohexanecarboxylic acid 1-furan-3-yl-2-propynyl ester (**I-1f**) (24.7 mg, 100  $\mu\text{mol}$ ) and 2-Oxocycloheptanecarboxylic acid 1-phenyl-2-propynyl ester (**I-1q**) (26.7 mg, 100  $\mu\text{mol}$ ) in dioxane (2.0 mL) were added  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (5.2 mg, 5.0  $\mu\text{mol}$ ) and DPPF (11.1 mg, 20.1  $\mu\text{mol}$ ) at rt, and stirring was continued for 1 h at 65 °C. The reaction mixture was filtered through a small amount of silica gel, and then concentrated. The residue was chromatographed on silica gel with hexane-AcOEt (99:1 v/v) as eluent to give the mixture of tetrasubstituted furans **I-8a**, **I-8f**, **I-8j** and **I-8q** (26.1 mg, **I-8a** : **I-8f** : **I-8j** : **I-8q** = 1 : 1.2 : 1 : 1.1, 61% total yields) as a colorless oil.

**Procedure for the reaction of propargyl ester with cyclohexanone using palladium catalyst (Scheme I-10).** To a stirred solution of propargyl carbonate **I-14** (50.7 mg, 267  $\mu\text{mol}$ ) and cyclohexanone (**I-6c**) (26.2 mg, 267  $\mu\text{mol}$ ) in dioxane (2.7 mL) were added  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (13.8 mg, 13.3  $\mu\text{mol}$ ) and DPPF (29.6 mg, 53.3  $\mu\text{mol}$ ) at rt, and stirring was continued for 2 h at 65 °C. The reaction mixture was filtered through a small amount of silica gel, and then concentrated. The residue was chromatographed on silica gel with hexane-AcOEt (99:1 v/v) as eluent to give complex mixture.

**Procedure for the reaction of propargyl ester with silyl enol ether using palladium catalyst and CsF (Scheme I-10)** <sup>22</sup>. To a stirred solution of propargyl carbonate **I-14** (23.3 mg, 123  $\mu\text{mol}$ ) and silyl enol ether **I-15** (20.9 mg, 123  $\mu\text{mol}$ ) in dioxane (1.5 mL) were added  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (3.2 mg, 3.06  $\mu\text{mol}$ ), DPPF (6.8 mg, 12.3  $\mu\text{mol}$ ) and CsF (22.3 mg, 147  $\mu\text{mol}$ ) at rt, and stirring was continued for 30 min. The reaction mixture was allowed to heat to 65 °C, and stirred for 20 h. The reaction mixture was allowed to cool to rt, and 0.15 mL of TBAF (1 M in THF) was added. After stirring for 45 min, the reaction mixture

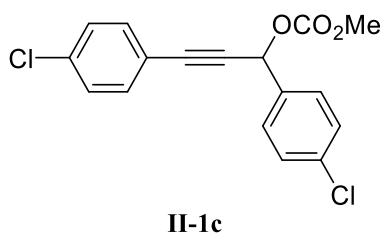
was diluted with Et<sub>2</sub>O, quenched with sat. NH<sub>4</sub>Cl aq. and extracted with Et<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and filtered through a short bed of Celite. The solvents were removed in vacuo to give decomposition product.

**Procedure for the reaction of propargyl ester with silyl enol ether using palladium catalyst and TBAT (Scheme I-10)**<sup>23</sup>. To a stirred suspension of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (9.4 mg, 9.10 μmol), DPPF (20.2 mg, 36.4 μmol) and TBAT (68.7 mg, 127 μmol) in dioxane (1.0 mL) were added propargyl carbonate **I-14** (69.2 mg, 364 μmol) and silyl enol ether **I-15** (62.0 mg, 364 μmol) in dioxane (2.6 mL) at rt, and stirring was continued for 30 min at 65 °C. The reaction mixture was filtered through a small amount of silica gel, and then concentrated. The residue was chromatographed on silica gel with hexane-AcOEt (99:1 v/v) as eluent to give propargyl carbonate **I-14** (45.9 mg, 66 %) as colorless oil.

## Experiments in Chapter II

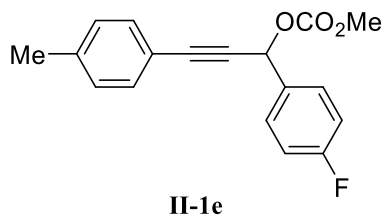
### General procedure for the synthesis of propargyl carbonates <sup>12)</sup>.

**Synthesis of II-1c (Scheme II-2).** To a stirred solution of propargyl alcohol **II-5c** (496 mg, 1.79 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (9 mL) were added pyridine (0.29 mL, 3.58 mmol) and methyl chloroformate (0.21 mL, 2.69 mmol) at 0 °C, and stirring was continued for 2 h at the same temperature. The reaction mixture was diluted with aqueous NH<sub>4</sub>Cl and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (95:5 v/v) as eluent to give propargyl carbonate **II-1c** (521 mg, 82%) as a colorless oil.



### Carbonic acid 1,3-bis-(4-chlorophenyl)- 2-propynyl ester methyl ester (**II-1c**)

Yield 82%; colorless oil; IR (neat) 2230, 1750, 1490, 1261 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 3.83 (3H, s), 6.47 (1H, s), 7.30 (2H, d, *J* = 8.4 Hz), 7.36–7.42 (4H, m), 7.53 (2H, d, *J* = 8.4 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 55.2 (CH<sub>3</sub>), 69.3 (CH), 85.4 (Cq), 120.2 (Cq), 128.7 (CH), 129.0 (CH), 129.1 (CH), 133.1 (CH), 134.9 (Cq), 135.2 (Cq), 135.31 (Cq), 135.33 (Cq), 154.8 (Cq); HRMS (ESI) *m/z* calcd for C<sub>17</sub>H<sub>12</sub>Cl<sub>2</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup> 335.0242, found 335.0249.

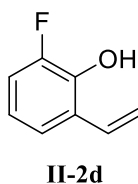


**Carbonyl acid 1-(4-fluorophenyl)-3-*p*-tolyl-2-propynyl ester methyl ester (II-1e)**

Yield 82%; colorless oil; IR (neat) 2230, 1750, 1606, 1509, 1263  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.35 (3H, s), 3.82 (3H, s), 6.50 (1H, s), 7.07 (2H, dt,  $J = 8.0$  and 2.0 Hz), 7.12 (2H, d,  $J = 8.0$  Hz), 7.36 (2H, dd,  $J = 8.0$  and 2.0 Hz), 7.60 (2H, dd,  $J = 8.0$  and 5.2 Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.5 ( $\text{CH}_3$ ), 55.0 ( $\text{CH}_3$ ), 69.6 (CH), 83.9 (Cq), 88.4 (Cq), 115.6 (CH, d,  $J = 21.5$  Hz), 118.7 (Cq), 129.1 (CH), 129.8 (CH, d,  $J = 9.0$  Hz), 131.8 (CH), 132.6 (Cq, d,  $J = 3.3$  Hz), 139.2 (Cq), 154.8 (Cq), 163.1 (Cq, d,  $J = 247.0$  Hz); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{16}\text{O}_3\text{F}$   $[\text{M}+\text{H}]^+$  299.1083, found 299.1083.

**General procedure for preparation of vinylphenols.**

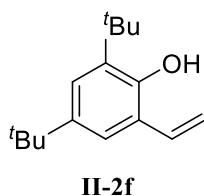
**Synthesis of II-2d (Scheme II-3).** To a stirred solution of  $\text{Ph}_3\text{PMeBr}$  (278 mg, 780  $\mu\text{mol}$ ) in THF (2 mL) were added *n*-BuLi (1.55 M in hexane, 0.6 mL) at 0  $^\circ\text{C}$ . After stirring for 30 min at same temperature, salicylaldehyde **II-6d** (50 mg, 354  $\mu\text{mol}$ ) in THF (1 mL) were added at 0  $^\circ\text{C}$ , and stirring was continued for 4 h at rt. The reaction mixture was diluted with aqueous  $\text{NH}_4\text{Cl}$  and extracted with  $\text{Et}_2\text{O}$ . The combined extracts were washed with water and brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (97:3 v/v) as eluent to give vinylphenol **II-2d** (36 mg, 73%) as a colorless oil.



**2-Fluoro-6-vinylphenol (II-2d)**



Yield 73%; colorless oil; IR (neat) 3567, 1619, 1474, 1260  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.29 (1H, s), 5.36 (1H, dd,  $J = 11.2$  and 1.2 Hz), 5.82 (1H, dd,  $J = 17.6$  and 1.2 Hz), 6.82 (1H, m), 6.97 (1H, dd,  $J = 17.6$  and 11.2 Hz), 6.99 (1H, td,  $J = 8.0$  and 1.6 Hz), 7.21 (1H, dd,  $J = 8.0$  and 1.6 Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  114.1 (CH, d,  $J = 18.2$  Hz), 116.0 ( $\text{CH}_2$ ), 119.9 (CH, d,  $J = 7.4$  Hz), 122.1 (CH, d,  $J = 3.3$  Hz), 126.7 (Cq, d,  $J = 1.7$  Hz), 130.4 (Cq, d,  $J = 3.3$  Hz), 141.1 (Cq, d,  $J = 14.1$  Hz), 151.3 (Cq, d,  $J = 234.6$  Hz); HRMS (ESI)  $m/z$  calcd for  $\text{C}_8\text{H}_7\text{FN}\text{aO}$   $[\text{M}+\text{Na}]^+$  161.0379, found 161.0378.

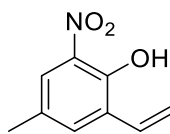


#### **2,4-Di-*tert*-butyl-6-vinylphenol (II-2f)**

Yield 91%; colorless oil; IR (neat) 3541, 2960, 1627, 1477  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (9H, s), 1.43 (9H, s), 5.21 (1H, s), 5.46 (1H, dd,  $J = 11.2$  and 1.6 Hz), 5.66 (1H, dd,  $J = 17.6$  and 1.6 Hz), 6.85 (1H, dd,  $J = 17.6$  and 11.2 Hz), 7.13 (1H, d,  $J = 2.4$  Hz), 7.25 (1H, d,  $J = 2.4$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  29.8 ( $\text{CH}_3$ ), 31.6 ( $\text{CH}_3$ ), 34.3 (Cq), 34.9 (Cq), 117.7 ( $\text{CH}_2$ ), 122.4 (CH), 123.8 (CH), 124.7 (Cq), 133.0 (CH), 135.6 (Cq), 142.3 (Cq), 149.3 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{24}\text{NaO}$   $[\text{M}+\text{Na}]^+$  255.1725, found 255.1719.

**Preparation of vinylphenol II-2c (Scheme II-3).** To a stirred solution of 2-hydroxy-5-methyl-3-nitro-benzaldehyde (**II-6c**) (205 mg, 1.13 mmol) in THF (11 mL) were added Tebbe reagent (0.5 M in toluene, 5 mL) at 0 °C, and stirring was continued for 1 h at the same temperature. The reaction mixture was quenched with 0.1 M NaOH aq. and extracted with  $\text{Et}_2\text{O}$ . The residue upon workup was chromatographed on silica gel with hexane-

AcOEt (93:7 v/v) as eluent to give vinylphenol **II-2c** (34 mg, 17%) as a yellow solid.

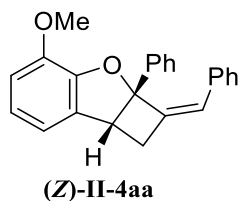


**II-2c**

Yield 17%; yellow solid; IR (neat) 3162, 2924, 1848, 1632, 1538  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (3H, s), 5.41 (1H, dd,  $J = 11.2$  and  $1.2$  Hz), 5.83 (1H, dd,  $J = 17.6$  and  $1.2$  Hz), 7.04 (1H, dd,  $J = 17.6$  and  $11.2$  Hz), 7.57 (1H, d,  $J = 1.6$  Hz), 7.83 (1H, d,  $J = 1.6$  Hz), 10.91 (1H, s);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.4 ( $\text{CH}_3$ ), 116.9 ( $\text{CH}_2$ ), 123.7 ( $\text{CH}$ ), 128.9 ( $\text{Cq}$ ), 129.2 ( $\text{Cq}$ ), 129.6 ( $\text{CH}$ ), 135.2 ( $\text{CH}$ ), 150.8 ( $\text{Cq}$ ); HRMS (ESI)  $m/z$  calcd for  $\text{C}_9\text{H}_9\text{NNaO}_3$   $[\text{M}+\text{Na}]^+$  202.0480, found 202.0484.

### General procedure for the reaction of propargyl esters with phenols using palladium catalyst.

**Synthesis of II-4aa (Table II-1, entry 7).** To a stirred solution of propargyl carbonate **II-1a** (160 mg, 602  $\mu\text{mol}$ ) and vinylphenol **II-2a** (60 mg, 402  $\mu\text{mol}$ ) in dioxane (4.0 mL) were added  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (21 mg, 20  $\mu\text{mol}$ ) and  $\text{P}(2\text{-furyl})_3$  (19 mg, 80  $\mu\text{mol}$ ) at rt, and stirring was continued for 30 min at the same temperature under argon atmosphere. The reaction mixture was then allowed to heat to 100  $^\circ\text{C}$ , and stirred for 1 h. After filtration of the reaction mixture using small amount of silica gel followed by concentration, the residue was chromatographed on silica gel with hexane-AcOEt (99:1 v/v) as eluent to give (**Z**)-**II-4aa** and (**E**)-**II-4aa** (116.0 mg, 3.5 : 1, 85% total yield).



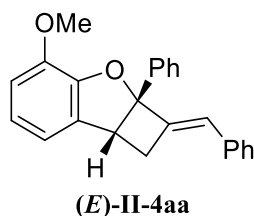
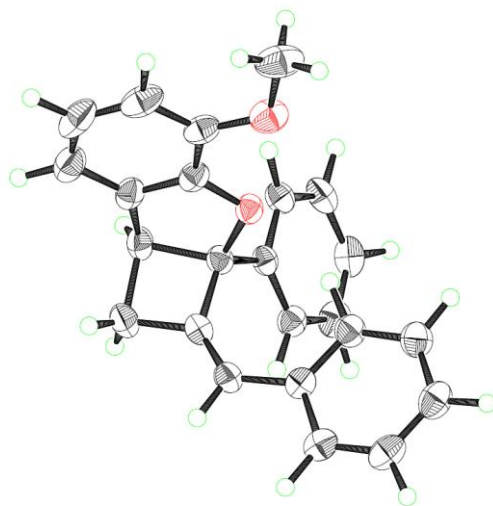
**(2a*S*,7b*R*,*Z*)-2-Benzylidene-4-methoxy-2a-phenyl-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*Z*)-II-4aa]**

Colorless plates (chloroform–hexane, mp. 153.9–154.9 °C); IR (neat) 2938, 1589, 1490  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.84 (1H, dt,  $J = 16.0$  and  $2.8$  Hz), 3.35 (1H, ddd,  $J = 16.0$ ,  $8.4$  and  $2.8$  Hz), 3.80 (3H, s), 3.88 (1H, dd,  $J = 8.4$  and  $2.8$  Hz), 6.44 (1H, t,  $J = 2.8$  Hz), 6.81 (1H, dd,  $J = 7.2$  and  $2.4$  Hz), 6.87 (2H, d,  $J = 0.8$  Hz), 7.11 (1H, d,  $J = 7.2$  Hz), 7.18 (2H, t,  $J = 7.2$  Hz), 7.26–7.34 (3H, m), 7.42 (2H, d,  $J = 7.2$  Hz), 7.55 (2H, d,  $J = 7.2$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  37.0 ( $\text{CH}_2$ ), 48.9 (CH), 56.6 ( $\text{CH}_3$ ), 95.7 (Cq), 113.1 (CH), 117.5 (CH), 121.8 (CH), 126.1 (CH), 127.1 (CH), 128.06 (CH), 128.14 (CH), 128.6 (CH), 128.9 (CH), 129.8 (CH), 132.1 (Cq), 135.1 (Cq), 138.7 (Cq), 140.6 (Cq), 145.0 (Cq), 149.8 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{20}\text{NaO}_2$  [ $\text{M}+\text{Na}$ ] $^+$  363.1361, found 363.1358.

**X-Ray crystallographic analysis of compound (Z)-II-4aa.** A colorless block crystal having approximate dimensions of 0.80 x 0.60 x 0.50 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo- $\text{K}\alpha$  radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 16969 observed reflections ( $I > 0.00\sigma(I)$ ) and 256 variable parameters, and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of  $R = 0.041$  and  $R_w = 0.062$ . Crystal data for **(Z)-II-4aa**:  $\text{C}_{24}\text{H}_{20}\text{O}_2$ ,  $M = 340.42$ , orthorhombic, space

group Pnn2,  $a = 13.5222(5) \text{ \AA}$ ,  $b = 17.8222(6) \text{ \AA}$ ,  $c = 7.5009(3) \text{ \AA}$ ,  $V = 1807.7(1) \text{ \AA}^3$ ,  $Z = 4$ ,  $D_c = 1.251 \text{ g/cm}^3$ ,  $F(000) = 720$ ,  $\mu(\text{MoK}\alpha) = 0.78 \text{ cm}^{-1}$ .

**Figure E-1.** ORTEP drawing of (*Z*)-II-4aa.



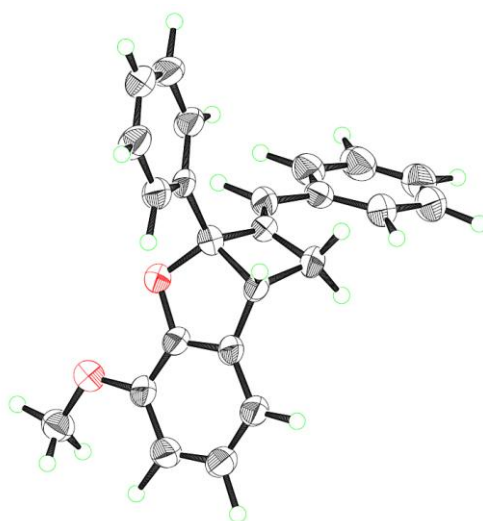
**(2a*S*,7b*R*,*E*)-2-Benzylidene-4-methoxy-2a-phenyl-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*E*)-II-4aa]**

Colorless needles (acetone–MeOH, mp. 131.0–133.4 °C); IR (neat) 3027, 1615, 1588, 1489  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.13 (1H, dt,  $J = 16.8$  and 2.8 Hz), 3.57 (1H, ddd,  $J = 16.8$ , 8.0 and 2.8 Hz), 3.90 (3H, s), 4.12 (1H, dd,  $J = 8.0$  and 2.8 Hz), 6.74 (1H, t,  $J = 2.8$  Hz), 6.79 (1H, dd,  $J = 8.0$  and 2.0 Hz), 6.81–6.89 (2H, m), 7.16–7.22 (1H, m), 7.24–7.34 (5H, m), 7.35–7.41 (2H, m), 7.63 (2H, d,  $J = 8.0$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  38.1 ( $\text{CH}_2$ ), 49.6 (CH), 56.0 ( $\text{CH}_3$ ), 96.1 (Cq), 111.7 (CH), 117.2 (CH), 121.6 (CH), 126.2 (CH), 127.3 (CH), 127.93 (CH), 127.99 (CH), 128.04 (CH), 128.37 (CH),

128.44 (CH), 131.9 (Cq), 136.5 (Cq), 139.7 (Cq), 143.9 (Cq), 144.9 (Cq), 149.7 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{24}H_{21}O_2$   $[M+H]^+$  341.1542, found 341.1546.

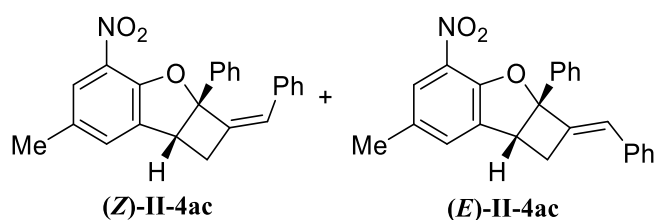
**X-Ray crystallographic analysis of compound (*E*)-II-4aa.** A colorless block crystal having approximate dimensions of 0.40 x 0.30 x 0.20 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-K $\alpha$  radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 16302 observed reflections ( $I > 0.00\sigma(I)$ ) and 255 variable parameters, and converged (largest parameter shift was 0.94 times its esd) with unweighted and weighted agreement factors of  $R = 0.094$  and  $R_w = 0.228$ . Crystal data for (*E*)-II-4aa:  $C_{24}H_{20}O_2$ ,  $M = 340.42$ , monoclinic, space group  $P2_{1/n}$ ,  $a = 5.7517(9)$  Å,  $b = 11.218(2)$  Å,  $c = 27.558(4)$  Å,  $\beta = 95.332(4)^\circ$ ,  $V = 1770.4(5)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.277$  g/cm<sup>3</sup>,  $F(000) = 720$ ,  $\mu(\text{MoK}\alpha) = 0.80$  cm<sup>-1</sup>.

**Figure E-2.** ORTEP drawing of (*E*)-II-4aa.





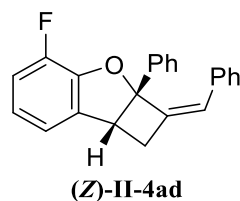
d,  $J = 7.2$  Hz);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  15.6 ( $\text{CH}_3$ ), 38.3 ( $\text{CH}_2$ ), 49.5 ( $\text{CH}$ ), 95.1 ( $\text{Cq}$ ), 120.5 ( $\text{Cq}$ ), 120.9 ( $\text{CH}$ ), 122.4 ( $\text{CH}$ ), 126.0 ( $\text{CH}$ ), 127.3 ( $\text{CH}$ ), 127.5 ( $\text{CH}$ ), 127.9 ( $\text{CH}$ ), 128.0 ( $\text{CH}$ ), 128.4 ( $\text{CH}$ ), 128.5 ( $\text{CH}$ ), 129.7 ( $\text{CH}$ ), 130.1 ( $\text{Cq}$ ), 136.6 ( $\text{Cq}$ ), 140.3 ( $\text{Cq}$ ), 144.6 ( $\text{Cq}$ ), 159.8 ( $\text{Cq}$ ); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{21}\text{O}$   $[\text{M}+\text{H}]^+$  325.1592, found 325.1593.



**(Z)- and (E)-(2a*S*,7b*R*)-2-Benzylidene-6-methyl-4-nitro-2a-phenyl-**

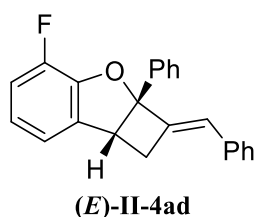
**1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(Z)-II-4ac and (E)-II-4ac] (ratio 3:2)**

Yellow solid; IR (neat) 2957, 1622, 1587, 1524, 1327  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.35 (1.2H, s), 2.37 (1.8H, s), 2.85 (0.4H, dt,  $J = 16.0$  and  $2.4$  Hz), 3.13 (0.6H, dt,  $J = 16.8$  and  $2.8$  Hz), 3.43(0.4H, ddd,  $J = 16.0$ ,  $8.4$  and  $2.4$  Hz), 3.65 (0.6H, ddd,  $J = 16.8$ ,  $8.0$  and  $2.8$  Hz), 3.89 (0.4H, dd,  $J = 8.4$  and  $2.4$  Hz), 4.12 (0.6H, dd,  $J = 8.0$  and  $2.8$  Hz), 6.48 (0.4H, t,  $J = 2.8$  Hz), 6.72 (0.6H, t,  $J = 2.4$  Hz), 7.11–7.55 (10H, m), 7.63 (1.2H, d,  $J = 7.2$  Hz), 7.80 (0.8H, d,  $J = 7.2$  Hz);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ) for mixture of diastereomers:  $\delta$  20.4 ( $\text{CH}_3$ ), 20.5 ( $\text{CH}_3$ ), 37.0 ( $\text{CH}_2$ ), 38.0 ( $\text{CH}_2$ ), 47.3 ( $\text{CH}$ ), 47.9 ( $\text{CH}$ ), 98.0 ( $\text{Cqx}2$ ), 124.0 ( $\text{CHx}2$ ), 125.8 ( $\text{CH}$ ), 125.9 ( $\text{CH}$ ), 127.6 ( $\text{CH}$ ), 127.7 ( $\text{CH}$ ), 128.15 ( $\text{CH}$ ), 128.22 ( $\text{CH}$ ), 128.4 ( $\text{CHx}2$ ), 128.5 ( $\text{CHx}2$ ), 128.6 ( $\text{CHx}2$ ), 129.0 ( $\text{CHx}2$ ), 130.9 ( $\text{Cq}$ ), 131.1 ( $\text{Cq}$ ), 132.0 ( $\text{CHx}2$ ), 132.9 ( $\text{Cqx}2$ ), 134.4 ( $\text{Cqx}2$ ), 135.8 ( $\text{Cqx}2$ ), 137.5 ( $\text{Cq}$ ), 138.8 ( $\text{Cq}$ ), 142.0 ( $\text{Cqx}2$ ), 153.8 ( $\text{Cqx}2$ ); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{19}\text{NNaO}_3$   $[\text{M}+\text{Na}]^+$  392.1263, found 392.1262.



**(2a*S*,7b*R*,*Z*)-2-Benzylidene-4-fluoro-2a-phenyl-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*Z*)-II-4ad]**

Colorless oil; IR (neat) 3061, 1625, 1595, 1485, 1448  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.83 (1H, dt,  $J = 16.4$  and 2.8 Hz), 3.36 (1H, ddd,  $J = 16.4$ , 8.4 and 2.8 Hz), 3.88 (1H, dd,  $J = 8.4$  and 2.8 Hz), 6.44 (1H, t,  $J = 2.8$  Hz), 6.84 (1H, dt,  $J = 4.4$  and 7.6 Hz), 6.92–6.99 (2H, m), 7.11 (1H, dt,  $J = 7.6$  and 1.6 Hz), 7.13–7.21 (2H, m), 7.21–7.33 (3H, m), 7.40 (2H, d,  $J = 6.8$  Hz), 7.53 (2H, dt,  $J = 7.6$  and 1.6 Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  37.0 ( $\text{CH}_2$ ), 48.8 (CH, d,  $J = 2.5$  Hz), 96.8 (Cq), 115.6 (CH), 115.8 (CH), 120.4 (CH, d,  $J = 3.3$  Hz), 121.6 (CH, d,  $J = 5.8$  Hz), 125.9 (CH), 127.3 (CH), 128.1 (CH), 128.2 (CH, d,  $J = 2.5$  Hz), 128.7 (CH, d,  $J = 25.6$  Hz), 130.2 (CH), 134.3 (Cq, d,  $J = 3.3$  Hz), 134.8 (Cq), 138.2 (Cq), 139.7 (Cq), 147.77 (Cq, d,  $J = 10.7$  Hz), 147.80 (Cq, d,  $J = 245.3$  Hz); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{17}\text{FNaO}$   $[\text{M}+\text{Na}]^+$  351.1161, found 351.1172

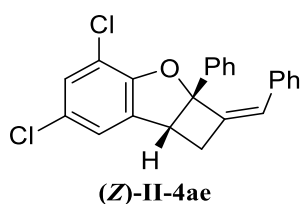


**(2a*S*,7b*R*,*E*)-2-Benzylidene-4-fluoro-2a-phenyl-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*E*)-II-4ad]**

Colorless oil; IR (neat) 3029, 1625, 1595, 1494  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.14 (1H, dt,  $J = 16.8$  and 2.8 Hz), 3.60 (1H, ddd,  $J = 16.8$ , 8.2 and 2.8 Hz), 4.15 (1H, dd,  $J = 8.2$  and 2.8 Hz), 6.72 (1H, t,  $J = 2.8$  Hz), 6.83 (1H, dt,  $J = 4.8$  and 7.2 Hz), 6.98 (2H, t,  $J = 7.2$  Hz), 7.20–7.38 (6H, m), 7.42 (2H, t,  $J = 7.2$  Hz), 7.63 (2H, d,  $J = 7.2$  Hz);  $^{13}\text{C-NMR}$

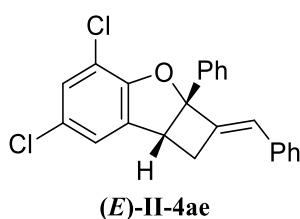


(100 MHz, CDCl<sub>3</sub>)  $\delta$  38.0 (CH<sub>2</sub>), 49.3 (CH), 97.2 (Cq), 115.6 (CH), 115.8 (CH), 120.4 (CH, d,  $J = 2.5$  Hz), 121.5 (CH, d,  $J = 4.9$  Hz), 126.1 (CH), 127.5 (CH), 128.0 (CH), 128.2 (CH, d,  $J = 26.4$  Hz), 128.3 (CH), 128.5 (CH), 134.3 (Cq, d,  $J = 3.3$  Hz), 136.2 (Cq), 139.1 (Cq), 143.1 (Cq), 147.79 (Cq, d,  $J = 244.5$  Hz), 147.81 (Cq); HRMS (ESI)  $m/z$  calcd for C<sub>23</sub>H<sub>18</sub>FO [M+H]<sup>+</sup> 329.1342, found 329.1340.



**(2a*S*,7b*R*,*Z*)-2-Benzylidene-4,6-dichloro-2a-phenyl-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*Z*)-II-4ae]**

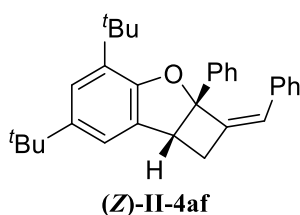
Colorless oil; IR (neat) 3082, 2950, 1577, 1447 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.83 (1H, dt,  $J = 16.4$  and 2.4 Hz), 3.36 (1H, ddd,  $J = 16.4$ , 8.8 and 2.4 Hz), 3.87 (1H, dd,  $J = 8.8$  and 2.4 Hz), 6.45 (1H, t,  $J = 2.4$  Hz), 7.09 (1H, dd,  $J = 7.2$  Hz), 7.12 (1H, d,  $J = 7.2$  Hz), 7.17 (2H, d,  $J = 7.2$  Hz), 7.20 (1H, d,  $J = 7.2$  Hz), 7.24–7.36 (3H, m), 7.41 (2H, d,  $J = 6.8$  Hz), 7.49 (2H, d,  $J = 6.8$  Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  37.0 (CH<sub>2</sub>), 49.0 (CH), 96.6 (Cq), 116.3 (Cq), 123.7 (CH), 125.88 (CH), 125.95 (Cq), 127.5 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.9 (CH), 130.6 (CH), 133.7 (Cq), 134.6 (Cq), 137.6 (Cq), 139.0 (Cq), 155.9 (Cq); HRMS (ESI)  $m/z$  calcd for C<sub>23</sub>H<sub>17</sub>Cl<sub>2</sub>O [M+H]<sup>+</sup> 379.0656, found 379.0658.



**(2a*S*,7b*R*,*E*)-2-Benzylidene-4,6-dichloro-2a-phenyl-1,2,2a,7b-**

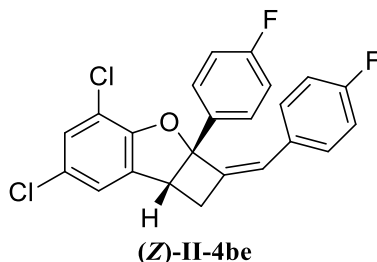
**tetrahydrocyclobuta[*b*]benzofuran [(*E*)-II-4ae]**

Colorless oil; IR (neat) 3028, 1577, 1449  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.14 (1H, dt,  $J = 16.8$  and 2.8 Hz), 3.62 (1H, ddd,  $J = 16.8$ , 8.0 and 2.8 Hz), 4.12 (1H, dd,  $J = 8.0$  and 2.8 Hz), 6.70 (1H, t,  $J = 2.8$  Hz), 7.07 (1H, d,  $J = 2.0$  Hz), 7.19 (1H, d,  $J = 2.0$  Hz), 7.21 (1H, t,  $J = 6.8$  Hz), 7.24–7.39 (5H, m), 7.42 (2H, t,  $J = 6.8$  Hz), 7.59 (2H, d,  $J = 8.0$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  38.1 ( $\text{CH}_2$ ), 49.6 (CH), 97.2 (Cq), 116.1 (Cq), 123.7 (CH), 125.9 (Cq), 126.0 (CH), 127.7 (CH), 128.1 (CH), 128.4 (CH), 128.54 (CH), 128.58 (CH), 128.62 (CH), 128.64 (CH), 133.76 (Cq), 136.0 (Cq), 138.7 (Cq), 142.2 (Cq), 156.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{17}\text{Cl}_2\text{O}$  [ $\text{M}+\text{H}$ ] $^+$  379.0656, found 379.0650.



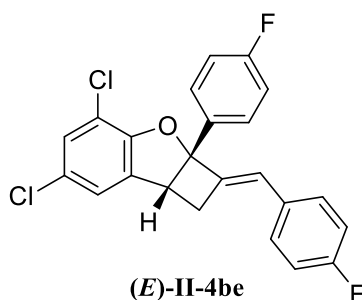
**(2*aS*,7*bR*,*Z*)-2-Benzylidene-4,6-di-*tert*-butyl-2*a*-phenyl-1,2,2*a*,7*b*-tetrahydrocyclobuta[*b*]benzofuran [(*Z*)-II-4af]**

Yellow oil; IR (neat) 2954, 1475, 1232  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.29 (9H, s), 1.31 (9H, s), 2.84 (1H, dt,  $J = 16.0$  and 2.4 Hz), 3.38 (1H, ddd,  $J = 16.0$ , 8.4 and 2.4 Hz), 3.79 (1H, dd,  $J = 8.4$  and 2.4 Hz), 6.38 (1H, t,  $J = 2.8$  Hz), 7.06–7.18 (4H, m), 7.29 (2H, d,  $J = 7.6$  Hz), 7.32–7.38 (4H, m), 7.58 (2H, d,  $J = 7.6$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  29.5 ( $\text{CH}_3$ ), 31.8 ( $\text{CH}_3$ ), 34.3 (Cq), 34.6 (Cq), 37.3 ( $\text{CH}_2$ ), 48.6 (CH), 94.7 (Cq), 119.6 (CH), 122.4 (CH), 125.7 (CH), 126.9 (CH), 127.7 (CH), 127.9 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 130.4 (Cq), 130.9 (Cq), 132.7 (Cq), 135.1 (Cq), 140.1 (Cq), 141.9 (Cq), 143.7 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{35}\text{O}_2$  [ $\text{M}+\text{H}$ ] $^+$  423.2688, found 423.2691.



**(2a*S*,7b*R*,*Z*)-4,6-Dichloro-2-(4-fluorobenzylidene)-2a-(4-fluorophenyl)-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*Z*)-II-4be]**

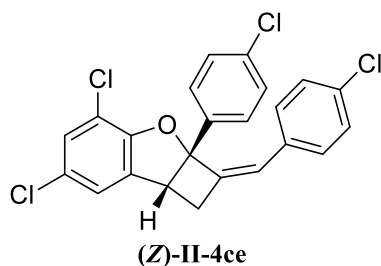
Colorless oil; IR (neat) 3080, 2952, 1602, 1509, 1453  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.83 (1H, dt,  $J = 16.4$  and  $2.4$  Hz), 3.35 (1H, ddd,  $J = 16.4$ ,  $8.4$  and  $2.4$  Hz), 3.85 (1H, dd,  $J = 8.4$  and  $2.4$  Hz), 6.43 (1H, t,  $J = 2.4$  Hz), 6.88 (2H, t,  $J = 8.4$  Hz), 7.00 (2H, d,  $J = 8.4$  Hz), 7.09 (1H, d,  $J = 2.0$  Hz), 7.20 (1H, d,  $J = 2.0$  Hz), 7.37 (2H, dd,  $J = 8.4$  and  $5.2$  Hz), 7.44 (2H, dd,  $J = 8.4$  and  $5.2$  Hz);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  36.8 ( $\text{CH}_2$ ), 48.9 (CH), 95.9 (Cq), 115.1 (CH, d,  $J = 21.0$  Hz), 115.7 (CH, d,  $J = 21.0$  Hz), 116.3 (Cq), 123.7 (CH), 126.2 (Cq), 127.8 (CH, d,  $J = 8.0$  Hz), 128.6 (CH), 129.5 (CH), 130.6 (CH, d,  $J = 8.1$  Hz), 130.7 (Cq, d,  $J = 3.1$  Hz), 133.3 (Cq, d,  $J = 3.1$  Hz), 133.5 (Cq), 138.4 (Cq, d,  $J = 2.5$  Hz), 155.7 (Cq), 162.2 (Cq, d,  $J = 246.6$  Hz), 162.7 (Cq, d,  $J = 245.4$  Hz); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{15}\text{F}_2\text{Cl}_2$   $[\text{M}+\text{H}]^+$  415.0468, found 415.0466.



**(2a*S*,7b*R*,*E*)-4,6-Dichloro-2-(4-fluorobenzylidene)-2a-(4-fluorophenyl)-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*E*)-II-4be]**

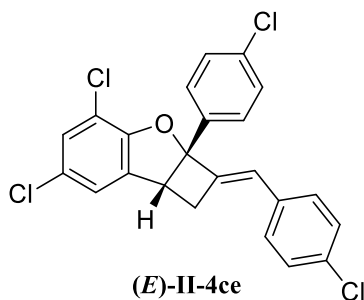
Colorless oil; IR (neat) 2948, 1603, 1508, 1453  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.10 (1H, dt,  $J = 16.8$  and  $2.8$  Hz), 3.56 (1H, ddd,  $J = 16.8$ ,  $8.2$  and  $2.8$  Hz), 4.09 (1H, dd,  $J =$

8.2 and 2.8 Hz), 6.66 (1H, t,  $J = 2.8$  Hz), 6.98–7.13 (5H, m), 7.18–7.25 (3H, m), 7.53–7.58 (2H, m);  $^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  37.7 ( $\text{CH}_2$ ), 49.6 (CH), 96.6 (Cq), 115.4 (CH, d,  $J = 5.0$  Hz), 115.7 (CH, d,  $J = 5.0$  Hz), 116.2 (Cq), 123.7 (CH), 126.1 (Cq), 127.6 (CH), 128.0 (CH, d,  $J = 8.7$  Hz), 128.6 (CH), 129.8 (CH, d,  $J = 8.1$  Hz), 132.0 (Cq), 133.4 (Cq), 134.4 (Cq, d,  $J = 3.1$  Hz), 141.4 (Cq, d,  $J = 2.5$  Hz), 155.9 (Cq), 162.1 (Cq, d,  $J = 246.6$  Hz), 162.8 (Cq, d,  $J = 246.0$  Hz); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{15}\text{Cl}_2\text{F}_2\text{O}$   $[\text{M}+\text{H}]^+$  415.0468, found 415.0473.



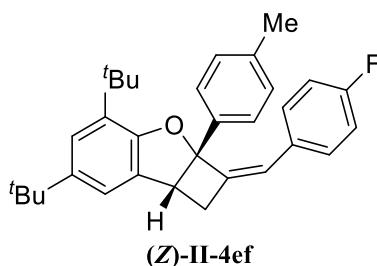
**(2a*S*,7b*R*,*Z*)-4,6-Dichloro-2-(4-chlorobenzylidene)-2a-(4-chlorophenyl)-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*Z*)-II-4ce]**

Colorless oil; IR (neat) 2952, 1580, 1491, 1450  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.85 (1H, dt,  $J = 16.0$  and 2.4 Hz), 3.36 (1H, ddd,  $J = 16.0$ , 8.4 and 2.4 Hz), 3.86 (1H, dd,  $J = 8.4$  and 2.4 Hz), 6.43 (1H, t,  $J = 2.4$  Hz), 7.09 (1H, d,  $J = 1.2$  Hz), 7.17 (2H, d,  $J = 8.4$  Hz), 7.21 (1H, d,  $J = 1.2$  Hz), 7.29 (2H, d,  $J = 8.4$  Hz), 7.32 (2H, d,  $J = 8.4$  Hz), 7.40 (2H, d,  $J = 8.4$  Hz);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  37.0 ( $\text{CH}_2$ ), 49.0 (CH), 95.8 (Cq), 116.4 (Cq), 123.7 (CH), 126.4 (Cq), 127.2 (CH), 128.5 (CH), 128.7 (CH), 129.0 (CH), 129.7 (CH), 130.0 (CH), 132.9 (Cq), 133.3 (Cq), 133.5 (Cq), 134.5 (Cq), 136.0 (Cq), 139.6 (Cq), 155.6 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{15}\text{Cl}_4\text{O}$   $[\text{M}+\text{H}]^+$  446.9877, found 446.9872.



**(2a*S*,7b*R*,*E*)-4,6-Dichloro-2-(4-chlorobenzylidene)-2a-(4-chlorophenyl)-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*E*)-II-4ce]**

Colorless oil; IR (neat) 2924, 1491, 1452  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.13 (1H, dt,  $J = 17.2$  and 2.4 Hz), 3.58 (1H, ddd,  $J = 17.2$ , 8.2 and 2.4 Hz), 4.10 (1H, dd,  $J = 8.2$  and 2.4 Hz), 6.27 (1H, t,  $J = 2.4$  Hz), 7.08 (1H, d,  $J = 1.2$  Hz), 7.18 (2H, d,  $J = 8.4$  Hz), 7.21 (1H, d,  $J = 1.2$  Hz), 7.29 (2H, d,  $J = 8.4$  Hz), 7.39 (2H, d,  $J = 8.4$  Hz), 7.51 (2H, d,  $J = 8.4$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  38.0 (CH<sub>2</sub>), 49.7 (CH), 96.5 (Cq), 116.3 (Cq), 123.7 (CH), 126.2 (Cq), 127.4 (CH), 127.9 (CH), 128.75 (CH), 128.84 (CH), 128.9 (CH), 129.3 (CH), 133.3 (Cq), 133.6 (Cq), 134.2 (Cq), 134.5 (Cq), 137.1 (Cq), 142.6 (Cq), 155.9 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{15}\text{Cl}_4\text{O}$  [ $\text{M}+\text{H}$ ]<sup>+</sup> 446.9877, found 446.9872.



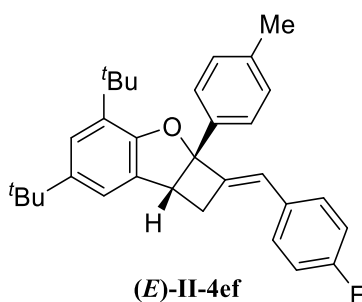
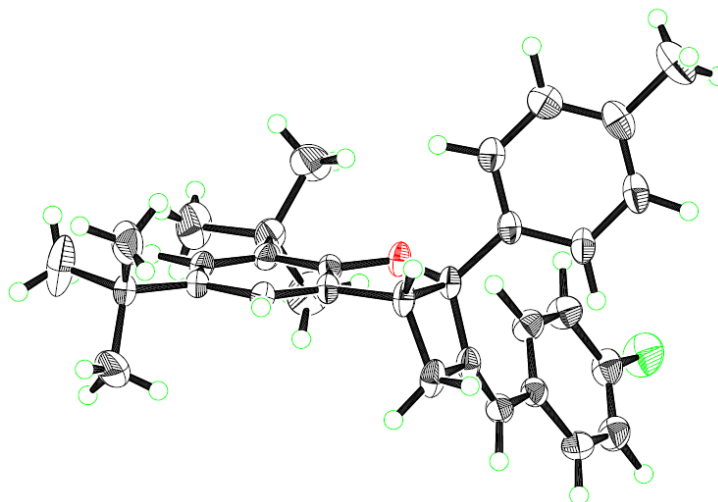
**(2a*S*,7b*R*,*Z*)-4,6-Di-*tert*-butyl-2-(4-fluorobenzylidene)-2a-(*p*-tolyl)-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*Z*)-II-4ef]**

Colorless plates (AcOEt–hexane, mp. 192.5–192.7 °C); IR (neat) 2955, 1509, 1231  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.28 (9H, s), 1.31 (9H, s), 2.34 (3H, s), 2.80 (1H, dt,  $J = 16.0$  and 2.4 Hz), 3.34 (1H, ddd,  $J = 16.0$ , 8.2 and 2.4 Hz), 3.75 (1H, dd,  $J = 8.2$  and 2.4 Hz), 6.32 (1H, t,  $J = 2.4$  Hz), 6.84 (2H, t,  $J = 8.0$  Hz), 7.10 (1H, d,  $J = 1.6$  Hz), 7.15 (2H,

d,  $J = 3.6$  Hz), 7.17 (1H, d,  $J = 1.6$  Hz), 7.33 (2H, dd,  $J = 8.0$  and  $3.6$  Hz), 7.44 (2H, d,  $J = 8.0$  Hz);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.2 ( $\text{CH}_3$ ), 29.5 ( $\text{CH}_3$ ), 31.8 ( $\text{CH}_3$ ), 34.3 (Cq), 34.6 (Cq), 37.2 ( $\text{CH}_2$ ), 48.6 (CH), 94.6 (Cq), 114.8 (CH, d,  $J = 20.7$  Hz), 119.6 (CH), 122.4 (CH), 125.7 (CH), 127.7 (CH), 129.4 (CH), 130.40 (CH, d,  $J = 7.4$  Hz), 130.40 (Cq), 131.50 (Cq), 132.7 (Cq), 137.0 (Cq), 137.6 (Cq), 141.66 (Cq, d,  $J = 1.7$  Hz), 143.7 (Cq), 156.5 (Cq), 161.8 (Cq, d,  $J = 244.5$  Hz); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{35}\text{FNaO}$   $[\text{M}+\text{Na}]^+$  477.2570, found 477.2563.

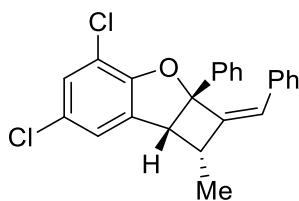
**X-Ray crystallographic analysis of compound (Z)-II-4ef.** A colorless block crystal having approximate dimensions of 0.80 x 0.40 x 0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-K $\alpha$  radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on  $F$  was based on 6046 observed reflections ( $I > 0.00\sigma(I)$ ) and 342 variable parameters, and converged (largest parameter shift was 0.22 times its esd) with unweighted and weighted agreement factors of  $R = 0.078$  and  $R_w = 0.157$ . Crystal data for (Z)-II-4ef:  $\text{C}_{32}\text{H}_{35}\text{FO}$ ,  $M = 454.63$ , triclinic, space group P1,  $a = 10.976(1)$  Å,  $b = 11.126(1)$  Å,  $c = 12.110(1)$  Å,  $\alpha = 65.261(3)^\circ$ ,  $\beta = 86.075(3)^\circ$ ,  $\gamma = 89.777(4)^\circ$ ,  $V = 1339.5(2)$  Å $^3$ ,  $Z = 2$ ,  $D_c = 1.127$  g/cm $^3$ ,  $F(000) = 488$ ,  $\mu(\text{MoK}\alpha) = 0.71$  cm $^{-1}$ .

**Figure E-3.** ORTEP drawing of (*Z*)-II-4ef.



**(2*aS*,7*bR*,*E*)-4,6-Di-*tert*-butyl-2-(4-florobenzylidene)-2*a*-(*p*-tolyl)-1,2,2*a*,7*b*-tetrahydrocyclobuta[*b*]benzofuran [(*E*)-II-4ef]**

Colorless oil; IR (neat) 2956, 1603, 1508, 1231  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (9H, s), 1.42 (9H, s), 2.37 (3H, s), 3.05 (1H, dt,  $J = 16.8$  and 2.4 Hz), 3.54 (1H, ddd,  $J = 16.8, 8.0$  and 2.4 Hz), 4.00 (1H, dd,  $J = 8.0$  and 2.4 Hz), 6.57 (1H, t,  $J = 2.4$  Hz), 6.98 (2H, t,  $J = 8.8$  Hz), 7.09 (1H, s), 7.16 (1H, s), 7.19–7.24 (4H, m), 7.50 (2H, d,  $J = 8.0$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  29.4 ( $\text{CH}_3 \times 2$ ), 31.8 ( $\text{CH}_3$ ), 34.4 (Cq), 34.5 (Cq), 38.1 ( $\text{CH}_2$ ), 49.1 (CH), 100.6 (Cq), 115.4 (CH, d,  $J = 21.5$  Hz), 119.5 (CH), 122.3 (CH), 125.8 (CH), 125.9 (CH), 129.1 (CH), 129.4 (CH, d,  $J = 8.3$  Hz), 130.6 (Cq), 130.7 (Cq), 132.5 (Cq), 137.5 (Cq), 143.6 (Cq), 145.2 (Cq), 147.5 (Cq), 154.7 (Cq), 156.6 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{32}\text{H}_{36}\text{FO}$   $[\text{M}+\text{H}]^+$  455.2750, found 455.2750.



(1 $\alpha$ , Z)-II-4ah

**(1R,2aR,7bR,Z)-2-Benzylidene-4,6-dichloro-1-methyl-2a-phenyl-1,2,2a,7b-tetrahydrocyclobuta[b]benzofuran [(1 $\alpha$ ,Z)-II-4ah]**

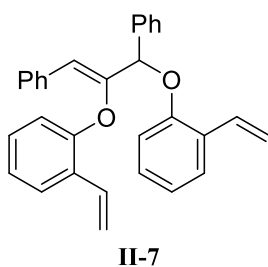
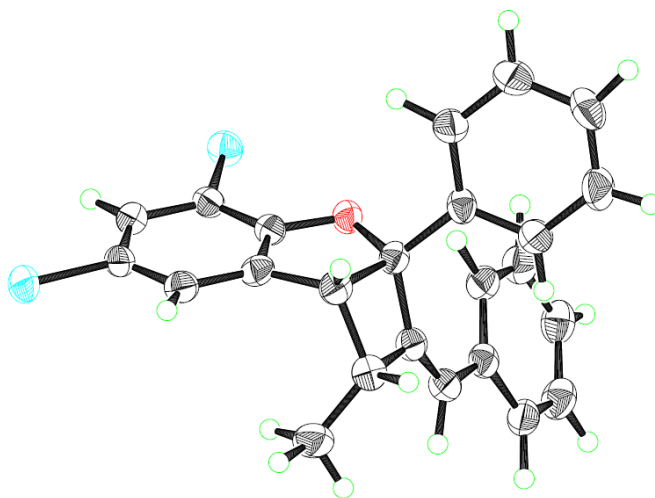
Colorless plates (AcOEt–hexane, mp. 140.0–140.5 °C); IR (neat) 2961, 1578, 1452 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.15 (3H, d,  $J$  = 6.8 Hz), 3.54 (1H, dq,  $J$  = 2.8 and 6.8 Hz), 3.99 (1H, d,  $J$  = 6.8 Hz), 6.38 (1H, d,  $J$  = 2.8 Hz), 7.01 (1H, d,  $J$  = 1.2 Hz), 7.11–7.25 (4H, m), 7.32–7.40 (3H, m), 7.45 (2H, d,  $J$  = 7.2 Hz), 7.51 (2H, dd,  $J$  = 7.8 and 1.2 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  13.8 (CH<sub>3</sub>), 40.0 (CH), 54.3 (CH), 95.4 (Cq), 116.7 (Cq), 125.0 (CH), 125.6 (Cq), 126.2 (CH), 127.4 (CH), 127.8 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 129.7 (Cq), 134.6 (Cq), 137.8 (Cq), 145.4 (Cq), 156.3 (Cq); HRMS (ESI)  $m/z$  calcd for C<sub>24</sub>H<sub>18</sub>Cl<sub>2</sub>NaO [M+Na]<sup>+</sup> 415.0632, found 415.0618.

**X-Ray crystallographic analysis of compound (1 $\alpha$ ,Z)-II-4ah.** A colorless platelet crystal having approximate dimensions of 0.50 x 0.40 x 0.10 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-K $\alpha$  radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 3745 observed reflections ( $I > 0.00\sigma(I)$ ) and 262 variable parameters, and converged (largest parameter shift was 0.07 times its esd) with unweighted and weighted agreement factors of  $R = 0.041$



and  $R_w = 0.057$ . Crystal data for **(1 $\alpha$ ,Z)-II-4ah**:  $C_{24}H_{18}Cl_2O$ ,  $M = 393.31$ , monoclinic, space group  $Cc$ ,  $a = 13.6140(9) \text{ \AA}$ ,  $b = 16.9487(9) \text{ \AA}$ ,  $c = 8.4595(5) \text{ \AA}$ ,  $\beta = 96.490(2)^\circ$ ,  $V = 1939.4(2) \text{ \AA}^3$ ,  $Z = 4$ ,  $D_c = 1.347 \text{ g/cm}^3$ ,  $F(000) = 816$ ,  $\mu(\text{MoK}\alpha) = 3.45 \text{ cm}^{-1}$ .

**Figure E-4.** ORTEP drawing of **(1 $\alpha$ ,Z)-II-4ah**.

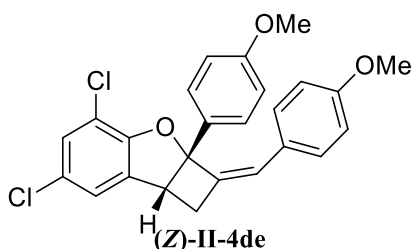


**(E)-2-Propen-1,2-di-2'-vinylphenoxy-1,3-diyldibenzene (II-7)**

Colorless oil; IR (neat) 3061, 3027, 1482, 1230  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.17 (1H, dd,  $J = 11.2$  and  $1.2$  Hz), 5.25 (1H, dd,  $J = 11.2$  and  $1.2$  Hz), 5.67 (1H, s), 5.68 (1H, dd,  $J = 17.2$  and  $1.2$  Hz), 5.72 (1H, dd,  $J = 17.2$  and  $1.2$  Hz), 6.52 (1H, s), 6.67 (1H, d,  $J = 8.0$  Hz), 6.87 (2H, t,  $J = 8.0$  Hz), 6.92 (1H, dd,  $J = 8.0$  and  $1.2$  Hz), 6.99 (2H, t,  $J = 8.0$  Hz), 7.04 (1H, dd,  $J = 8.0$  and  $1.2$  Hz), 7.06–7.10 (1H, m), 7.15 (1H, t,  $J = 8.0$  Hz), 7.18–7.23 (2H, m), 7.27–7.35 (3H, m), 7.39 (2H, dd,  $J = 6.0$  and  $1.2$  Hz), 7.46 (1H, dd,  $J = 8.0$  and  $1.2$  Hz), 7.48–7.52 (3H, m);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  79.5 (CH), 114.1 (CH), 114.4

(CH<sub>2</sub>), 114.9 (CH<sub>2</sub>), 115.7 (CH), 117.0 (CH), 121.4 (CH), 122.7 (CH), 126.4 (CH), 126.7 (CH), 127.3 (CH), 127.5 (CH), 127.78 (Cq), 127.83 (Cq), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.9 (CH), 131.0 (CH), 131.7 (CH), 133.9 (Cq), 138.4 (Cq), 150.2 (Cq), 152.4 (Cq), 154.5 (Cq); HRMS (ESI) *m/z* calcd for C<sub>31</sub>H<sub>27</sub>O<sub>2</sub> [M+H]<sup>+</sup> 431.2011, found 431.2014.

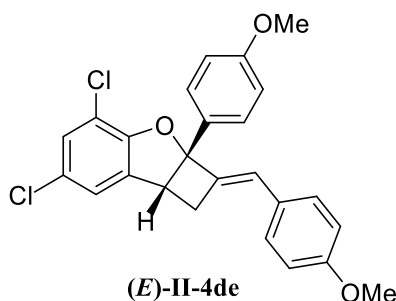
**Synthesis of II-4de (Table II-3, entry 3).** To a stirred solution of propargyl acetate **II-1d** (90 mg, 289 μmol), vinylphenol **II-2e** (49 mg, 259 μmol) and K<sub>3</sub>PO<sub>4</sub> (110 mg, 517 μmol) in dioxane (2.6 mL) were added Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (13 mg, 13 μmol) and P(2-furyl)<sub>3</sub> (12 mg, 51 μmol) at rt, and stirring was continued for 30 min at the same temperature under argon atmosphere. The reaction mixture was then allowed to heat to 100 °C, and stirred for 1 h. After filtration of the reaction mixture using small amount of silica gel followed by concentration, the residue was chromatographed on silica gel with hexane-AcOEt (99:1 v/v) as eluent to give (**Z**)-**II-4de** and (**E**)-**II-4de** (81 mg, 10 : 1, 72% total yield).



**(2a*S*,7b*R*,*Z*)-4,6-Dichloro-2-(4-methoxybenzylidene)-2a-(4-methoxyphenyl)-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*Z*)-II-4de]**

Colorless powders (CH<sub>2</sub>Cl<sub>2</sub>–hexane, mp. 125.3–126.5 °C); IR (neat) 2954, 2836, 1669, 1607, 1513 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 2.77 (1H, dt, *J* = 16.0 and 2.4 Hz), 3.29 (1H, ddd, *J* = 16.0, 8.4 and 2.4 Hz), 3.72 (3H, s), 3.76 (3H, s), 3.81 (1H, dd, *J* = 8.4 and 2.4 Hz), 6.37 (1H, t, *J* = 2.4 Hz), 6.73 (2H, d, *J* = 8.8 Hz), 6.84 (2H, d, *J* = 8.8 Hz), 7.07 (1H, d, *J* = 2.0 Hz), 7.18 (2H, d, *J* = 2.0 Hz), 7.37 (2H, d, *J* = 8.8 Hz), 7.41 (2H, d, *J* = 8.8 Hz);

<sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) for mixture of rotamers: δ 48.2 (CH<sub>2</sub>x2), 49.46 (CH), 49.49 (CH), 55.7 (CH<sub>3</sub>x2), 55.8 (CH<sub>3</sub>x2), 96.5 (Cq), 96.6 (Cq), 113.0 (CH), 113.5 (CH), 114.2 (CH), 114.6 (CH), 116.2 (Cqx2), 123.4 (CH), 125.7 (CH), 127.38 (CH), 127.40 (CH), 127.7 (Cqx2), 127.8 (CH), 128.2 (CH), 128.5 (CH), 129.21 (Cqx2), 129.22 (CH), 129.72 (Cq), 129.74 (Cq), 130.2 (CH), 130.5 (CH), 134.0 (Cqx2), 136.29 (Cq), 136.34 (Cq), 155.92 (Cq), 155.95 (Cq), 158.96 (Cq), 158.99 (Cq) 159.70 (Cq), 159.72 (Cq); HRMS (ESI) *m/z* calcd for C<sub>25</sub>H<sub>21</sub>Cl<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup> 439.0868, found 439.0861.

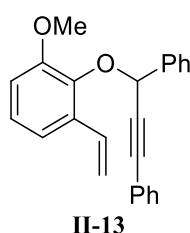


**(2a*S*,7b*R*,*E*)-4,6-Dichloro-2-(4-methoxybenzylidene)-2a-(4-methoxyphenyl)-1,2,2a,7b-tetrahydrocyclobuta[*b*]benzofuran [(*E*)-II-4de]**

Colorless oil; IR (neat) 2932, 1606, 1511, 1452 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 3.07 (1H, dt, *J* = 16.4 and 2.8 Hz), 3.53 (1H, ddd, *J* = 16.4, 8.2 and 2.8 Hz), 3.80 (3H, s), 3.82 (3H, s), 4.06 (1H, dd, *J* = 8.2 and 2.8 Hz), 6.66 (1H, t, *J* = 2.8 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 6.93 (2H, d, *J* = 8.4 Hz), 7.07 (1H, d, *J* = 2.4 Hz), 7.18 (1H, d, *J* = 2.4 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 7.51 (2H, d, *J* = 8.4 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 37.7 (CH<sub>2</sub>), 49.6 (CH), 55.30 (CH<sub>3</sub>), 55.35 (CH<sub>3</sub>), 97.2 (Cq), 113.9 (CH), 114.0 (CH), 116.0 (Cq), 123.7 (CH), 125.6 (Cq), 127.6 (CH), 127.9 (CH), 128.4 (CH), 129.0 (CH), 129.4 (CH), 130.9 (Cq), 134.0 (Cq), 139.6 (Cq), 156.2 (Cq), 159.1 (Cq), 159.7 (Cq); HRMS (ESI) *m/z* calcd for C<sub>25</sub>H<sub>20</sub>Cl<sub>2</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup> 461.0687, found 461.0696.

**Synthesis of II-13 (Scheme II-6).** To a stirred solution of vinylphenol **II-2a** (82 mg, 552

$\mu\text{mol}$ ), propargyl alcohol **II-5a** (96 mg, 460  $\mu\text{mol}$ ),  $\text{Et}_3\text{N}$  (13  $\mu\text{L}$ , 92  $\mu\text{mol}$ ) in THF (7.5 mL) were added diisopropyl azodicarboxylate (0.11 mL, 552  $\mu\text{mol}$ ) in THF (4 mL) at 0 °C, and stirring was continued for 22 h at rt under argon atmosphere. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and then filtered a pad of basic alumina and concentrated. The residue was chromatographed on silica gel with hexane-AcOEt (99:1 v/v) as eluent to give 7:1 mixture of (**Z**)-**II-4aa** and **II-13** (48 mg, 30% total yields) as a colorless oil.

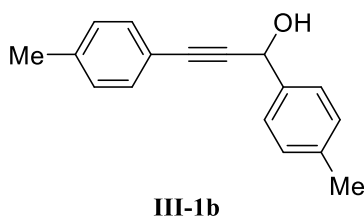


### 2-(1,3-Diphenyl-2-propynyloxy)-1-methoxy-3-vinylbenzene (**II-13**)

Colorless oil; IR (neat) 3063, 2224, 1688, 1575  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.90 (3H, s), 5.22 (1H, d,  $J = 11.2$  Hz), 5.70 (1H, d,  $J = 17.6$  Hz), 6.21 (1H, s), 6.87 (1H, d,  $J = 8.0$  Hz), 7.07 (1H, t,  $J = 8.0$  Hz), 7.19 (1H, d,  $J = 8.0$  Hz), 7.26–7.31 (3H, m), 7.31–7.46 (5H, m), 7.76 (2H, d,  $J = 6.8$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  55.8 ( $\text{CH}_3$ ), 73.9 (CH), 87.0 (Cq), 88.2 (Cq), 111.4 (CH), 114.2 ( $\text{CH}_2$ ), 117.4 (CH), 122.6 (Cq), 124.4 (CH), 127.8 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 131.5 (CH), 132.2 (CH), 133.3 (Cq), 138.4 (Cq), 143.7 (Cq), 153.1 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{20}\text{NaO}_2$  [ $\text{M}+\text{Na}$ ] $^+$  363.1361, found 363.1365.

## Experiments in Chapter III

**Preparation of propargyl alcohol of III-1b.** To a stirred solution of *p*-iodotoluene (952 mg, 4.37 mmol) in Et<sub>3</sub>N (4.9 mL) and THF (7.3 mL) were added 1-(*p*-tolyl)-2-propyn-1-ol<sup>38)</sup> (319 mg, 2.18 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (31 mg, 44 μmol) and CuI (17 mg, 87 μmol) at 0 °C, and stirring was continued for 18 h at rt. The reaction mixture was diluted with aqueous NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O. The combined extracts were washed with aqueous NH<sub>4</sub>Cl and brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (88:12 v/v) as eluent to give propargyl alcohol **III-1b** (368 mg, 71%) as gray needles.

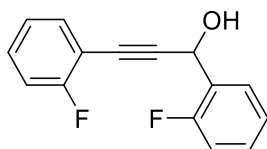


### 1,3-Di-*p*-tolyl-2-propyn-1-ol (III-1b)

Yield 71%; gray needles (Et<sub>2</sub>O–hexane, mp. 65.0–66.9 °C); IR (neat) 3357, 3027, 2920, 2227, 1509, 816 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 2.19 (1H, d, *J* = 6.0 Hz), 2.35 (3H, s), 2.37 (3H, s), 5.65 (1H, d, *J* = 6.0 Hz), 7.12 (2H, d, *J* = 8.0 Hz), 7.21 (2H, d, *J* = 8.0 Hz), 7.36 (2H, d, *J* = 8.0 Hz), 7.50 (2H, d, *J* = 8.0 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 21.2 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 65.0 (CH), 86.6 (Cq), 119.4 (Cq), 126.7 (CH), 129.0 (CH), 129.3 (CH), 133.6 (CH), 137.9 (Cq), 138.0 (Cq), 138.2 (Cq), 138.7 (Cq); HRMS (ESI) *m/z* calcd for C<sub>17</sub>H<sub>17</sub>O [M+H]<sup>+</sup> 237.1279, found 237.1287.

**Preparation of propargyl alcohol of III-1c.** To a stirred solution of 1-ethynyl 2-fluorobenzene (1.1 mL, 9.67 mmol) in THF (8 mL) were added *n*-BuLi (2.65 M in hexane,

3.6 mL) at  $-78\text{ }^{\circ}\text{C}$ , and stirring continued for 15 min at  $0\text{ }^{\circ}\text{C}$ . After the reaction mixture was cooled to  $-78\text{ }^{\circ}\text{C}$ , 2-fluorobenzaldehyde (0.84 mL, 8.06 mmol) in THF (8 mL) was added dropwise, and stirring was continued for 30 min at the same temperature. The reaction mixture was then warmed to  $0\text{ }^{\circ}\text{C}$ , and further stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with aqueous  $\text{NH}_4\text{Cl}$  and extracted with AcOEt. The combined extracts were washed with brine. The residue upon workup was chromatographed on silica gel with hexane-AcOEt (88:12 v/v) as eluent to give propargyl alcohol **III-1c** (2.12 g, quantitative yield) as a colorless oil.



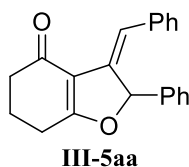
**III-1c**

### **1,3-Bis(2-fluorophenyl)-2-propyn-1-ol (III-1c)**

Quantitative yield; colorless oil; IR (neat) 3357, 2236, 1492, 755  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.61 (1H, d,  $J = 6.4$  Hz), 6.00 (1H, d,  $J = 6.4$  Hz), 7.03–7.12 (3H, m), 7.20 (1H, t,  $J = 7.6$  Hz), 7.28–7.36 (2H, m), 7.45 (1H, dt,  $J = 1.6$  and 7.6 Hz), 7.76 (1H, dt,  $J = 1.6$  and 7.6 Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  59.6 (CH, d,  $J = 4.9$  Hz), 80.0 (Cq), 92.7 (Cq, d,  $J = 4.1$  Hz), 110.8 (Cq, d,  $J = 14.9$  Hz), 115.5 (CH, d,  $J = 14.1$  Hz), 115.7 (CH, d,  $J = 14.0$  Hz), 123.9 (CH, d,  $J = 4.1$  Hz), 124.4 (CH, d,  $J = 3.3$  Hz), 127.5 (Cq, d,  $J = 13.2$  Hz), 128.5 (CH, d,  $J = 3.3$  Hz), 130.3 (CH, d,  $J = 8.3$  Hz), 130.5 (CH, d,  $J = 8.2$  Hz), 133.6 (Cq, d,  $J = 1.7$  Hz), 160.3 (Cq, d,  $J = 246.9$  Hz), 162.9 (Cq, d,  $J = 251.1$  Hz); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{11}\text{F}_2\text{O}$   $[\text{M}+\text{H}]^+$  245.0778, found 245.0777.

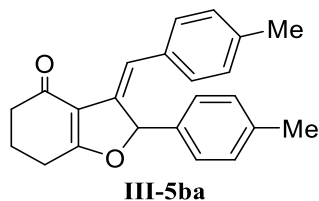
**General procedure for the reaction of propargyl alcohols III-1 with  $\beta$ -ketoesters III-2 using palladium catalyst.**

**Synthesis of III-5aa (Table III-3, entry 6).** To a stirred solution of Pd(OAc)<sub>2</sub> (5.8 mg, 26 μmol) and BINAP (32 mg, 51 μmol) in dioxane (1.0 mL) were heated to 100 °C, and stirring was continued for 5 min. After the resulting solution was cooled to rt, propargyl alcohol **III-1a** (54 mg, 257 μmol), 1,3-cyclohexanedione (**III-2a**) (35 mg, 308 μmol) and boric acid (3.2 mg, 51 μmol) in dioxane (1.6 mL) were added. The reaction mixture was then allowed to heat to 100 °C, and stirring was continued for 2 h. After filtration of the reaction mixture using small amount of silica gel followed by concentration, the residue was chromatographed on silica gel with hexane-AcOEt (80:20 v/v) as eluent to give **III-5aa** (66 mg, 84% yield).



**(Z)-3-Benzylidene-2-phenyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (III-5aa)**

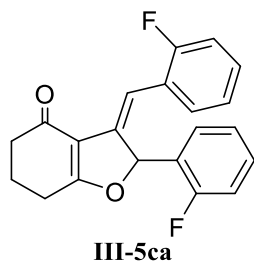
Yield 84%; colorless plates (AcOEt, mp. 179.7–190.0 °C); IR (neat) 2951, 1651, 1631 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 2.10 (2H, tt, *J* = 6.4 and 6.4 Hz), 2.50 (2H, t, *J* = 6.4 Hz), 2.56 (2H, dt, *J* = 1.6 and 6.4 Hz), 6.56 (1H, d, *J* = 2.8 Hz), 7.00–7.08 (3H, m), 7.09–7.14 (2H, m), 7.29–7.33 (3H, m), 7.38–7.42 (2H, m), 7.67 (1H, d, *J* = 2.8 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 21.3 (CH<sub>2</sub>), 24.7 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 89.0 (CH), 115.4 (Cq), 120.2 (CH), 126.1 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.8 (CH), 129.2 (CH), 135.0 (Cq), 136.1 (Cq), 136.7 (Cq), 180.5 (Cq), 194.2 (Cq); HRMS (ESI) *m/z* calcd for C<sub>21</sub>H<sub>18</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup> 325.1204, found 325.1208.



**(Z)-3-(4-Methylbenzylidene)-2-(*p*-tolyl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one**

**(III-5ba)**

Yield 81%; colorless plates (AcOEt–hexane, mp. 145.8–151.0 °C); IR (neat) 2948, 1653, 1599  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.08 (2H, quint,  $J = 6.4$  Hz), 2.22 (3H, s), 2.31 (3H, s), 2.48 (2H, t,  $J = 6.4$  Hz), 2.54 (2H, t,  $J = 6.4$  Hz), 6.51 (1H, d,  $J = 2.8$  Hz), 6.94 (2H, d,  $J = 8.4$  Hz), 6.98 (2H, d,  $J = 8.4$  Hz), 7.13 (2H, d,  $J = 8.0$  Hz), 7.31 (2H, d,  $J = 8.0$  Hz), 7.63 (1H, d,  $J = 2.8$  Hz);  $^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  21.0 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 21.3 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ), 37.7 ( $\text{CH}_2$ ), 88.9 (CH), 115.4 (Cq), 120.1 (CH), 128.0 (CH), 128.2 (CH), 128.8 (CH), 129.6 (CH), 133.3 (Cq), 133.9 (Cqx2), 135.9 (Cq), 139.1 (Cq), 180.2 (Cq), 194.3 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{22}\text{NaO}_2$   $[\text{M}+\text{Na}]^+$  353.1517, found 353.1518.

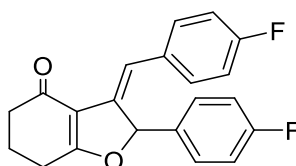


**(Z)-3-(2-Fluorobenzylidene)-2-(2-fluorophenyl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (III-5ca)**

Yield 85%; colorless needles (AcOEt–hexane, mp. 113.5–135.8 °C); IR (neat) 2951, 1659, 1600  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.13 (2H, quint,  $J = 6.4$  Hz), 2.52 (2H, t,  $J = 6.4$  Hz), 2.60 (2H, q, 6.4 Hz), 6.79 (1H, d,  $J = 2.8$  Hz), 6.80–6.87 (2H, m), 6.90–7.02 (4H, m), 7.12–7.23 (2H, m), 7.60 (1H, d,  $J = 2.8$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3 ( $\text{CH}_2$ ), 24.7 ( $\text{CH}_2$ ), 37.6 ( $\text{CH}_2$ ), 82.8 (CH, dd,  $J = 5.8$  and 3.3 Hz), 112.2 (CH, d,  $J = 3.3$  Hz), 115.08



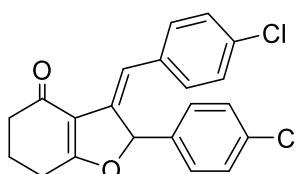
(Cq), 115.13 (CH, d,  $J = 22.3$  Hz), 115.3 (CH, d,  $J = 21.5$  Hz), 123.1 (Cq, d,  $J = 14.0$  Hz), 123.4 (CH, d,  $J = 3.3$  Hz), 124.2 (CH, d,  $J = 3.3$  Hz), 124.6 (Cq, d,  $J = 14.0$  Hz), 128.0 (CH, d,  $J = 8.3$  Hz), 128.8 (CH, d,  $J = 4.1$  Hz), 129.2 (CH, d,  $J = 3.3$  Hz), 131.0 (CH, d,  $J = 8.3$  Hz), 137.7 (Cq), 159.5 (Cq, d,  $J = 247$  Hz), 161.1 (Cq, d,  $J = 249$  Hz), 181.7 (Cq), 194.0 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{21}H_{16}F_2NaO_2$   $[M+Na]^+$  361.1016, found 361.1012.



III-5da

**(Z)-3-(4-Fluorobenzylidene)-2-(4-fluorophenyl)-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (III-5da)**

Yield 62%; colorless oil; IR (neat) 2951, 1654, 1605, 1508  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  2.11 (2H, tt,  $J = 6.4$  and 6.4 Hz), 2.50 (2H, t,  $J = 6.4$  Hz), 2.57 (2H, dt,  $J = 3.2$  and 6.4 Hz), 6.50 (1H, d,  $J = 2.8$  Hz), 6.81 (2H, t,  $J = 8.4$  Hz), 6.95–7.15 (4H, m), 7.35 (2H, dd,  $J = 5.2$  and 8.4 Hz), 7.62 (1H, d,  $J = 2.8$  Hz);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  21.3 (CH<sub>2</sub>), 24.7 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 89.0 (CH), 115.0 (CH, d,  $J = 21.5$  Hz), 115.8 (CH, d,  $J = 21.4$  Hz), 119.2 (CH), 129.7 (CH, d,  $J = 8.3$  Hz), 130.1 (CH, d,  $J = 9.1$  Hz), 131.8 (Cq, d,  $J = 3.3$  Hz), 132.8 (Cq, d,  $J = 3.3$  Hz), 134.86 (Cq), 134.87 (Cq), 160.9 (Cq, d,  $J = 192$  Hz), 163.3 (Cq, d,  $J = 193$  Hz), 180.5 (Cq), 194.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{21}H_{17}F_2O_2$   $[M+H]^+$  339.1197, found 339.1191.



III-5ea

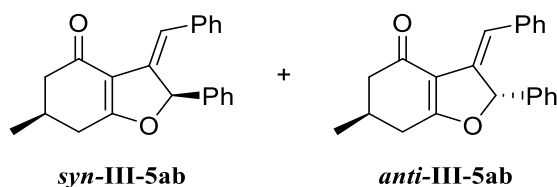
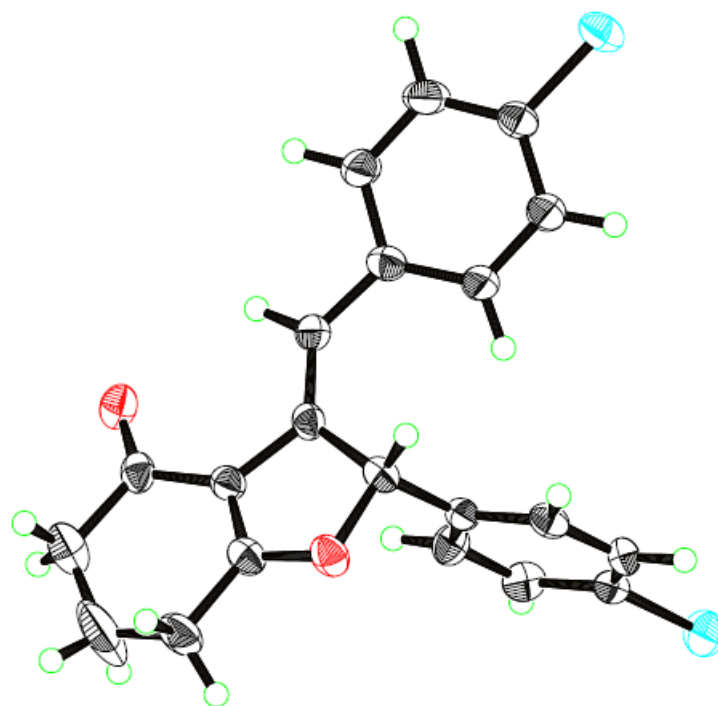
**(Z)-3-(4-Chlorobenzylidene)-2-(4-chlorophenyl)-3,5,6,7-tetrahydrobenzofuran-**

#### 4(2*H*)-one (III-5ea)

Yield 84%; colorless plates (acetone, mp. 168.0–169.7 °C); IR (neat) 2949, 1654, 1603  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.10 (2H, tt,  $J = 6.6$  and  $6.6$  Hz), 2.50 (2H, t,  $J = 6.6$  Hz), 2.56 (2H, dt,  $J = 2.4$  and  $6.4$  Hz), 6.50 (1H, d,  $J = 3.0$  Hz), 6.96 (2H, d,  $J = 8.4$  Hz), 7.10 (2H, d,  $J = 8.4$  Hz), 7.28–7.32 (4H, m), 7.61 (1H, d,  $J = 3.0$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3 ( $\text{CH}_2$ ), 24.7 ( $\text{CH}_2$ ), 37.6 ( $\text{CH}_2$ ), 87.9 (CH), 115.2 (Cq), 119.1 (CH), 128.3 (CH), 129.2 (CH), 129.3 (CH), 129.5 (CH), 132.0 (Cq), 134.1 (Cq), 135.0 (Cq), 135.3 (Cq), 135.4 (Cq), 180.7 (Cq), 194.2 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  371.0606, found 371.0608.

**X-Ray crystallographic analysis of compound III-5ea.** A colorless block crystal having approximate dimensions of 0.60 x 0.40 x 0.30 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-K $\alpha$  radiation. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF99). The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 16691 observed reflections ( $I > 0.00\sigma(I)$ ) and 243 variable parameters, and converged (largest parameter shift was 0.50 times its esd) with unweighted and weighted agreement factors of  $R = 0.065$  and  $R_w = 0.180$ . Crystal data for **III-5ea**:  $\text{C}_{21}\text{H}_{16}\text{O}_2\text{Cl}_2$ ,  $M = 371.26$ , monoclinic, space group  $\text{P}2_1/c$  (#14),  $a = 12.0101(5)$  Å,  $b = 9.0739(3)$  Å,  $c = 17.4689(7)$  Å,  $\beta = 110.131(1)^\circ$ ,  $V = 1787.4(1)$  Å $^3$ ,  $Z = 4$ ,  $D_c = 1.380$  g/cm $^3$ ,  $F(000) = 768$ ,  $\mu(\text{MoK}\alpha) = 3.74$  cm $^{-1}$ .

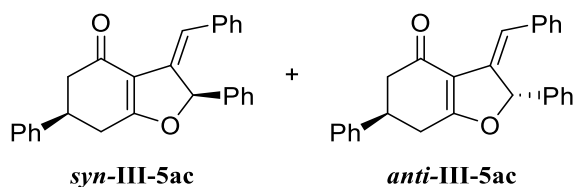
**Figure E-5.** ORTEP drawing of (*Z*)-**III-5ea**.



**(2*R*,6*R*)- and (2*R*,6*S*)-3- (*Z*)-Benzylidene-6-methyl-2-phenyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (*syn*-**III-5ab** and *anti*-**III-5ab**)**

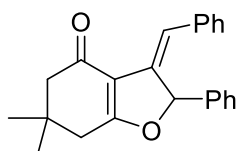
Yield 82%; colorless needles (AcOEt–hexane, mp. 146.6–167.2 °C) 1:1 mixture of diastereomers; IR (neat) 2953, 1652, 1602  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) for 1 : 1 mixture of diastereomers:  $\delta$  1.13 (1.5H, s), 1.15 (1.5H, s), 2.20–2.32 (2H, m), 2.32–2.44 (1H, m), 2.54 (1H, dt,  $J = 16.4$  and 3.2 Hz), 2.61 (1H, dt,  $J = 17.6$  and 4.0 Hz), 6.57 (1H, d,  $J = 2.8$  Hz), 7.00–7.08 (3H, m), 7.08–7.14 (2H, m), 7.29–7.33 (3H, m), 7.37–7.42 (2H, m), 7.64 (0.5H, d,  $J = 2.8$  Hz), 7.66 (0.5H, d,  $J = 2.8$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ) for mixture of diastereomers:  $\delta$  20.88 ( $\text{CH}_3$ ), 20.91 ( $\text{CH}_3$ ), 29.3 (CH), 29.5 (CH), 32.6 ( $\text{CH}_2$ ), 32.7 ( $\text{CH}_2$ ), 46.20( $\text{CH}_2$ ), 46.22 ( $\text{CH}_2$ ), 89.35 (CH), 89.38 (CH), 115.0 (Cq), 115.1 (Cq), 120.0 (CH), 120.2 (CH), 126.1 ( $\text{CH}_2$ ), 128.01 ( $\text{CH}_2$ ), 128.08 (CH), 128.15 (CH), 128.20

(CH), 128.22 (CH), 128.8 (CH<sub>x2</sub>), 129.2 (CH<sub>x2</sub>), 135.0 (C<sub>qx2</sub>), 136.1 (C<sub>qx2</sub>), 136.7 (C<sub>qx2</sub>), 180.2 (C<sub>qx2</sub>), 193.8 (C<sub>qx2</sub>); HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>21</sub>O<sub>2</sub> [M+H]<sup>+</sup> 317.1542, found 317.1546.



**(2*R*,6*R*)- and (2*R*,6*S*)-3-(*Z*)-Benzylidene-2,6-diphenyl-3,5,6,7-tetrahydrobenzofuran-4(2*H*)-one (*syn*-III-5ac and *anti*-III-5ac)**

Yield 80%; colorless needles (acetone–AcOEt, mp. 171.0–184.1 °C); mixture of diastereomers; IR (neat) 3029, 1654, 1605 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) for 3 : 1 mixture of diastereomers: δ 2.74–2.84 (4H, m), 3.94 (1H, tt, *J* = 8.0 and 8.0 Hz), 6.62 (1H, d, *J* = 2.8 Hz), 7.01–7.09 (3H, m), 7.09–7.16 (2H, m), 7.24–7.30 (3H, m), 7.30–7.38 (5H, m), 7.38–7.42 (0.5H, m), 7.42–7.46 (1.5H, m), 7.68 (0.25H, d, *J* = 2.8 Hz), 7.71 (0.75H, d, *J* = 2.8 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) for mixture of diastereomers: δ 32.2 (CH<sub>2</sub>), 32.3 (CH<sub>2</sub>), 39.8 (CH), 40.1 (CH), 45.0 (CH<sub>2</sub>), 45.3 (CH<sub>2</sub>), 89.7 (CH), 89.8 (CH), 115.4(C<sub>q</sub>), 115.5 (C<sub>q</sub>), 120.5 (CH), 120.8 (CH), 126.32 (CH), 126.33 (CH), 126.69 (CH), 126.72 (CH), 127.2 (CH), 128.1 (CH), 128.2 (CH), 128.28 (CH), 128.31 (CH), 128.4 (CH), 128.85 (CH), 128.88 (CH), 128.91 (CH), 128.93 (CH), 129.31 (CH), 129.32 (CH), 134.67 (C<sub>q</sub>), 134.73 (C<sub>q</sub>), 136.06 (C<sub>q</sub>), 136.07 (C<sub>q</sub>), 136.63 (C<sub>q</sub>), 136.66 (C<sub>q</sub>), 142.2 (C<sub>q</sub>), 142.3 (C<sub>q</sub>), 179.6 (C<sub>qx2</sub>), 192.75 (C<sub>q</sub>), 192.80 (C<sub>q</sub>); HRMS (ESI) *m/z* calcd for C<sub>27</sub>H<sub>22</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup> 401.1517, found 401.1525.

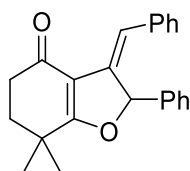


III-5ad

**(Z)-3-Benzylidene-6,6-dimethyl-2-phenyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one**

**(III-5ad)**

Yield 77%; colorless needles (AcOEt–hexane, mp. 126.7–136.6 °C); IR (neat) 2958, 1654, 1606  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.13 (3H, s), 1.16 (3H, s), 2.39 (2H, s), 2.43 (2H, s), 6.58 (1H, d,  $J = 2.8$  Hz), 7.00–7.15 (5H, m), 7.28–7.34 (3H, m), 7.38–7.43 (2H, m), 7.66 (1H, d,  $J = 2.8$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  28.5 ( $\text{CH}_3$ ), 28.6 ( $\text{CH}_3$ ), 34.0 (Cq), 38.5 ( $\text{CH}_2$ ), 52.1 ( $\text{CH}_2$ ), 89.4 (CH), 114.2 (Cq), 120.0 (CH), 126.1 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.8 (CH), 129.2 (CH), 135.0 (Cq), 136.3 (Cq), 136.7 (Cq), 179.6 (Cq), 193.5 (Cq); HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{22}\text{O}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  353.1517, found 353.1517.



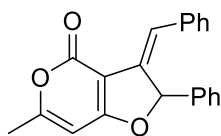
III-5ae

**(Z)-3-Benzylidene-7,7-dimethyl-2-phenyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one**

**(III-5ae)**

Yield 25% (53% brsm); colorless plates (AcOEt, mp. 138.3–144.0 °C); IR (neat) 2965, 2928, 1655, 1589  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.17 (3H, s), 1.29 (3H, s), 1.85–1.98 (2H, m), 2.56 (2H, t,  $J = 6.4$  Hz), 6.51 (1H, d,  $J = 2.8$  Hz), 7.00–7.08 (3H, m), 7.09–7.15 (2H, m), 7.27–7.30 (3H, m), 7.32–7.36 (2H, m), 7.61 (1H, d,  $J = 2.8$  Hz);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  24.9 ( $\text{CH}_3 \times 2$ ), 33.4 (Cq), 35.5 ( $\text{CH}_2$ ), 36.6 ( $\text{CH}_2$ ), 88.7 (CH), 113.1 (Cq), 120.4 (CH), 126.2 (CH), 128.00 (CH), 128.03 (CH), 128.2 (CH), 128.7 (CH), 129.0 (CH), 136.2 (Cq), 136.6 (Cq), 136.9 (Cq), 186.3 (Cq), 194.1 (Cq); HRMS (ESI)  $m/z$  calcd for

C<sub>23</sub>H<sub>22</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup> 353.1517, found 353.1510.

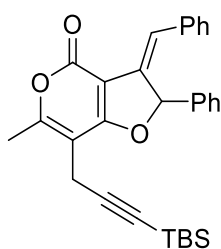


III-5af

**(Z)-3-Benzylidene-6-methyl-2-phenyl-2,3-dihydro-4H-furo[3,2-c]pyran-4-one**

**(III-5af)**

Yield 62%; colorless plates (acetone–hexane, mp. 166.9–176.4 °C); IR (neat) 3030, 1724, 1626, 1569 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 2.30 (3H, s), 5.99 (1H, s), 6.72 (1H, d, *J* = 2.8 Hz), 7.03–7.17 (5H, m), 7.30–7.34 (3H, m), 7.38–7.46 (2H, m), 7.49 (1H, d, *J* = 2.8 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 20.6 (CH<sub>3</sub>), 91.1 (CH), 96.1 (CH), 103.5 (Cq), 121.1 (CH), 126.7 (CH), 128.2 (CH<sub>x2</sub>), 128.4 (CH), 129.0 (CH), 129.5 (CH), 132.9 (Cq), 135.7 (Cq), 136.0 (Cq), 159.5 (Cq), 165.9 (Cq), 171.6 (Cq); HRMS (ESI) *m/z* calcd for C<sub>21</sub>H<sub>16</sub>NaO<sub>3</sub> [M+Na]<sup>+</sup> 339.0997, found 339.1005.



III-5ag

**(Z)-3-Benzylidene-7-{3-(*tert*-butyldimethylsilyl)-2-propyn-1-yl}-6-methyl-2-phenyl-2,3-dihydro-4H-furo[3,2-c]pyran-4-one (III-5ag)**

Yield 72%; yellow needles (acetone–hexane, mp. 170.0–174.8 °C); IR (neat) 2952, 2928, 2856, 2175, 1730, 1559 cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 0.03 (6H, s), 0.86 (9H, s), 2.39 (3H, s), 3.30 (2H, q, *J* = 18.0 Hz), 6.74 (1H, d, *J* = 2.8 Hz), 7.05–7.12 (3H, m), 7.12–7.16 (2H, m), 7.31 (2H, t, *J* = 3.2 Hz), 7.40–7.44 (2H, m), 7.49 (1H, d, *J* = 2.8 Hz); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ -4.7 (CH<sub>3</sub>), 15.0 (CH<sub>2</sub>), 16.4 (Cq), 17.7 (CH<sub>3</sub>), 26.0 (CH<sub>3</sub>),

84.2 (Cq), 90.3(CH), 101.8 (Cq), 103.7 (Cq), 104.4 (Cq), 121.3 (CH), 126.7 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.9 (CH), 129.4 (CH), 133.5 (Cq), 135.7 (Cq), 136.1 (Cq), 159.0 (Cq), 163.2 (Cq), 170.5 (Cq); HRMS (ESI)  $m/z$  calcd for  $C_{30}H_{32}NaO_3Si$   $[M+Na]^+$  491.2018, found 491.2011.

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