Efficient Tandem Organic Synthesis Involving C−C and C−O Bonds Cleavage Reactions *via* Oxametallacycles

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Contents

Preface

The studies presented in this thesis have been carried out under the direction of Professor Dr. Masanari Kimura at the Graduate School of Engineering, Nagasaki University during 2014 to 2019.   This thesis is concerned with the development of Efficient Tandem Organic Synthesis Involving C–C and C–O Bonds Cleavage Reactions *via* Oxametallacycles.   The author has been a Research Fellow of the Japan Society for the Promotion of Science during 2018 to 2019.

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Ryo Ninokata

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General Introduction

Our surroundings are full of organic compounds such as pharmaceuticals, functional materials, pesticides, perfumes, and paints.   Thus, the academic and social contribution of synthetic organic chemistry supporting the basis of our living is extremely high.   However, it is still far from the ultimate craftsmanship of "carbon skeleton construction by freely molecular transformation reaction".   Various molecular transformation reactions have been reported so far, but many of them require preparation of highly reactive bonds beforehand and require multiple stages, so that byproducts accompanied by it are inevitable to generate.   In other words, when designing complex molecules including development of pharmaceuticals and functional materials, it is important how to synthesize the target compound in a short process while controlling the reaction with high selectivity and efficiency.   Therefore, reducing the number of reaction steps as much as possible, and developing the high regio- and stereoselective carbon skeleton formation is extremely attractive from the viewpoint of resource saving, energy saving, and atomic economics.

Research on organic synthetic chemistry is roughly divided into "reaction" and "synthesis". Research on "reaction" is the main purpose of developing "novel synthesis means" that has never existed before.   On the other hand, research on "synthesis" is aimed at "establishment of synthesis method of desired compound", which leads to understanding and exploration of the chemical properties of the compound itself and related compounds.   Therefore, research on "reaction" and "synthesis" becomes "two sides of the same coin" and development of organic synthetic chemistry will eventually be applied to "creation of new compounds" and "development of mass synthesis method".   In this trend of organic synthetic chemistry, we focus on "development of reaction" and are conducting research.   In developing reactions to establish new synthetic means, we

approach organometallic chemistry as a base. This organometallic chemistry has achieved the development of synthetic means that breaks common sense by maximizing the features of transition metal complexes. Catalytic reactions using transition-metals, such as cross-coupling reactions, are extremely useful in organic synthesis, from the synthesis of physiologically active substances to the synthesis of biaryls that can be used for liquid crystal materials, so the application range is extremely broad.[1] The author focused on "activation of multiple bonds" which is a feature of transition metal complexes. That is, molecules having multiple bonds such as olefins, alkynes, and carbonyl compounds are coordinated to the transition metal complex and activated, whereby oxidative cyclization proceeds to form metallacycle.[2] Transition-metal-catalyzed reactions *via* metallacycles generated by oxidative cyclization are one of the most efficient methods to connect multiple components in one step, because it shows various reactivity and can be converted into various compounds.[3] For example, metallacycles has been used as important intermediates in the olefin metathesis, cyclization, oligomerization, and polymerization, and various catalytic reactions have been reported numerous. On the other hand, the development of reactions using oxametallacycles in which the carbon next to the metal has been replaced by oxygen has developed much less. Formation of oxametallacycle containing the early transition metal was reported, but it was difficult to use it as an efficient reaction intermediate because of stronger oxygen affinity (ex. Ti−O: 157.6 kcal/mol, V−O: 153.3 kcal/mol). That is, many of them required stoichiometric amounts of transition metal complexes. In recent years, attempts have been made to develop catalytic reactions through oxametallacycle formation by late transition metals. In particular, nickel and palladium have relatively low affinity with oxygen, and oxidation addition and reductive elimination are relatively easy to proceed, so that reactions using oxanickelacycle and oxapalladacycle as active species are actively researched.[2,4]

As a pioneering example, in 1997, Montgomery and co-workers have reported that the reductive coupling reaction of alkynes with aldehydes proceeded to give the corresponding enyl alcohols *via* oxanickelacycles (**Scheme 1**, top).[5]   In 1998, Kimura, Tamaru, and co-workers have reported that the reductive coupling of conjugated diene and aldehyde *via* oxanickelacycle proceeds to provide bishomoallylalcohol (**Scheme 1**, bottom).[6]
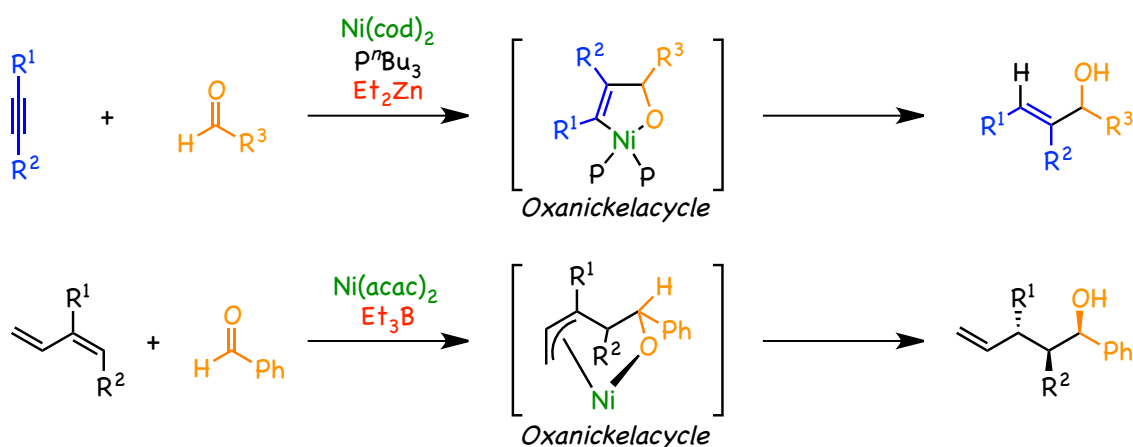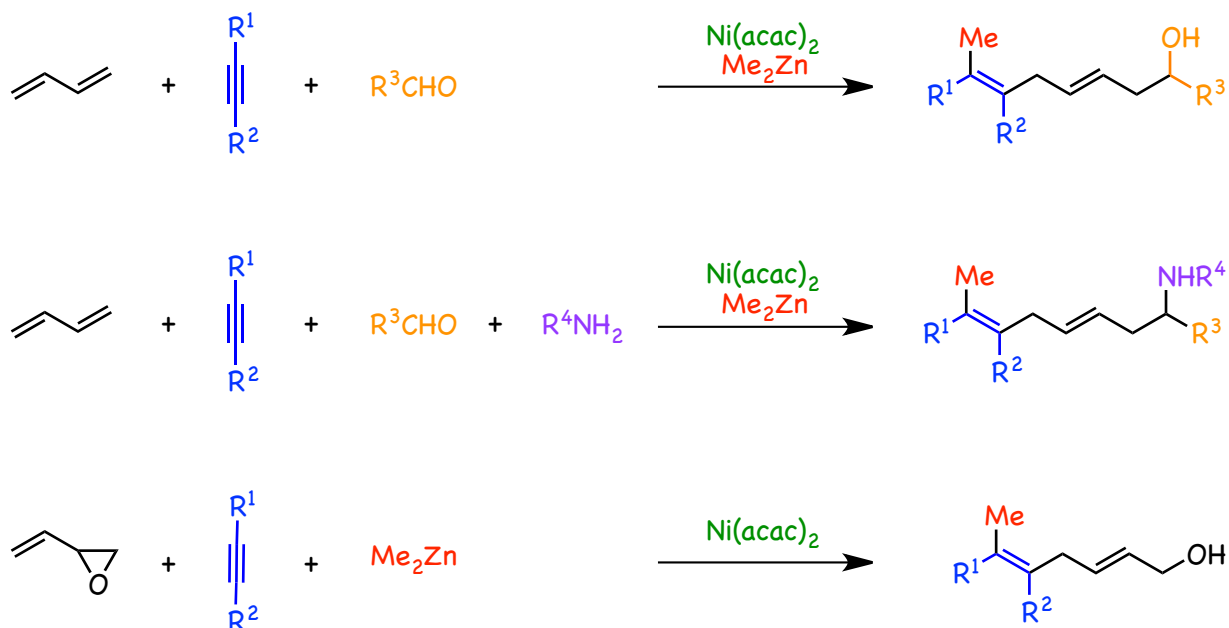

Scheme 1. Ni-Catalyzed C−C Bond Formation Reactions *via* Oxanickelacycles

In 2004, the elegant work by Kurosawa, Ogoshi, and co-workers for the first time isolated and identified the oxanickelacycle, demonstrated the reaction mechanism, and is spurring the development of a new catalytic reaction (**Scheme 2**).[7]
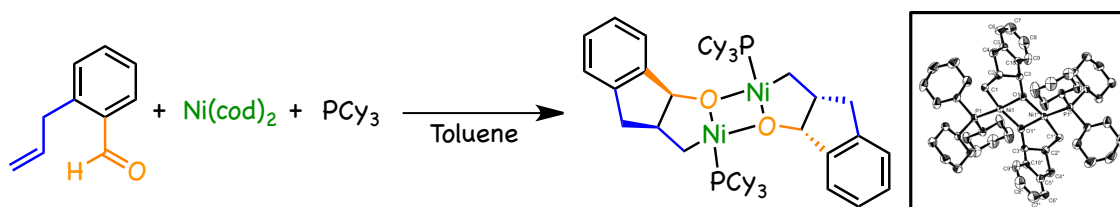
Scheme 2. Observation and Structure Determination of an Oxanickelacycle

Our research group is actively studying C−C bond formation[8] reactions to construct the carbon

skeleton at once utilizing oxametallacycles as key active species.　　For example, Kimura, Tamaru,

and co-workers have previously demonstrated that Ni-catalyzed four-component coupling reaction

of 1,3-butadiene, alkyne, aldehyde, and Me_2Zn proceeds to furnish ($3E, 6Z$)-octadien-1-ol with high

stereoselectivity and in excellent yield (**Scheme 3**, top).[8a]　　Furthermore, our group have

developed that Ni-catalyzed five-component coupling reaction of 1,3-butadiene, alkyne, aldehyde,

amine, and Me_2Zn to afford dienyl amine in excellent yield (**Scheme 3**, middle).[8b, 8c]　　Recently,

our group have reported that Ni-catalyzed stereoselective coupling reaction of vinylepoxide, alkyne,

and Me_2Zn proceeded to give the corresponding 2,5-heptadienyl alcohol in good yield　(**Scheme 3**,

bottom).[8d, 8e]

Scheme 3. Ni-Catalyzed C−C Bond Formation Reactions *via* Oxanickelacycles

Our research group is also studying C−C bond cleavage reactions *via* oxametallacycles as key

intermediate.[9]　　For example, Kimura, Tamaru, and co-workers have previously demonstrated a

smooth transformation of vinyl cyclic carbonates into the corresponding ω-dienyl aldehydes by decarboxylative fragmentation through a key oxapalladacycle intermediates (**Scheme 4**, top).[9a] 4-Pentene-1,3-diols also underwent the dehydrative β-carbon elimination of oxapalladacycles promoted by Pd(0) catalyst and organoboran reagent (**Scheme 4**, bottom).[9b]　　　 Despite the conflicting reactions of bond cleavage and bond formation, it is very interesting that the reaction proceeds through a common oxametallacycle key active species. 　　From such a point of view, the author has started to develop a highly efficient tandem organic synthesis reaction using the characteristics of the transition metal catalyst for the purpose of exploring new possibilities of oxametallacycle exhibiting unique reactivity.
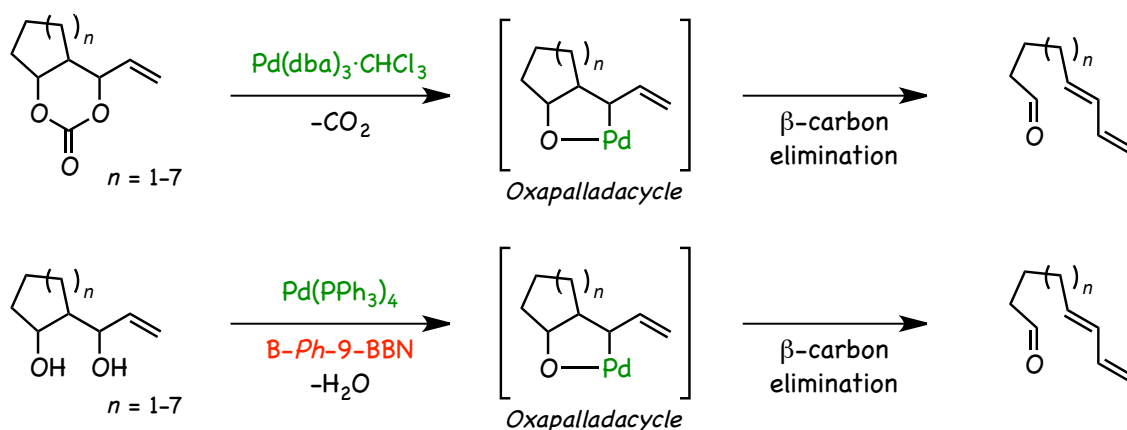

Scheme 4. Pd-Catalyzed C−C Bond Cleavage Reaction *via* Oxapalladacycles

　　This thesis consists of four chapters.
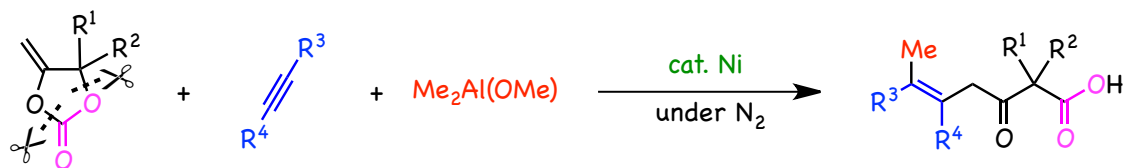
　　Chapter 1 describes that Ni-catalyzed selective formation of unsaturated carboxylic acids and phenylacetic acids *via* cleavage of the C=C double bond.[10]　　In the presence of Ni(0) catalyst and PPh$_3$, the regio- and stereoselective three-component coupling reaction of diketene, alkyne, and Me$_2$Al(OMe) proceeds to furnish 3,5-hexadienoic acids (**Scheme 5**, path A).　　Using Et$_2$Al(OEt)

instead of Me$_2$Al(OMe) as organoalminium reagent, [2+2+1+1] type cycloaddition reaction of diketene and two equivalents of alkynes provided phenylacetic acids (**Scheme 5**, path B).   The structures of the products suggested that these reactions might proceed *via* C=C bond cleavage of diketene.
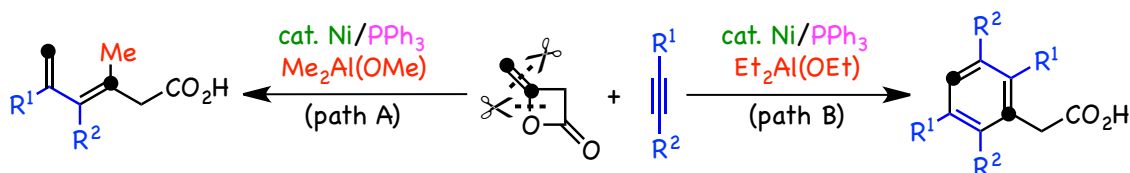

Scheme 5. Nickel-Catalyzed Multicoupling Reaction of Diketene, Alkyne, and Organometallic Reagents

Chapter 2 deals with Ni-catalyzed CO$_2$ rearrangement of enol metal carbonates for the efficient synthesis of β-ketocarboxylic acids (**Scheme 6**).[11]   In the presence of Ni(0) catalyst, the three-component coupling reaction of 4-methylene-1,3-dioxolan-2-one, alkyne, and Me$_2$Al(OMe) proceeded to give δ,ε-unsaturated β-ketocarboxylic acids with high regio- and stereoselectivities. The main difference compared with the decarboxylation conversion of the previously reported vinyl-substituted cyclic carbonates is that all atoms of the carbonate substrate are retained in the final product, that is, this is not a decarboxylative transformation.   The presence of Me$_2$Al(OMe) is crucial toward the selective formation of β-ketocarboxylic acids, and other organometallic reagents such as Me$_3$B and Me$_2$Zn proved to be less efficient. An eight-membered nickelacycle and enol aluminium carbonate were proposed to be the key intermediate in this process.

Scheme 6. Nickel-Catalyzed CO_2 Rearrangement of Enol Metal Carbonates for the Efficient Synthesis of δ,ε-Unsaturated β-Ketocarboxylic Acids

Chapter 3 describes that Ni-catalyzed three-component coupling of 4-methylene-2-oxazolidinone, alkyne, and trimethylaluminium (**Scheme 7**).[12]   In the presence of Ni(0) catalyst, the regio- and stereoselective three-component coupling reaction of 4-methylene-2-oxazolidinone, alkynes, and Me_3Al accompanied by extrusion of carbon dioxide to furnish 2-amino-1,4-hexadiene in good yields.   The products are useful as the synthetic enamine key intermediates for the preparation of nitrogen containing compounds.   The study is in progress to apply our protocol to the synthesis of physiologically active molecules, such as unsaturated amines and amino acids.
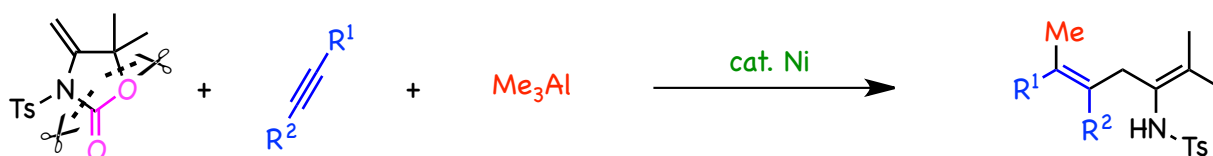
Scheme 7. Ni-Catalyzed Three-Component Coupling Reaction of 4-Methylene-2-oxazolidinone, Alkyne, and Me_3Al

Chapter 4 deals with Reconstruction of Carbon Bond Frameworks *via* Oxapalladacycle Promoted by Synergistic Effect of Palladium Catalyst and Triethylborane (**Scheme 8**).[13]   In the presence of Pd and Xantphos catalyst with Et_3B, the coupling reactions of 3-hydroxy-4-pentenoic

acids with aldehydes proceeds to provide the corresponding 3,5-hexadien-1-ols with good

stereoselectivities.   3-Hydroxy-4-pentenoic acid behaved as a conjugated diene equivalent in this

reaction system.   Notably, the reaction proceeded through an unique process of the C–C bond

cleavage and successive C–C bond formation under single operation.
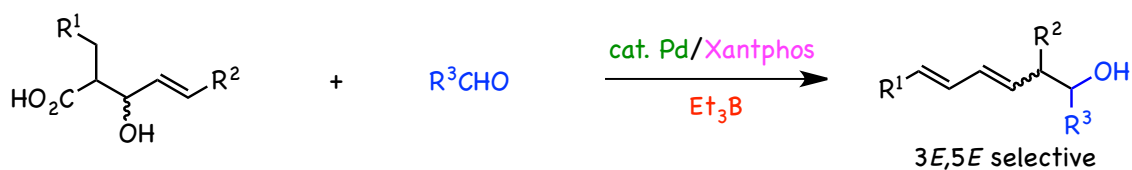
Scheme 8. Pd-Catalyzed C–C Bond Formation Utilizing 3-Hydroxy-4-pentenoic Acids as an

Equivalent of Conjugated Diene with Aldehyde

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13. **R. Ninokata**, R. Korogi, J. Nakao, T. Fukuda, G. Onodera, M. Kimura, *submitted for publication.*

Chapter 1

Nickel-Catalyzed Selective Formation of Unsaturated Carboxylic Acids and Phenylacetic Acids *via* Cleavage of the C=C Double Bond
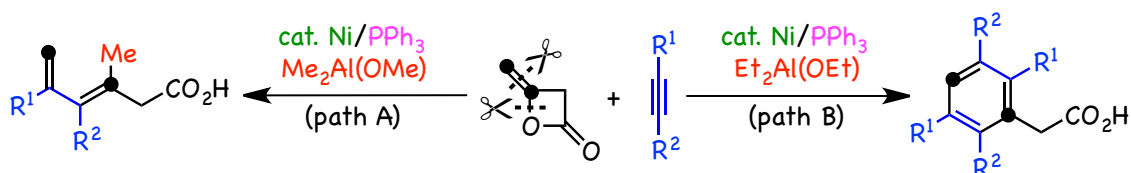
Summary: In the presence of Nickel catalyst and PPh_3, the regio- and stereoselective multicomponent coupling reaction of diketene, alkyne, and $Me_2Al(OMe)$ proceeded to give 3,5-hexadienoic acids (path A). On the other hand, by use of $Et_2Al(OEt)$ instead of $Me_2Al(OMe)$ under the similar reaction conditions, [2+2+1+1] cycloaddition reaction of diketene and two equivalents of alkynes provided phenylacetic acids (path B). These reactions might proceeds *via* C=C double bond cleavage of diketene.

Introduction

Metallacycles formed from unsaturated hydrocarbon and transition metal complex, are attractive and convenient key intermediates for C−C bond cleavage and C−C bond formation reactions.[1] Above all, the reaction *via* nickelacycle is an efficient synthetic method for the construction of useful and complicated molecules in modern organic chemistry.[2] We reported the Nickel(0)-catalysed multicomponent coupling reaction of vinylcyclopropane, alkyne, and Me₂Zn to accomplish the C−C bond formations with high regio- and stereoselectivity (**Scheme 1**).[3] These coupling reactions proceeded *via* oxanickelacyle intermediates by oxidative cyclization of unsaturated hydrocarbons and a Nickel(0) catalyst.
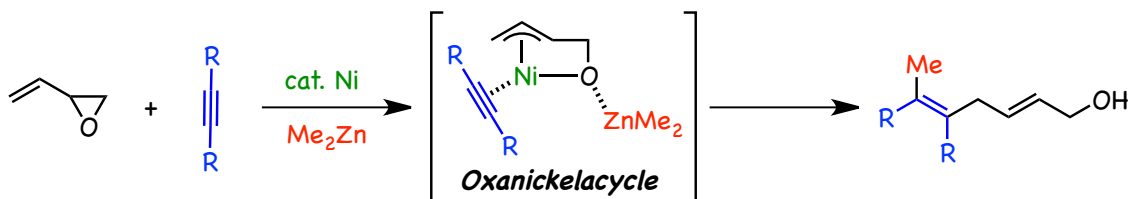
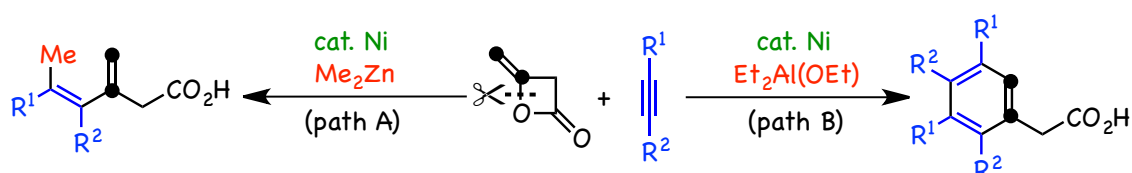**Scheme 1**. Nickel-Catalyzed Coupling Reaction of Vinylcyclopropane, Alkyne, and Me₂Zn

In the course of our study on the multicomponent coupling reaction, we have focused on a diketene as a starting material for the efficient formation of oxanickelacycle species. Diketene is a unique and important key intermediate formed by dimerization of ketene,[4] and is often used as an acetoacetylation reagent for versatile nucleophiles, such as alcohols, amines, thiols and carbanions, in organic synthesis (**Scheme 2**, path A).[5] On the other hand, in the presence of transition metal catalysts, diketene smoothly reacts with organometallic compounds, such as Grignard reagents and organozinc reagents, to construct 3-substituted 3-butenoic acids *via* cleavage of the vinyl-oxygen

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bond (**Scheme 2**, path B).[6]   The 3-butenoic acid skeleton serves as a synthon for the preparation

of physiologically active molecules and the fine chemicals.[7]
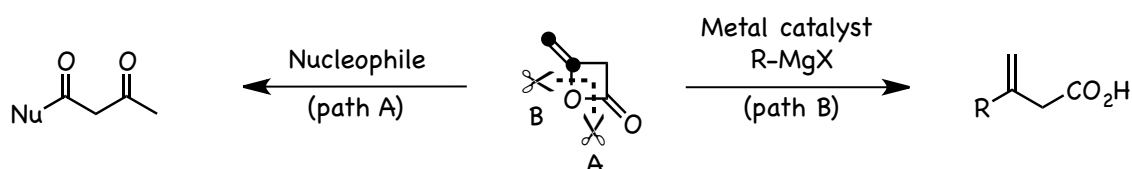
**Scheme 2**. Reactivity of Diketene with Nucleophiles

We have previously demonstrated the Nickel-catalyzed three-component coupling reaction of

diketene, alkyne, and Me_2Zn provided 3-methylene-4-hexenoic acids with excellent regio- and

stereoselectivity (**Scheme 3**, path A).[8]   By use of $Et_2Al(OEt)$ instead of Me_2Zn, [2+2+2]

cycloaddition reaction of diketene and two equivalents of alkynes proceeded to give phenylacetic

acids (**Scheme 3**, path B).

Scheme 3. Nickel-Catalyzed Multicoupling Reaction of Diketene, Alkyne, and Organometallic

Reagents

Herein, we disclose the multi-component coupling reaction of diketene, alkyne, and

$Me_2Al(OMe)$ under a Ni/PPh_3 catalytic system *via* oxanickelacycles proceeded to give

3,5-hexadienoic acids (**Scheme 4**, path A).   Furthermore, by use of $Et_2Al(OEt)$ instead of

$Me_2Al(OMe)$ under the similar reaction conditions, [2+2+1+1] cycloaddition reaction of diketene

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and two equivalents of alkynes provided phenylacetic acids (**Scheme 4**, path B).   The structure of the product suggested that these reactions proceeded *via* C=C bond cleavage of diketene. Although nickel-catalyzed cycloaddition reactions with alkynes have been developed, efficient syntheses of phenylacetic acids by a cycloaddition reaction between an alkyne and diketene have not been reported to date.
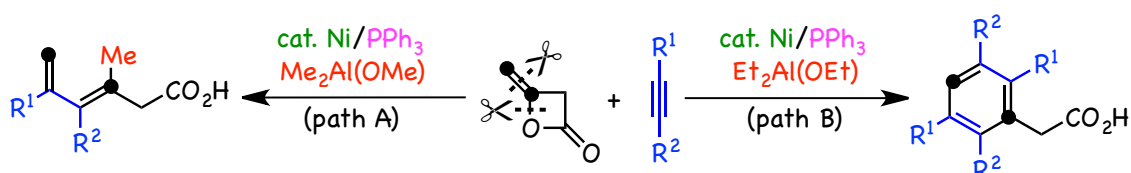

Scheme 4. Nickel-Catalyzed Multicoupling Reaction of Diketene, Alkyne, and Organometallic Reagents *via* Cleavage of the C=C Bond

Results and Discussion

The optimization of the reaction conditions are summarized in **Table 1**.   In the presence of Ni catalyst, diketene underent a coupling reaction with 3-hexyne and Me_2Zn to afford 3-methylene-4-hexenoic acid **3a** in 58% yield (Entry 1, **Table 1**).   By use of PPh_3 as a ligand, **3a** was obtained in 45% yield, along with the isomeric product, 3,5-hexadienoic acid **4a**, in 6% yield as a byproduct (Entry 2, **Table 1**). Interestingly, when Me_3Al was used as an organometallic reagent instead of Me_2Zn, the desired reaction proceeded to give **4a** as a main product (Entry 3, **Table 1**). $Me_2Al(OMe)$ was the most efficient organoaluminium reagent for this reaction (Entry 4, **Table 1**). The features of the coupling reaction of diketene and alkyne, promoted by a nickel/PPh_3 catalytic system, changed dramatically when organoaluminum reagents bearing an ethyl group were used in place of $Me_2Al(OMe)$.   By use of Et_3Al and $Et_2Al(OEt)$, a formal [2+2+1+1] cycloaddition reaction proceeds to afford the phenylacetic acid derivatives **5a** in 46% and 73% yields, respectively (Entries 5 and 6, **Table 1**).   Encouraged by these results, we examined the effects of various ligands in the presence of $Ni(cod)_2$.   However, n-Bu_3P, PCy_3, XPhos, DPPE, DPPF, Xantphos, and IPr were not effective for these reactions (Entries 7-18, **Table 1**).

Table 1. Optimization of the Reaction Conditions for Nickel-Catalyzed Multicoupling Reaction of Diketene, Alkyne, and Organometallic Reagents *via* C=C Bond Cleavage[a]
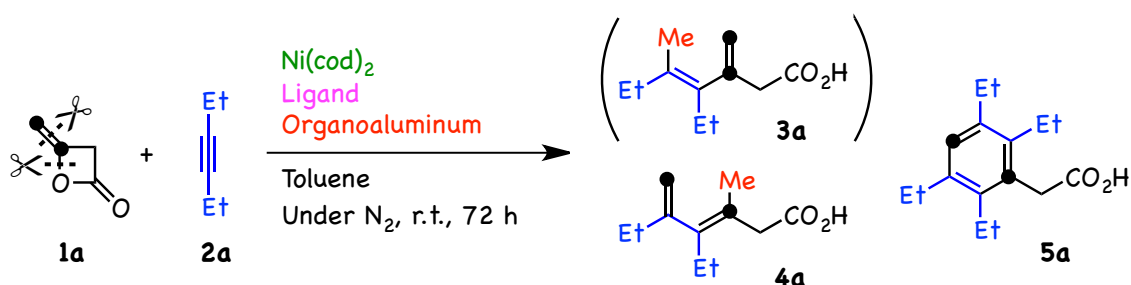

Entry	Ligand (mol%)		Organoaluminum	Isolated Yield [%]		
				3a	4a	5a
1	none		Me$_2$Zn	58	0	0
2	PPh$_3$	(20)	Me$_2$Zn	45	6	0
3	PPh$_3$	(20)	Me$_3$Al	20	60	0
4	**PPh$_3$**	**(20)**	**Me$_2$Al(OMe)**	**22**	**77**	**0**
5	PPh$_3$	(20)	Et$_3$Al	0	0	46
6	**PPh$_3$**	**(20)**	**Et$_2$Al(OEt)**	**0**	**0**	**73**
7	*n*–Bu$_3$P	(20)	Me$_2$Al(OMe)	trace	trace	0
8	PCy$_3$	(20)	Me$_2$Al(OMe)	trace	trace	0
9	XPhos	(20)	Me$_2$Al(OMe)	0	trace	0
10	DPPE	(10)	Me$_2$Al(OMe)	0	0	0
11	DPPF	(10)	Me$_2$Al(OMe)	0	0	0
12	Xantphos	(10)	Me$_2$Al(OMe)	0	9	0
13	IPr	(10)	Me$_2$Al(OMe)	0	11	0
14	*n*–Bu$_3$P	(20)	Et$_2$Al(OEt)	0	0	0
15	PCy$_3$	(20)	Et$_2$Al(OEt)	0	0	20
16	DPPF	(10)	Et$_2$Al(OEt)	0	0	23
17	Xantphos	(10)	Et$_2$Al(OEt)	0	0	3
18	IPr	(10)	Et$_2$Al(OEt)	0	0	0

[a]The reaction was undertaken in the presence of [Ni(cod)$_2$] (10 mol%), ligand (10-20 mol%), diketene (3.0 mmol), alkyne (1.0 mmol), and organoaluminium reagent (1.2 mmol) at room temperature under nitrogen atmosphere for 72 h.

Next, we considered the desired product **4a** and the by-product **3a** possibly being isomerized with each other, and examined the reaction time. The results are summarized in **Table 2**. Although the reaction time was examined, there was almost no change in the formation ratio of products **4a** and **3a** (Entries 1-3, **Table 2**).

Table 2. Investigation of the Reaction Time[a]
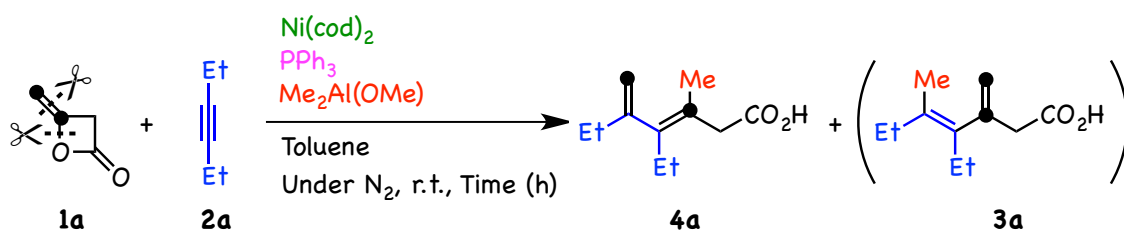
Entry	Time (h)	Isolated Yield [%]		
		4a	**3a**	**4a : 3a**
1	3	61	18	3.4 : 1
2	24	74	22	3.4 : 1
3	72	77	22	3.5 : 1

[a]The reaction was undertaken in the presence of [Ni(cod)$_2$] (10 mol%), PPh$_3$ (20 mol%), diketene (3.0 mmol), 3-hexyne (1.0 mmol), and Me$_2$Al(OMe) (1.2 mmol) at room temperature under nitrogen atmosphere for 3-72 h.

Furthermore, separately isolated **3a** was unreacted under the optimized conditions and no isomerization was observed but **3a** was recovered (**Scheme 5**). Based on these experimental results, we believe that products **4a** and **3a** were provided via completely different reaction mechanism, not mutually isomerizing in the system.
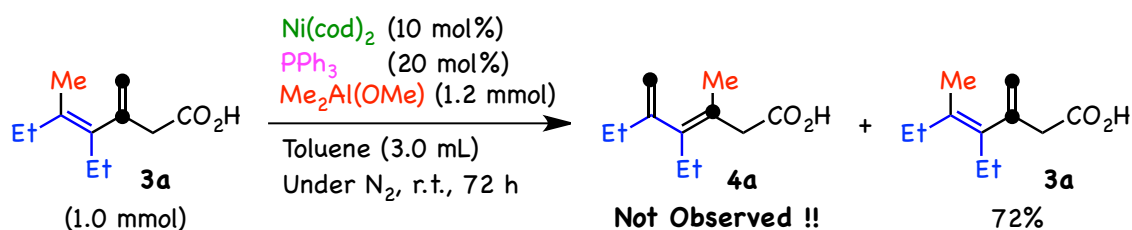
Scheme 5. Isomerization Experiment under the Optimized Conditions

Then, a similar coupling reaction using a wide variety of alkynes under optimized conditions was investigated.   At first, we examined the three-component coupling reaction with a variety of alkynes, diketene and $Me_2Al(OMe)$, and the results are summarized in **Table 3**.   Symmetrical substituted alkynes, such as 2-butyne, 3-hexyne, 4-octyne, 5-decyne, and diphenyl acetylene reacted with diketene and $Me_2Al(OMe)$ smoothly to provide unsaturated carboxylic acids **4a-e** in moderate to good yields (Entries 1-5, **Table 3**).   However, when dimethyl acetylenedicarboxylate was used, the desired reaction did not proceed (Entry 6, **Table 3**).   In the case of terminal alkynes, such as 3,3-dimethyl-1-butyne and phenylacetylene, the reaction provided the corresponding unsaturated carboxylic acids **4f-g** in low to moderate yields as a single product.

Table 3. Ni-Catalyzed Three-Component Coupling Reaction of Diketene, Alkyne, and Me$_2$Al(OMe) *via* C=C Bond Cleavage^a
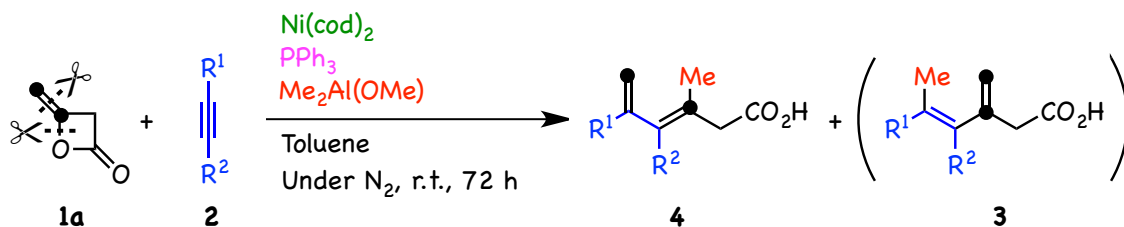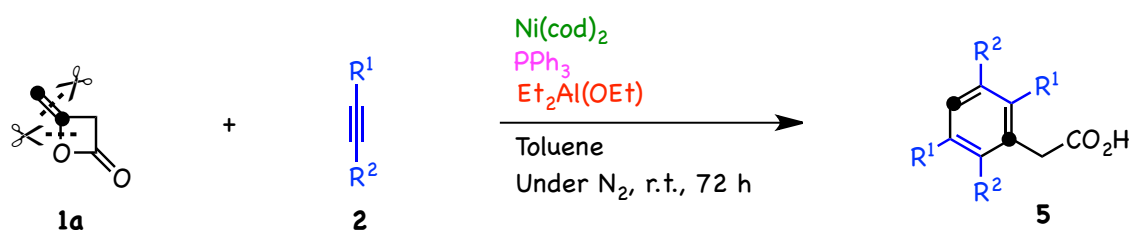

Entry	R^1	R^2	Isolated Yield [%]		
			4	3	Total
1	Me	Me	4b : 61	3b : 26	87
2	Et	Et	4a : 77	3a : 22	99
3	n–Pr	n–Pr	4c : 77	3c : 14	91
4	n–Bu	n–Bu	4d : 66	3d : 10	76
5	Ph	Ph	4e : 50	3e : 17	67
6	CO$_2$Me	CO$_2$Me	0	0	0
7	t–Bu	H	4f : 47 [single]	0	47
8	Ph	H	4g : 17 [single]	0	17

^{a}The reaction was undertaken in the presence of [Ni(cod)$_2$] (10 mol%), PPh$_3$ (20 mol%), diketene (3.0 mmol), alkyne (1.0 mmol), and Me$_2$Al(OMe) (1.2 mmol) at room temperature under nitrogen atmosphere for 72 h.

Next, we investigated the multicoupling reaction with a variety of alkynes and diketene using Ni/PPh$_3$/Et$_2$Al(OEt) system, and the results are summarized in **Table 4**.   In the case of symmetrical substituted alkynes, such as 2-butyne, 3-hexyne, 4-octyne, 5-decyne, and diphenyl acetylene reacted with diketene and Et$_2$Al(OEt) smoothly to provide phenylacetic acids **5a-e** in moderate to good yields (Entries 1-5, **Table 4**).   On the other hand, dimethyl acetylenedicarboxylate was not effective for this reaction (Entry 6, **Table 4**).   When 1-trimethylsilyl-1-pronyne was used, the reaction proceeded to afford the phenylacetic acids **5f** in

good yields (Entry 7, **Table 4**).   In the case of 4-methyl-2-pentyne, the desired product **5g** was

obtained in low yield as a mixture of regioisomers (Entry 8, **Table 4**).   Terminal alkynes, such as

trimethylsilylacetylene and 3,3-dimethyl-1-butyne, the multicoupling reaction provided the

corresponding phenylacetic acids **5h-i** in low to moderate yields as a single product   (Entries 9-10,

Table 4).

Table 4. Ni-Catalyzed Multicoupling Reaction of Diketene and Alkyne Using Ni/PPh$_3$/Et$_2$Al(OEt)

System *via* C=C Bond Cleavage[a]

Entry	R^1	R^2	Isolated Yield of **5** [%]
1	Me	Me	**5b** : 60
2	Et	Et	**5a** : 73
3	*n*-Pr	*n*-Pr	**5c** : 80
4	*n*-Bu	*n*-Bu	**5d** : 71
5	Ph	Ph	**5e** : 50
6	CO$_2$Me	CO$_2$Me	0
7	TMS	Me	**5f** : 45 [single]
8	*i*-Pr	Me	**5g** : 25 [2:1]
9	TMS	H	**5h** : 60 [single]
10	*t*-Bu	H	**5i** : 34 [single]

[a]The reaction was undertaken in the presence of [Ni(cod)$_2$] (10 mol%), PPh$_3$ (20 mol%), diketene (3.0 mmol),

alkyne (1.0 mmol), and Et$_2$Al(OEt) (1.2 mmol) at room temperature under nitrogen atmosphere for 72 h.

The structures of the products were determined based on coupling constants from ^{1}H NMR spectral data and NOE experiment.   The selected data for the NOE observed by the irradiation are illustrated in **Figure 1**.
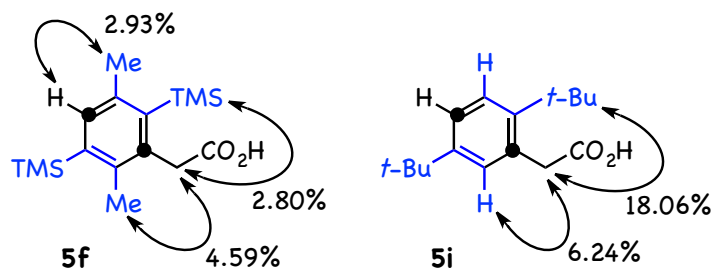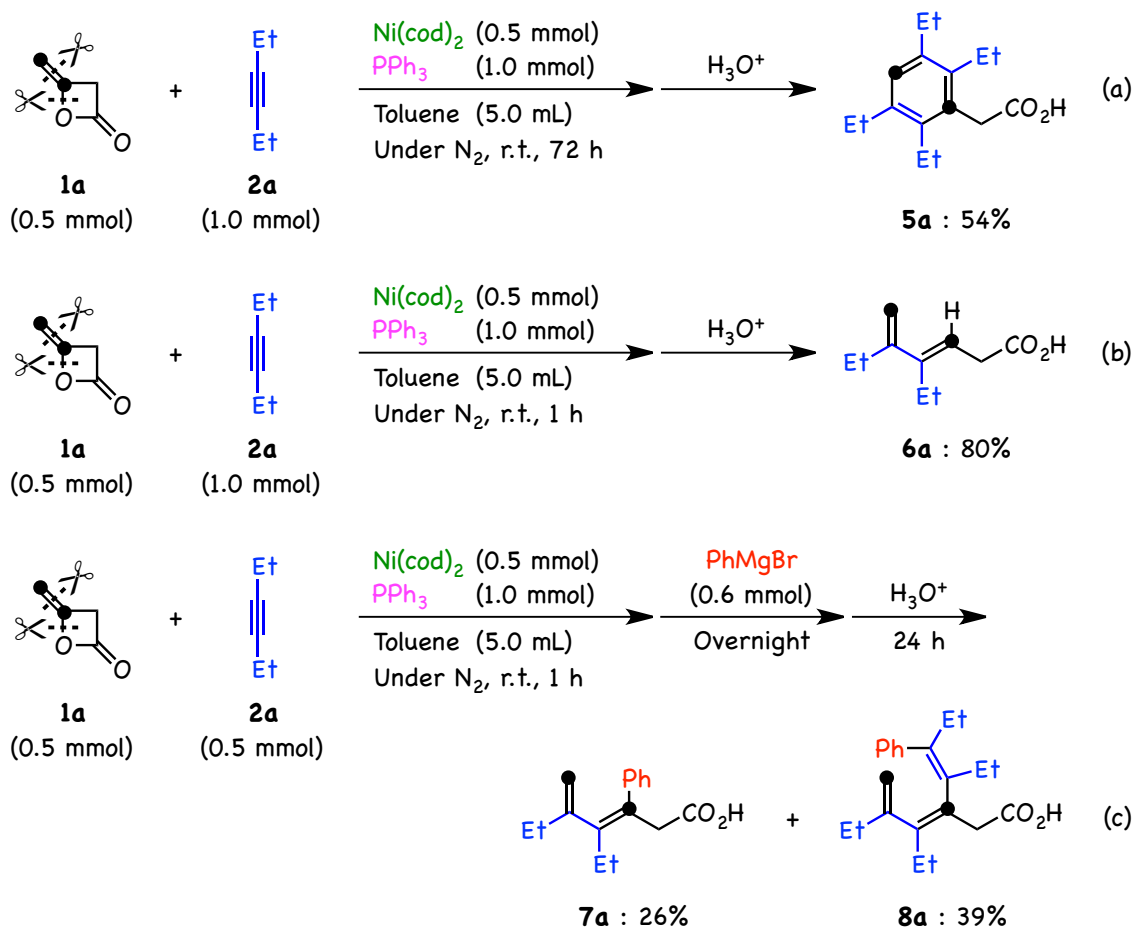

Figure 1. Structure Determination for NOE Data of Phenylacetic Acids **5f** and **5i**

The reactions of a stoichiometric amount of Ni(cod)$_2$, PPh$_3$, alkyne, and diketene without Et$_2$Al(OEt) were conducted (**Scheme 6**).

Scheme 6. C=C Bond Cleavage Reaction of Diketene Prompted by Stoichiometric Amount of Ni(cod)$_2$ and PPh$_3$

The reaction mixture of Ni(cod)$_2$ (0.5 mmol), PPh$_3$ (1.0 mmol), 3-hexyne (1.0 mmol), and diketene (0.5 mmol) stirred for 72 hours followed by hydrolysis with acidic water provided the phenylacetic acid **5a** in 54% (**Scheme 6**, Eq. (a)). Hydrolysis of the reaction mixture at 1 hour afforded (3*E*)-4-ethyl-5-methylene-3-heptenoic acid **6a** as a sole product in 80% yield with high *E*-stereoselectivity involving C-C double bond cleavage of diketene (**Scheme 6**, Eq. (b)).

Furthermore, as for the stoichiometric reaction of a mixture of Ni(cod)$_2$ (0.5 mmol), PPh$_3$ (1 mmol), 3-hexyne (0.5 mmol), and diketene (0.5 mmol), addition of PhMgBr to the reaction mixture provided (3Z)-4-ethyl-5-methylene-3-phenyl-3-heptenoic acid **7a** in 26% along with (3Z)-4-ethyl-5-methylene-3-[(3Z)-4-phenyl-3-hexenyl]-3-heptenoic acid **8a** in 39% (**Scheme 6**, Eq. (c)).   These results suggest that scission of the C-C double bond is triggered by synergistic effects of both Ni(0) metal and PPh$_3$ ligand, and Et$_2$Al(OEt) seems to serve as a promoter to regenerate active Ni(0) species for the catalytic reaction system through an important key intermediate.[9]

A plausible reaction mechanism for the coupling reactions of diketene and alkyne promoted by a nickel catalyst, PPh$_3$, and organoaluminium reagents are illustrated in **Scheme 7** and **8**.   In the presence of Ni(cod)$_2$ and PPh$_3$ ligand, promotes diketene to undergo the oxidative cyclization with alkyne to form the nickelacyclopentene intermediate **I**.   The active metallacycle **I** having PPh$_3$ ligand invokes C-C bond cleavage reaction via nickel carbene cyclopropane rearrangement to form the nickelacyclopentene **IV**.[10]   [1,2]-Shift of the Ni atom proceeds to avoid the distortion of the spiro-β-lactone ring giving rise to the oxanickelacycle **V**.   In the case of Me$_2$Al(OMe), the methyl group transfer from Me$_2$Al(OMe) to nickel provides unsaturated carboxylic acids **4** by reductive elimination and liberation of the active Ni(0) catalyst (**Scheme 7**). On the other hands, in the case of Et$_2$Al(OEt), cycloaddition reaction of oxanickelacycle **V** and alkyne to form vinylnickel intermediate **VI** (**Scheme 8**).[11]   Intramolecular carbonickelation follows by aromatization provides phenylacetic acids **5** by transmetalation with Et$_2$Al(OEt) accompanying the regeneration of catalytically active Ni(0) species.[12]
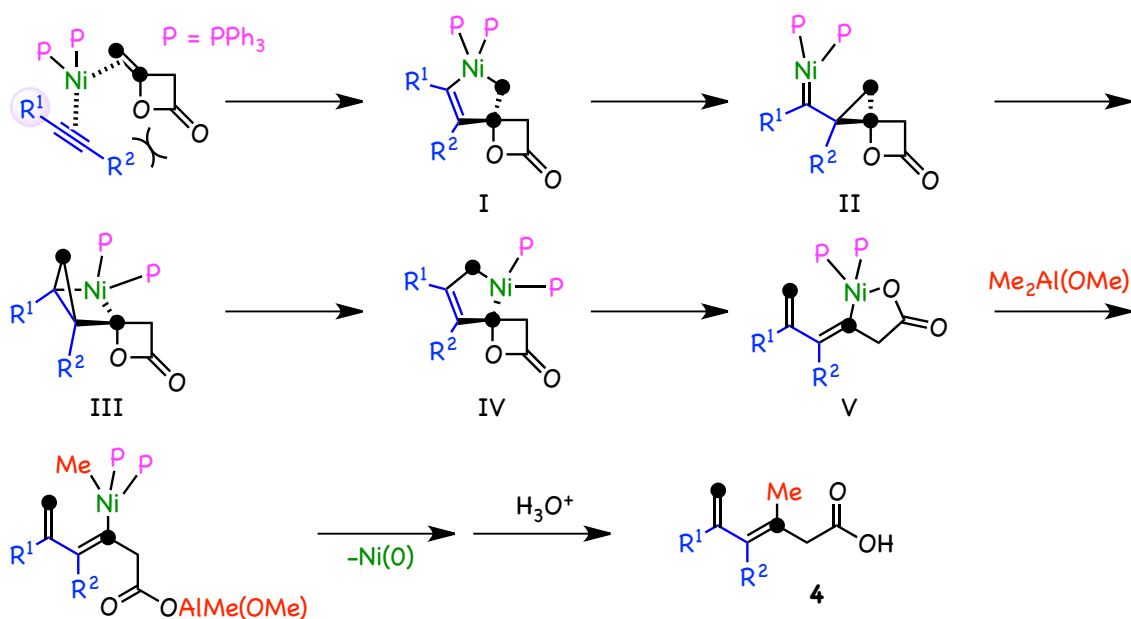
Scheme 7. Plausible Reaction Mechanism for the Formation of 3,5-Hexadienoic Acid **4**
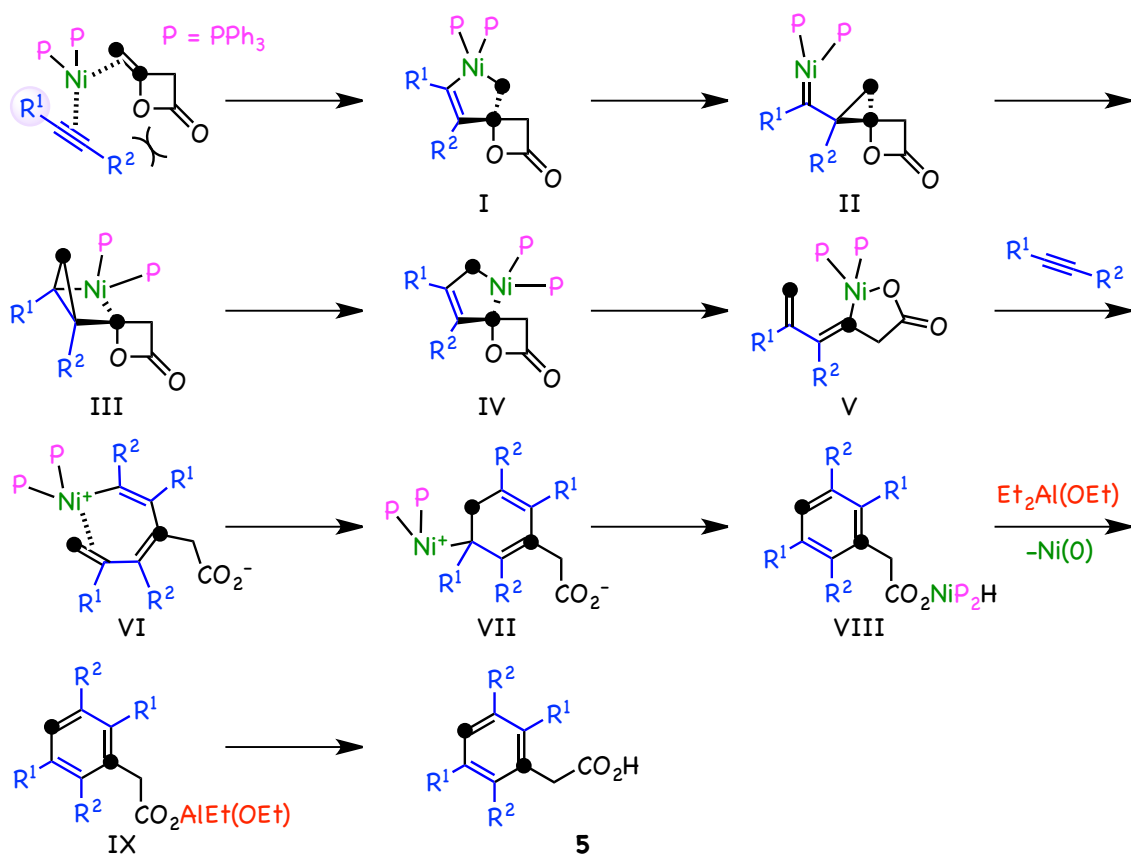
Scheme 8. Plausible Reaction Mechanism for the Formation of Phenylacetic Acid **5**

Conclusion

In conclusion, in the presence of nickel catalyst and PPh$_3$, the regio- and stereoselective multicomponent coupling reaction of diketene, alkyne, and Me$_2$Al(OMe) demonstrated to give 3,5-hexadienoic acids **4** *via* C=C bond cleavage reaction.   Interestingly, by use of Et$_2$Al(OEt) instead of Me$_2$Al(OMe) under the similar reaction conditions, phenylacetic acids derivatives **5** are constructed *via* the formal [2+2+1+1] cycloaddition reactions with diketene and 2 equivalents of alkyne accompanying the cleavage reaction of methylene C=C bond of diketene.   This is the first example of the selective formation of unsaturated carboxylic acids and phenylacetic acids from diketene involving oxanickelacycles.   This protocol might be a powerful and useful tool in the expedient synthesis of the physiologically active molecules, such as isoprenoid acids and non-steroidal anti-inflammatory drugs (NSAIDs).

Reactions employed oven-dried glassware unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator (Merck, Silica gel 60F$_{254}$). Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. Proton and carbon NMR data were obtained with a JEOL-GX400 with tetramethylsilane as an internal standard. Chemical shift values were given in ppm downfield from the internal standard. Infrared spectra were recorded with a JASCO A-100 FT-IR spectrophotometer. High resolution mass spectra (HRMS) were measured with a JEOL JMS-DX303.

Solvents and Reagents

Anhydrous toluene were purchased (Aldrich) and used without further purification. Ni(cod)$_2$, PPh$_3$, *n*-Bu$_3$P, PCy$_3$, XPhos, DPPE, DPPF Xantphos [4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene], Ipr, Me$_2$Zn (1.0 M hexane solution), Me$_3$Al (1.0 M hexane solution), Et$_3$Al (1.0 M hexane solution), Et$_2$Al(OEt) (1.0 M hexane solution) (Kanto Kagaku) were purchased and used without further purification. 2-Butyne, 3-hexyne, 4-octyne, diphenyl acetylene, dimethyl acetylenedicarboxylate, 1-trimethylsilyl-1-propyne, 4-methyl-2-pentyne, 3,3-dimethyl-1-butyne, phenylacetylene, and trimethylsilylacetylene (Tokyo Kasei Kogyo Co., Ltd) were purchased and distilled prior to use. Diketene (Tokyo Kasei Kogyo Co., Ltd) was purchased and used without further purification.

Preparation of Me$_2$Al(OMe) Reagent

A 25 mL two-necked round-bottomed flask equipped with a rubber septum was charged with Me$_3$Al solution (2.0 mL of 1.0 M in hexane, 2 mmol, Kanto Kagaku) under argon atmosphere. Anhydrous MeOH (2.0 mmol, Wako) was added to the Me$_3$Al solution via syringe at 0 °C for 30 min.

General Procedure A: Formation of Unsaturated Carboxylic Acids from Diketene Promoted by Ni-Catalyst (Entry 4, **Table 1**)

To a solution of Ni(cod)$_2$ (27.5 mg, 0.1 mmol) in dry toluene (3.0 mL) were successively added diketene (252.2 mg, 3.0 mmol), 3-hexyne (82.1 mg, 1 mmol), and Me$_2$Al(OMe) (1.2 mmol, 1.0 M hexane solution) *via* syringe under nitrogen atmosphere. The mixture was stirred at room temperature for 72 h. The mixture was diluted with 30 mL of EtOAc and washed with 2 *N* HCl, and then brine. The extract was dried (MgSO$_4$) and concentrated in vacuo and the residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 4/1 v/v) to give **4a** along with **3a** as a minor product (180.3 mg, 77% and 22%, respectively, R_f = 0.33; hexane/EtOAc = 4/1 v/v).

General Procedure B: Formation of Phenylacetic Acids from Diketene Promoted by Ni-Catalyst (Entry 6, **Table 1**)

To a solution of Ni(cod)$_2$ (27.5 mg, 0.1 mmol) in dry toluene (3.0 mL) were successively added diketene (252.2 mg, 13.0 mmol), 3-hexyne (82.1 mg, 1 mmol), and Et$_2$Al(OEt) (1.2 mmol, 1 M hexane solution) *via* syringe under nitrogen atmosphere. The mixture was stirred at room temperature for 72 h. The mixture was diluted with 30 mL of EtOAc and washed with 2 *N* HCl, and then brine. The extract was dried (MgSO$_4$) and concentrated in vacuo and the residual oil

was subjected to column chromatography over silica gel (hexane/EtOAc = 2/1 v/v) to give **3a** (100.7 mg, 81%, R_f = 0.67; hexane/EtOAc = 4/1 v/v).

General Procedure C: C-C Bond Cleavage Reaction of Diketene Promoted by Stoichiometric Amount of Ni(0) Followed by Hydrolysis with Acid Aqueous Solution (**Scheme 6**, Eq.(b))

To a solution of Ni(cod)$_2$ (137.5 mg, 0.5 mmol), and PPh$_3$ (262.3 mg, 1.0 mmol) in dry toluene (5 mL) were successively added diketene (42.0 mg, 0.5 mmol), 3-hexyne (82.1 mg, 1.0 mmol) *via* syringe under nitrogen atmosphere.   The mixture was stirred at room temperature for 1 h.   After the reaction, added 2 *N* HCl and stirred for overnight at room temperature.   The mixture was diluted with 30 mL of EtOAc and washed with brine.   The extract was dried (MgSO$_4$) and concentrated in vacuo and the residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 4/1 v/v) to give **6a** (67.3 mg, 80%, R_f = 0.33; hexane/EtOAc = 4/1 v/v).

General Procedure D: C-C Bond Cleavage Reaction of Diketene Promoted by Stoichiometric Amount of Ni(0) Followed by Treatment with PhMgBr

To a solution of Ni(cod)$_2$ (137.5 mg, 0.5 mmol), and PPh$_3$ (262.3 mg, 1.0 mmol) in dry toluene (5 mL) were successively added diketene (42.0 mg, 0.5 mmol), 3-hexyne (41.1 mg, 0.5 mmol) *via* syringes under nitrogen atmosphere.   The mixture was stirred at room temperature for 1 h.   PhMgBr solution (0.6 mmol of 1M THF solution) was introduced *via* a syringe and the reaction mixture was stirred at room temperature for 24 h.   After the reaction, added 2 *N* HCl and stirred for overnight at room temperature.   The mixture was diluted with 30 mL of EtOAc

and washed with 2 *N* HCl, and extraction with EtOAc.   Combined organic phase was washed

with brine and the extracts were dried (MgSO$_4$) and concentrated in vacuo, and the residual oil

was subjected to column chromatography over silica gel (hexane/EtOAc = 4/1 v/v) to give a

mixture of (3*Z*)-4-Ethyl-5-methylene-3-phenyl-3-heptenoic acid **7a** (31.8 mg, 26%, R_f = 0.4;

hexane/EtOAc   =   4/1   v/v)   and

(3*Z*)-4-Ethyl-5-methylene-3-[(3*Z*)-4-phenyl-3-hexenyl]-3-heptenoic acid **8a** (31.9 mg, 39%, R_f =

0.43; hexane/EtOAc = 4/1 v/v)

4a
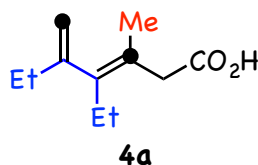
(*E*)-4-ethyl-3-methyl-5-methylenehept-3-enoic acid (4a).

IR (neat) 3095 (s), 2965 (s), 2876 (s), 2563 (br), 1697 (s), 1633 (m), 1410 (m), 1377 (m), 1196

(m), 899 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.93 (t, *J* = 7.3 Hz, 3 H), 0.99 (t, *J* = 7.3 Hz, 3

H), 1.74 (s, 3 H), 2.09 (q, *J* = 7.3 Hz, 2 H), 2.11 (q, *J* = 7.3 Hz, 2 H), 3.13 (s, 2 H), 4.63 (d, *J* =

1.9 Hz, 1 H), 4.96 (d, *J* = 1.9 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ12.0, 12.8, 20.4, 24.2,

28.5, 38.7, 111.1, 121.2, 142.3, 150.4, 178.1; High-resolution MS, calcd for C$_{11}$H$_{18}$O$_2$: 182.1307

Found *m/z* (relative intensity): 183 (M$^+$+1, 12), 182.1300(M$^+$, 100), 167(21), 153(91), 137(18).


3a
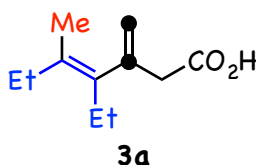
(*E*)-4-Ethyl-5-methyl-3-methylenehept-4-enoic acid (3a).

IR (neat) 2964 (s), 2934 (s), 2874 (s), 2584 (brs), 1711 (s), 1630 (m), 1406 (m), 1375 (m), 907 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (t, J = 7.6 Hz, 3 H), 0.98 (t, J = 7.6 Hz, 3 H), 1.67 (s, 3 H), 2.06 (q, J = 7.6 Hz, 2 H), 2.10 (q, J = 7.6 Hz, 2 H), 3.10 (s, 2 H), 4.84 (d, J = 1.9 Hz, 1 H), 5.18 (d, J = 1.9 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.0, 13.4, 19.0, 23.1, 26.5, 41.4, 116.9, 133.0, 135.6, 141.7, 175.7; High-resolution MS, calcd for C$_{11}$H$_{18}$O$_2$: 182.1307. Found m/z (relative intensity): 183 (M$^+$+1, 14), 182.1312 (M$^+$, 100), 137 (26).

4b
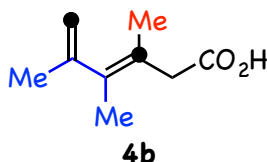
**(3E)-3,4,5-Trimethylhexa-3,5-dienoic acid (4b)**.

IR (neat) 3076 (s), 2916 (s), 2677 (br), 1715 (s), 1636 (m), 1437 (s), 1412 (s), 1375 (s), 1290 (s), 897 (s), 741 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.77 (s, 6 H), 1.79 (dd, J = 1.5, 1.0 Hz, 3 H), 3.11 (s, 2 H), 4.63 (dq, J = 2.4, 1.0 Hz, 1 H), 4.90 (dq, J = 2.4, 1.5 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 18.2, 20.1, 21.7, 39.0, 112.2, 121.0, 136.7, 147.2, 176.7; High-resolution MS, calcd for C$_9$H$_{14}$O$_2$: 154.0994. Found m/z (relative intensity): 155 (M$^+$+1, 6), 154.0995 (M$^+$, 57), 139 (100).

3b
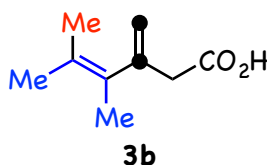
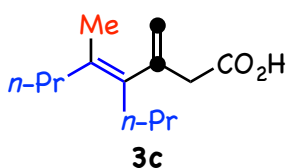**4,5-Dimethyl-3-methylenehex-4-enoic acid (3b)**.

IR (neat) 3085 (br), 2976 (s), 2920 (s), 2862 (s), 2679 (m), 2573 (m), 1713 (s), 1636 (m), 1412 (m), 1294 (s), 907 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.68 (s, 3 H), 1.70 (s, 3 H), 1.73 (s, 3 H), 3.14 (s, 2 H), 4.78 (d, J = 1.7 Hz, 1 H), 5.12 (d, J = 1.7 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 17.9,

20.1, 21.7, 41.1, 115.8, 127.4, 129.0, 143.5, 176.9; High-resolution MS, calcd for $C_9H_{14}O_2$: 154.0994. Found *m/z* (relative intensity): 155 (M$^+$+1, 45), 154.0989 (M$^+$, 100), 140 (68), 139 (100), 137 (24), 125 (32).

4c
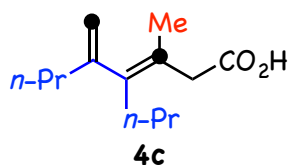
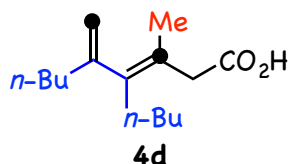**(*E*)-3-methyl-5-methylidene-4-propyloct-3-enoic acid (4c)**.

IR (neat) cm^{-1}; 3074 (s), 2961 (s), 2874 (s), 2654 (br), 1730 (s), 1632 (m), 1467 (m), 1379 (m), 1173 (m), 901 (m) cm^{-1} ; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (t, *J* = 7.3 Hz, 3 H), 0.92 (t, *J* = 7.6 Hz, 3 H), 1.31-1.38 (m, 4 H), 1.76 (s, 3 H), 2.02-2.08 (m, 4 H), 3.13 (s, 2 H), 4.63 (d, *J* = 2.4 Hz, 1 H), 4.95 (d, *J* = 2.4 Hz, 1 H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ13.9, 14.1, 20.5, 20.8, 21.4, 33.0, 37.9, 38.9, 112.3, 122.1, 141.0, 149.3, 177.9 ; High-resolution MS, calcd for $C_{13}H_{22}O_2$: 210.1620 Found *m/z* (relative intensity): 211 (M$^+$+1, 10), 210.1615 (M$^+$, 100), 195 (13), 181 (22), 167 (77).

3c

(*E*)-5-Methyl-3-methylene-4-propyloct-4-enoic acid (3c).

IR (neat) 3074 (br), 2931 (s), 2872 (s), 2682 (br), 2598 (br), 1713 (s), 1632 (m), 1410 (m), 1302 (s), 1223 (m), 905 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.87 (t, *J* = 7.6 Hz, 3 H), 0.89 (t, *J* = 7.6 Hz, 3 H), 1.32 (sext, *J* = 7.6 Hz, 2 H), 1.40 (sext, *J* = 7.6 Hz, 2 H), 1.67 (s, 3 H), 2.03 (t, *J* = 7.6 Hz, 2 H), 2.07 (t, *J* = 7.6 Hz, 2 H), 3.10 (s, 2 H), 4.83 (d, *J* = 2.0 Hz, 1 H), 5.17 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 13.9, 14.0, 19.5, 21.4, 21.7, 32.2, 35.6, 41.4, 116.8, 132.0, 134.8, 141.9,

177.3; High-resolution MS, calcd for $C_{13}H_{22}O_2$: 210.1620. Found m/z (relative intensity): 211 (M^++1, 2), 210.1612 (M^+, 10), 167 (9), 135 (22), 121 (100).

4d

**(3*E*)-4-Butyl-3-methyl-5-methylidenenon-3-enoic acid (4d)**.

IR (neat) 3082 (s), 2961(s), 2926 (s), 2669 (br), 1712 (s), 1630 (m), 1460 (s), 1410 (s), 934 (m), 899 (m), 735 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.90 (t, J = 7.1 Hz, 3 H), 0.91 (t, J = 6.8 Hz, 3 H), 1.41-1.28 (m, 8 H), 1.75 (s, 3 H), 2.02-2.07 (m, 4 H), 3.21 (s, 2H), 4.62 (d, J = 2.3 Hz, 1 H), 4.95 (dt, J = 2.3, 1.1 Hz, 1 H) ; ^{13}C NMR (CDCl$_3$, 100MHz) δ 14.0, 14.0, 20.5, 22.6, 22.7, 29.7, 30.5, 30.7, 35.4, 38.9, 112.2, 121.8, 141.3, 149.5, 178.0; High-resolution MS, calcd for $C_{15}H_{26}O_2$: 238.1933. Found m/z (relative intensity): 239 (M^++1, 11), 238.1933 (M^+, 65), 223 (11), 209 (6), 195 (24), 181 (100).

3e
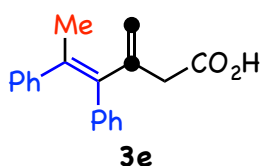
(*Z*)-3-Methylene-4,5-diphenylhex-4-enoic acid (1e).

IR (neat) 3020 (br), 2914 (m), 2856 (w), 1709 (s), 1599 (m), 1489 (m), 1443 (s), 1265 (m), 762 (s), 698 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.28 (s, 3 H), 3.00 (s, 2H), 5,36 (d, J = 1.7 Hz, 1 H), 5,44 (d, J = 1.7 Hz, 1 H), 6.94-7.19 (m, 10 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 23.1, 40.9, 118.9, 126.0, 126.2, 127.5, 127.5, 129.0, 130.2, 136.3, 138.7, 139.5, 141.8, 143.4, 176.8; High-resolution MS, calcd for $C_{19}H_{18}O_2$: 278.1307 Found m/z (relative intensity): 279 (M^++1, 8), 278.1312 (M^+,

33.7), 219 (100), 204 (26).

4f
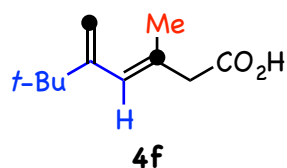
(3*E*)-3,6,6-Trimethyl-5-methylidenehept-3-enoic acid (4f).

IR (neat) 3090 (m), 2961 (s), 2872 (s), 2673 (br), 1715 (s), 1636 (m), 1412 (s), 1290 (s), 1221 (s), 910 (s), 735 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.06 (s, 9 H), 1.78 (s, 3 H), 3.11 (s, 2 H), 4.97 (s, 1 H), 5.18 (s, 1H), 5.69 (s, 1H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 14.5, 29.0, 31.2, 43.2, 115.2, 117.0, 121.0, 138.8, 177.4; High-resolution MS, calcd for C$_{11}$H$_{18}$O$_2$: 182.1307. Found *m/z* (relative intensity): 183 (M$^+$+1, 10), 182.1288 (M$^+$, 74), 181 (3), 167 (100), 152 (2).

4g
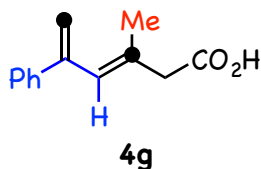
(3*E*)-3-Methyl-5-phenylhexa-3,5-dienoic acid (4g).

IR (neat) 3032 (m), 2918 (m), 2675 (br), 1709 (s), 1443 (m), 1413 (m), 1292 (m), 1223 (m), 908 (m), 760 (s), 735 (m), 698 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 2.16 (s, 3 H), 3.23 (s, 2 H), 5.18 (s, 1 H), 5.31 (s, 1 H), 6.20 (s, 1H), 7.24-7.42 (m, 5H); ^{13}C NMR (CDCl$_3$, 100MHz) δ 17.6, 43.0, 115.2, 118.3, 125.9, 127.1, 128.1, 137.7, 138.1, 143.4, 176.9 ; High-resolution MS, calcd for C$_{13}$H$_{14}$O$_2$: 202.2491. Found *m/z* (relative intensity): 203 (M$^+$+1, 10), 202.0984 (M$^+$, 67), 201 (1), 187 (3), 185 (2), 157 (44), 143 (100), 142 (95).
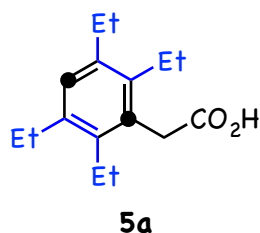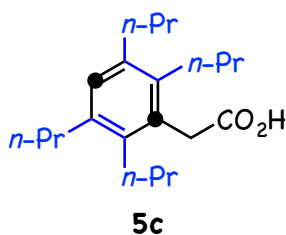
2-(2,3,5,6-Tetraethylphenyl)acetic acid (5a).

IR (KBr) 3103 (br), 2968 (s), 2936 (s), 2876 (s), 2719 (br), 2363 (m), 1699 (s), 1483 (m), 1416 (s), 1231 (s), 939 (m), 887 (s), 802 (m), 656 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.12 (t, J = 7.6 Hz, 6 H), 1.23 (t, J = 7.6 Hz, 6 H), 2.63 (q, J = 7.6 Hz, 4 H), 2.64 (q, J = 7.6 Hz, 4 H), 3.79 (s, 2 H), 6.98 (s, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.8, 15.5, 22.3, 25.7, 34.4, 128.1, 129.4, 138.2, 139.3, 177.8; High-resolution MS, calcd for C$_{16}$H$_{24}$O$_2$: 248.1776. Found m/z (relative intensity): 249 (M$^+$+1, 14), 248.1770 (M$^+$, 77), 233 (16), 203 (17), 189 (100).
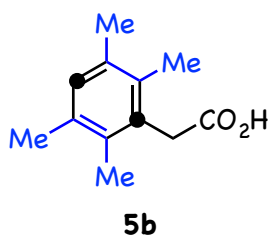
2-(2,3,5,6-Tetramethylphenyl)acetic acid (5b).

IR (KBr) 3086 (br), 3002 (s), 2924 (s), 2874 (s), 2732 (br), 2332 (m), 1695 (s), 1607 (m), 1408 (m), 1381 (m), 1213 (s), 1010 (m), 935 (m), 868 (m), 681 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.20 (s, 6 H), 2.23 (s, 3 H), 2.24 (s, 3 H), 3.79 (s, 2 H), 6.91 (s, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 16.1, 20.6, 35.5, 128.8, 129.4, 132.9, 133.7, 175.7; High-resolution MS, calcd for C$_{12}$H$_{16}$O$_2$: 192.1150. Found m/z (relative intensity): 193 (M$^+$+1, 13), 192.1144 (M$^+$, 76), 147 (100).

5c

2-(2,3,5,6-Tetrapropylphenyl)acetic acid (5c).

IR (KBr) 3103 (br), 2957 (s), 2932 (s), 2870 (s), 2711 (br), 2354 (m), 1703 (s), 1562 (m), 1454 (s), 1414 (m), 1018 (m), 912 (m), 791 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.99 (t, J = 7.6 Hz, 6 H), 1.01 (t, J = 7.6 Hz, 6 H), 1.45 (sext, J = 7.6 Hz, 4 H), 1.59 (sext, J = 7.6 Hz, 4 H), 2.50 (t, J = 7.6 Hz, 4 H), 2.54 (t, J = 7.6 Hz, 4 H), 3.75 (s, 2H), 6.91 (s, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.4, 14.8, 24.0, 24.5, 31.9, 34.8, 35.2, 129.7, 130.0, 137.3, 138.0, 177.7; High-resolution MS, calcd for C$_{20}$H$_{32}$O$_2$: 304.2402. Found m/z (relative intensity): 304.2392 (M$^+$, 100), 275 (56), 245 (57).


5d
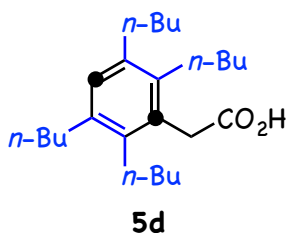
2-(2,3,5,6-Tetrabutylphenyl)acetic acid (5d).

IR (neat) 3075 (br), 2957(s), 2930 (s), 2860 (s), 2669 (m), 2343 (m), 1709 (s), 1464 (m), 1410 (m), 1379 (m), 1292 (m), 1227 (m), 930 (m), 899 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.95 (m, 12 H), 1.38-1.46 (m, 16 H), 2.52-2.58 (m, 8 H), 3.75 (s, 1 H), 6.91. (s, 2 H) ; ^{13}C NMR (CDCl$_3$, 100 MHz) δ 13.8, 13.9, 14.0, 23.0, 23.4, 29.4, 32.8, 32.9, 33.8, 34.9, 124.6, 129.7, 129.9, 137.3, 138.2, 140.1, 178.6 ; High-resolution MS, calcd for C$_{24}$H$_{40}$O$_2$: 360.3028. Found m/z (relative intensity): 361 (M$^+$+1, 26), 360.3055 (M$^+$, 100), 316 (9).

5e
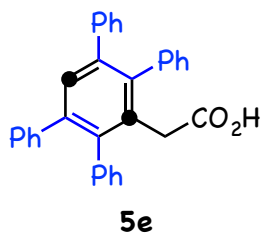
2-{(2,3,5,6-Tetrahenyl)phenyl}acetic acid (5e).

IR (neat) 3024 (br), 2866 (s), 2835 (s), 2500 (m), 1717 (s), 1653 (s), 1578 (m), 1420 (s), 1232 (s), 918 (m), 692 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.66 (s, 2 H), 7.34-7.69 (m, 21 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ37.0, 127.4, 127.5, 128.3, 128.4, 128.5, 128.7, 131.9, 132.0, 171.1; High-resolution MS, calcd for C$_{32}$H$_{24}$O$_2$: 440.1776. Found *m/z* (relative intensity): 441 (M$^+$+1, 29), 440.1769 (M$^+$, 43.8), 395 (100).

5f
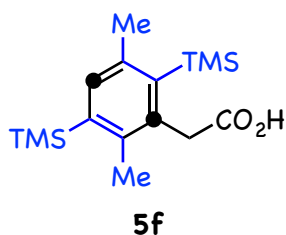
2-(2,5-Dimethyl-3,6-bis(trimethylsilyl)phenyl)acetic acid (5f).

IR(neat) 2959 (s), 2903 (s), 2667 (w), 1705 (s), 1636 (m), 1410 (m), 1252 (s), 1211 (m), 1150 (m), 1032 (m), 837 (s), 760 (s), 691 (m), 635 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.31 (s, 9 H), 0.41 (s, 9 H), 2.32 (s, 3 H), 2.45 (s, 3 H), 3.93 (s, 2 H), 7.19 (s, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 0.0, 0.8, 14.0, 20.1, 38.8, 136.2, 137.2, 139.3, 139.6, 140.0, 140.5, 176.4; High-resolution MS, calcd for C$_{16}$H$_{28}$O$_2$Si$_2$: 308.1628. Found *m/z* (relative intensity): 308.1634 (M$^+$, 11.1), 293 (100).
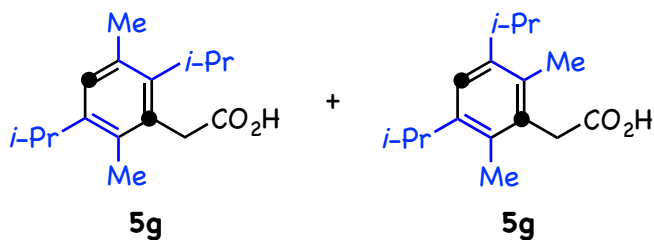
2-(2,6-diisopropyl-3,5-dimethylphenyl)acetic acid (5g) : (a mixture of regioisomers in a 2 : 1 ratio).

IR(neat) 2874 (s), 2899 (s), 2548 (m), 2341 (m), 1713 (s), 1653 (m), 1418 (s), 1265 (s), 1209 (s), 739 (s),704 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, major isomer) δ 1.31 (d, J = 7.3 Hz, 12 H), 2.35 (brs, 6 H), 3.38(br, 2 H), 3.88 (s, 2 H), 6.86 (s, 1 H) ; ^{13}C NMR (100 MHz, CDCl$_3$, major isomer) δ 21.1, 23.3, 29.4, 36.0, 129.7, 130.2, 133.5, 143.6, 178.0 ; ^{1}H NMR (400 MHz, CDCl$_3$, minor isomer) δ 1.20(d, J = 6.8 Hz, 6 H), 1.31(d, J = 7.3 Hz, 6 H), 2.38(s, 6 H), 3.13(sept, J = 6.8 Hz, 2 H), 3.85(s, 2 H), 6.96(s, 1 H) ; ^{13}C NMR (100 MHz, CDCl$_3$, minor isomer) δ 15.1, 21.7, 23.4, 27.6, 29.7, 30.0, 36.1, 130.9, 131.4, 133.2, 134.8, 141.7, 143.8, 178.4 ; High-resolution MS, calcd for C$_{16}$H$_{24}$O$_2$: 248.1776 Found m/z (relative intensity): 249 (M$^+$+1, 6), 248.1771 (M$^+$, 36.0), 233 (22), 206 (14).
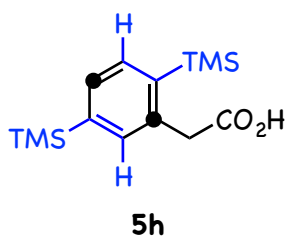
2-(2,5-Bis(trimethylsilyl)phenyl)acetic acid (5h).

IR(neat) 2955 (s), 2899 (s), 2856 (m), 1713 (s), 1410 (m), 1373 (m), 1250 (s), 839 (s), 752 (s), 691 (m),637 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.26 (s, 9 H), 0.33 (s, 9 H), 3.81 (s, 2 H), 7.40 (d, J = 1.0 Hz, 1 H), 7.42 (dd, J = 7.8, 1.0 Hz, 1 H), 7.51 (d, J = 7.3 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ -0.9, 0.6, 41.5, 131.8, 134.3, 135.5, 138.0, 140.0, 142.0, 177.8; High-resolution MS, calcd

for $C_{14}H_{24}O_2Si_2$: 280.1315. Found m/z (relative intensity): 281 (M$^+$+1, 6), 280.1320 (M$^+$, 0.6), 265 (100).

5i
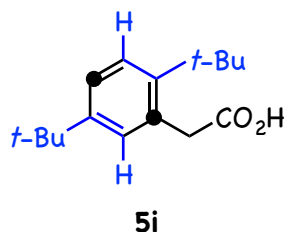
2-(2,5-Di-*tert*-butylphenyl)acetic acid (5i).

IR(neat) 2868 (s), 2550 (s), 2341 (m), 1699 (s), 1464 (s), 1416 (s), 1362 (s), 1231 (s), 1204 (s), 910 (s), 824 (s), 741 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.29 (s, 9 H), 1.39 (s, 9 H), 3.95 (s, 2 H), 7.21 (s, 1 H), 7. 33 (d, J = 8.5 Hz, 1 H), 7.38 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 31.2, 31.6, 34.0, 36.5, 40.2, 124.0, 126.0, 130.0, 130.8, 148.4, 149.6, 177.8; High-resolution MS, calcd for $C_{16}H_{24}O_2$: 248.1776. Found m/z (relative intensity): 248.1768 (M$^+$, 49.5), 233 (100), 216 (2.5), 203 (1.6).

6a
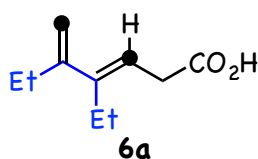
(3*E*)-4-Ethyl-5-methylene-3-heptenoic acid (6a).

IR(neat) 2970 (s), 2936 (s), 2878 (s), 1713 (s), 1607 (m), 1413 (s), 1288 (s), 1219 (s), 893 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.98 (t, J = 7.5 Hz, 3 H), 1.05 (t, J = 7.5 Hz, 3 H), 2.25 (qd, J = 7.5, 1.3 Hz, 2 H), 2.25 (q, J = 7.5 Hz, 2 H), 3.21 (d, J = 7.1 Hz, 2 H), 4.92 (d, J = 1.3 Hz, 1 H), 5.03 (s, 1 H), 5.64 (t, J = 7.1 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 13.2, 13.4, 21.5, 26.9, 33.5, 110.1,

116.1, 144.5, 149.2, 177.7; High-resolution MS, calcd for $C_{10}H_{16}O_2$: 168.1150. Found m/z (relative intensity): 169 (M$^+$+1, 83.7), 168.1143 (M$^+$, 51.1), 153 (100).
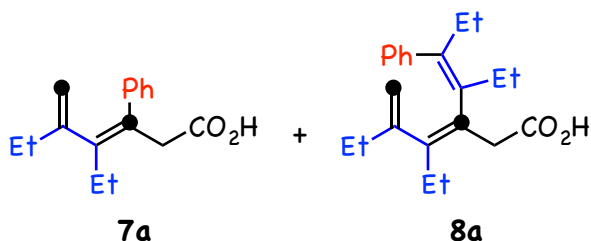
A mixture of (3Z)-4-ethyl-5-methylene-3-phenyl-3-heptenoic acid (7a) and (3Z)-4-ethyl-5-methylene-3-[(3Z)-4-phenyl-3-hexenyl]-3-heptenoic acid (8a) in a 1 : 2 ratio

IR(neat) 3402 (br), 3084 (s), 3028 (s), 2966 (s), 2934 (s), 1705 (s), 1636 (s), 1441 (m), 1410 (m), 1286 (m), 943 (s), 897 (s), 766 (s), 700 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, (**3g**)) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.05 (t, J = 7.5 Hz, 3 H), 2.31 (q, J = 7.5 Hz, 2 H), 2.33 (q, J = 7.5 Hz, 2 H), 2.78 (s, 2 H), 4.89 (s, 1 H), 5.01 (s, 1 H), 7.08-7.32 (m, 5 H); ^{13}C NMR (CDCl$_3$, 100 MHz, (**3g**)) δ 11.9, 12.5, 26.0, 28.5, 41.7, 118.4, 126.0, 127.6, 128.9, 139.1, 141.8, 143.0, 145.7, 176.2; High-resolution MS (**3g**), calcd for $C_{16}H_{20}O_2$: 244.1463. Found m/z (relative intensity): 245 (M$^+$+1, 19.0), 244.1458 (M$^+$, 100), 242 (2.9).

^{1}H NMR (CDCl$_3$, 400 MHz, (**3h**)) δ 0.86 (t, J = 7.5 Hz, 3 H), 0.87 (t, J = 7.5 Hz, 3 H), 1.02 (t, J = 7.5 Hz, 3 H), 1.06 (t, J = 7.5 Hz, 3 H), 1.85 (q, J = 7.5 Hz, 2 H), 2.31 (q, J = 7.5 Hz, 2 H), 2.33 (q, J = 7.5 Hz, 2 H), 2.40 (q, J = 7.5 Hz, 2 H), 3.47 (s, 2 H), 4.65 (d, J = 1.5 Hz, 1 H), 4.80 (d, J = 1.5 Hz, 1 H), 7.08-7.32 (m, 5 H); ^{13}C NMR (CDCl$_3$, 100 MHz, (**3h**)) δ 11.9, 12.5, 13.1, 13.2, 25.3, 25.9, 27.4, 28.4, 39.5, 113.2, 126.1, 126.3, 127.0, 127.5, 127.9, 128.7, 138.4, 142.9, 150.2, 176.2; High-resolution MS (**3h**), calcd for $C_{22}H_{30}O_2$: 326.2246. Found m/z (relative intensity): 327 (M$^+$+1, 42.6), 326.2242 (M$^+$, 72.7), 297 (100), 282 (60.3).

X-ray Crystal Structure Determinations

    X-ray quality single crystals were grown from solvent combinations of ethyl acetate/hexane for **5a**. This measurement was made on a Rigaku Saturn724 diffractometer using multi-layer mirror monochromated Mo-Ka radiation. Data was collected and processed using CrystalClear (Rigaku) at a temperature of -179±1 °C to a maximum 2q value of 55°. The structure was solved by direct method (SHELXL-97) and expanded using Fourier technique. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using the riding model. All calculations were performed using the CrystalStructure 4.0 (Crystal Structure Analysis Package, Rigaku Corporation) except for refinement, which was performed using SHELXL-97. Crystal data and refinement parameter for the structurally characterized compound **5a** is summarized in **Table 5**. An ORTEP drawing of **5a** is shown in **Figure 1**. CCDC 828924 contains the supplementary crystallographic data for **5a**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 5. Crystal data and data refinement for **5a**

Formula	$C_{16}H_{24}O_2$
formula weight	248.36
cryst system	triclinic
space group	P-1
cryst color	colorless, platelet
cryst size (mm)	0.155 x 0.083 x 0.027
a (Å)	4.876(3)
b (Å)	9.006(6)
c (Å)	16.659(10)
a (deg)	97.07(2)
b (deg)	94.054(8)
g (deg)	94.82(2)

V (Å^3)		721.0(8)
Z		2
r_{calc} (gcm^{-3})		1.144
μ (cm^{-1})	0.731	
$2q_{max}$ (deg)		54.9
no. of unique reflns		3284
R_{int}		0.0407
no. of parameters	171	
$R1$ ^{a}[I>2σ(I)]		0.0494
R ^{b}(all data)		0.0816
Rw ^{c}		0.1160
GOF ^{d}		1.087

^{a} $R1 = \Sigma \, ||Fo| - |Fc||/\Sigma \, |Fo|$. ^{b} $R = \Sigma \, |Fo^2 - Fc^2|/\Sigma \, Fo^2$. ^{c} $Rw = \{\Sigma w(Fo^2 - Fc^2)^2/\Sigma w \, (Fo^2)^2\}1/2$.

^{d} GOF $= [\{\Sigma w(Fo^2 - Fc^2)^2\}/(No - Np)]^{1/2}$, where No and Np denote the number of observations and parameters.

Figure 1. ORTEP drawing of **4a** with 50% probability ellipsoids.
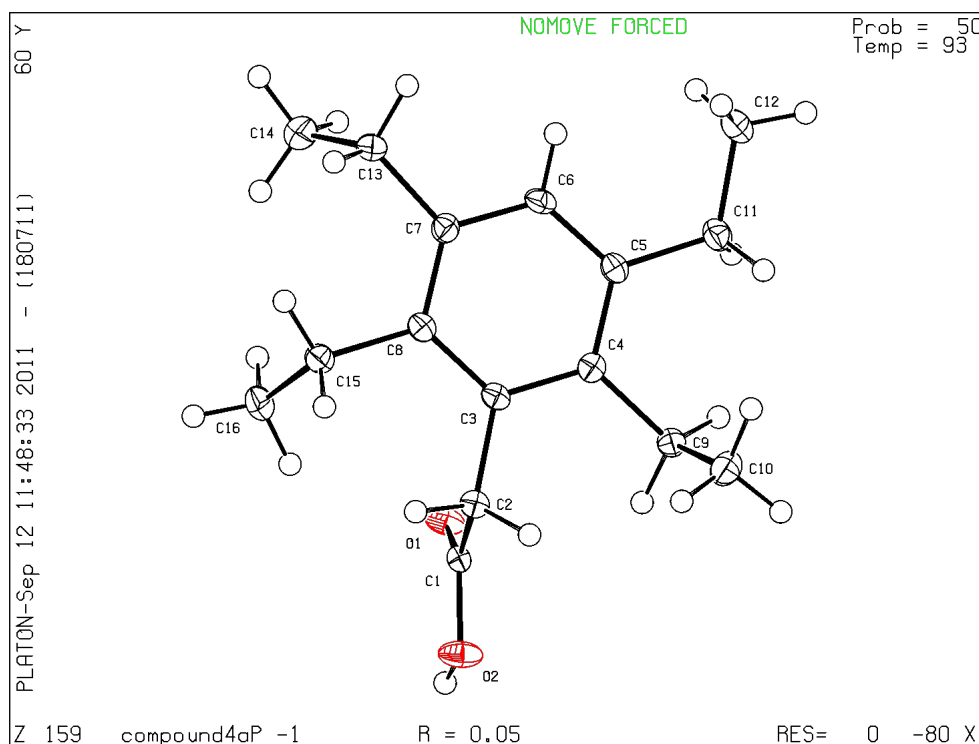
45

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Chapter 2

Nickel-Catalyzed CO$_2$ Rearrangement of Enol Metal Carbonates

for the Efficient Synthesis of β-Ketocarboxylic Acids
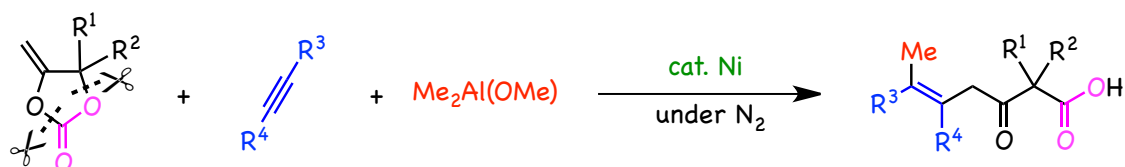
Summary: 4-Methylene-1,3-dioxolan-2-one undergoes oxidative addition of Ni(0) catalyst in the presence of Me$_2$Al(OMe) followed by a coupling reaction with alkynes to form δ,ε-unsaturated β-ketocarboxylic acids with high regio- and stereoselectivities. The reaction proceeds *via* [1,3]-rearrangement of an enolative metal carbonate intermediate and the formal reinsertion of CO$_2$ for efficient construction of the β-ketocarboxylic acid framework.

Introduction

β-Ketocarboxylic acids are useful and valuable key intermediates toward biologically active molecules.[1]   For example, crassulacean acid metabolism (CAM) is an important carbon resource utilization process in the photosynthesis of oxaloacetate from CO_2 by pyruvate carboxylase of green plants.[2]   However, as b-ketocarboxylic acids are thermodynamically unstable, many problems, such as easy extrusion of CO_2 via decarboxylation processes, often arise.[3]   Although metal enolates are highly reactive and convenient nucleophilic intermediates toward carbonyl compounds, little attention has been focused on the fixation of CO_2 using metal enolates.[4]

1,3-Dioxolan-2-ones are also among the most important industrial materials, including electrolytes in lithium ion battery half-cells and as predominant monomers for polycarbonates.[5] Although cyclic carbonates are utilized in fine chemicals and as monomers for polymerization in modern industrial synthesis, most synthetic utilities of 1,3-dioxolan-2-ones face difficulties due to the decarboxylation reaction.[6]

Nickel catalyzed C-C bond transformations have been successfully developed and are powerful tools in modern organic synthesis.[7]   Insertion reactions of CO_2,[8] reductive coupling with alkynes and enones,[9] and multicomponent coupling reactions with unsaturated hydrocarbons[10] are extremely attractive and potent methods for efficient organic synthesis.   Recently we developed the first example of a Ni-catalyzed multicomponent coupling of diketene and alkynes with organometallic reagents, providing unsaturated carboxylic acids and phenylacetic acids (**Scheme 1**).[11]   In this case, the combination of Ni-catalyst and Et$_2$Al(OEt) had a very important role in promoting C=C double bond cleavage reactions of diketene to undergo reconstruction of the molecular framework *via* cycloaddition and migratory processes.
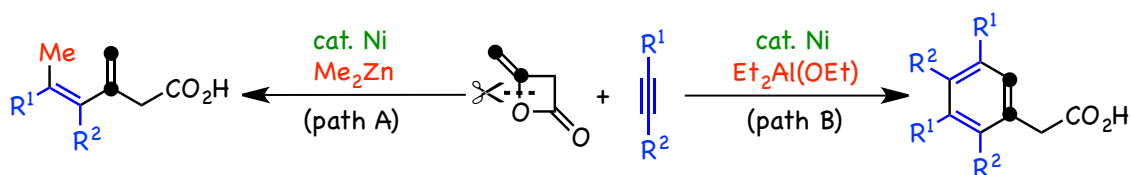
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Scheme 1. Nickel-Catalyzed Multicoupling Reaction of Diketene, Alkyne, and Organometallic Reagents *via* Cleavage of the C=C Bond

Herein, we disclose highly efficient and synthetic protocols for β-ketocarboxylic acids from 4-methylene-1,3-dioxolan-2-one as CO_2 and metal enolate equivalents, by treatment with alkynes and $Me_2Al(OMe)$ in the presence of Ni(0) catalyst (**Scheme 2**).   It is noteworthy that this reaction directly provides δ,ε-unsaturated β-ketocarboxylic acids under N_2 atmosphere without undergoing decarboxylation.
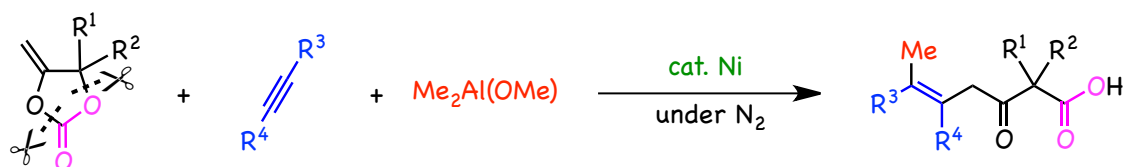

Scheme 2. Nickel-Catalyzed CO_2 Rearrangement of Enol Metal Carbonates for the Efficient Synthesis of δ,ε-Unsaturated β-Ketocarboxylic Acids

Results and Discussion

The optimization of the reaction conditions are summarized in **Table 1**.   At first, the reaction was undertaken in the presence of Ni(cod)$_2$ catalyst, 1,3-dioxolan-2-one **1a**, and 4-octyne by treatment with Me$_2$Al(OMe) at 60 ˚C under N$_2$ atmosphere in a wide variety of solvents. Non-polar solvents, such as hexane and toluene, and cyclic ethers were insufficient, with the desired product **2a**, obtained in low yields and most of substrate **1a** remaining (Entries 1-2, **Table 1**). Ether solvent, such as 1,4-dioxane and THF were used, the desired reaction proceeds in low yields (Entries 3-4, **Table 1**).   In the case of DMF and DMA, the desired product **2a** were obtained in 27% and 34% yields, respectively (Entries 5-6, **Table 1**).   Further screening revealed that the DMSO was the most efficient solvent for this reaction   (Entry 7, **Table 1**).   Next, we examined a variety of organometallic reagents.   In the presence of 5 mol% of Ni(cod)$_2$, the mixture of cyclic carbonate **1a**, 4-octyne, and Me$_3$Al underwent the coupling reaction at 60 ˚C in DMSO to give expected β-ketocarboxylic acid **2a** in 73% yield, with decarboxylated product **3a** in 21% yield (Entry 8, **Table 1**). Using Me$_2$Zn instead of Me$_2$Al(OMe), desired product **2a** was obtained in 65% yield (Entry 9, **Table 1**).   In the case of Me$_3$B, the desired transformation proceeded to give the corresponding product **2a** in low yield along with decarboxylated ketone **3a** as a major product (Entry 10, **Table 1**).   Et$_3$Al, Et$_2$Al(OEt), and Ph$_3$Al were not effective at promoting the coupling reactions via ethyl and phenyl group insertion, resulting in complex mixture (Entries 11-13, **Table 1**).   That is, Me$_2$Al(OMe) was the most efficient organometallic reagent for the desired coupling reaction.   In the case of CO$_2$ atmospheric pressure, total yields and the selectivities of formation of the desired product **2a** and by-product **3a** were almost same, irrespective of N$_2$ and CO$_2$ atmosphere (Entries 7 vs 14, **Table 1**).   These results suggest that intramolecular rearrangement of

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CO_2 is probable rather than the decarboxylation-carboxylation sequence.   When Ni(acac)$_2$ was used as a catalyst instead of Ni(cod)$_2$, the product yield was lower (Entry 15, **Table 1**).   As expected, control experiments revealed no product formation when each parameter was omitted from the mixture (Entries 16-17, **Table 1**).

Table 1. Optimization of the Reaction Conditions for Nickel-Catalyzed CO_2 Rearrangement of Enol Metal Carbonates for the Efficient Synthesis of δ,ε-Unsaturated β-Ketocarboxylic Acids[a]
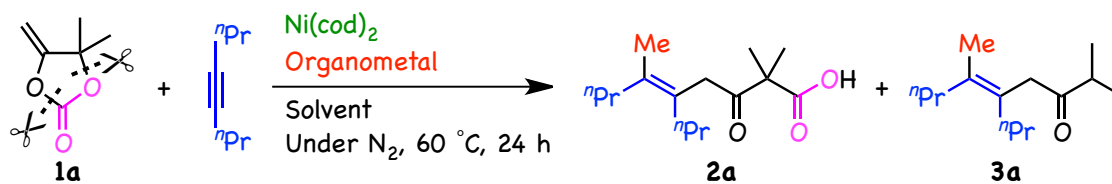

| Entry | Solvent | Organometal | Isolated Yield [%] | |
			2a	3a
1	Hexana	Me₂Al(OMe)	9	trace
2	Toluene	Me₂Al(OMe)	26	15
3	1,4-Dioxane	Me₂Al(OMe)	24	13
4	THF	Me₂Al(OMe)	34	23
5	DMF	Me₂Al(OMe)	27	12
6	DMA	Me₂Al(OMe)	34	10
7	**DMSO**	**Me₂Al(OMe)**	**82**	**14**
8	DMSO	Me₃Al	73	21
9	DMSO	Me₂Zn	65	19
10	DMSO	Me₃B	18	70
11	DMSO	Et₃Al	Complex Mixture	
12	DMSO	Et₂Al(OEt)	Complex Mixture	
13	DMSO	Ph₃Al	Complex Mixture	
14[b]	DMSO	Me₂Al(OMe)	84	12
15[c]	DMSO	Me₂Al(OMe)	67	10
16[d]	DMSO	Me₂Al(OMe)	0	0
17	DMSO	None	0	0

[a]The reaction was undertaken in the presence of [Ni(cod)₂] (5.0 mol%), cyclic carbonate **1a** (1.2 mmol), 4-octyne (1.0 mmol), and organoaluminium reagent (1.2 mmol) in solvent (3.0 mL) at 60 °C under nitrogen atmosphere for 24 h. [b]Under CO_2 (1.0 atm). [c]5.0 mol% of Ni(acac)₂ was used. [d]In the absence of Ni(cod)₂.

Next, we investigated the reaction of cyclic carbonate **1a** with a various kinds of alkynes, and the results summarized in **Table 2**. Symmetrical alkynes, such as 2-butyne, 3-hexyne, 4-octyne, and 5-decyne reacted smoothly with cyclic carbonate **1a** in the presence of Me$_2$Al(OMe) to provide corresponding β-ketocarboxylic acids **2a**-**2d** in good yields (Entries 1-4, **Table 2**).   In the case of unsymmetrical alkynes, such as 4-methyl-2-pentyne, 1-trimethylsilyl-1-propyne, and 1-phenyl-1-propyne, the corresponding β-ketocarboxylic acids **2e-2g** were obtained in modest to good yields (Entries 5-7, **Table 2**).   The less hindered substituted acetylenic carbon atoms tended to attack on the vinylogous carbon atoms of carbonate.   β-Keto acids **2e** and **2f** were obtained as a mixture of regioisomers, whereas **2g** was obtained as a single isomer.

Table 2. Ni-Catalyzed Coupling of Cyclic Carbonate **1a** with Various Alkyne and Me$_2$Al(OMe)[a]
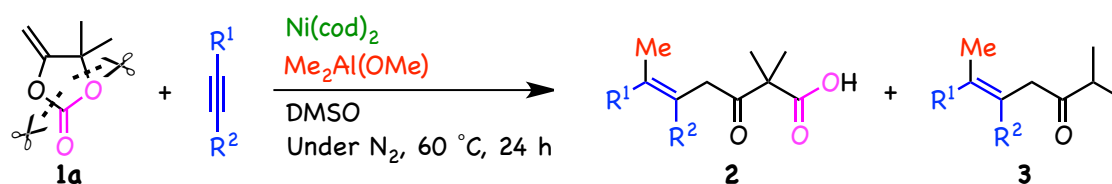
Entry	R^1	R^2	Isolated Yield [%]	
			2	3
1	Me	Me	**2b** : 82	**3b** : 12
2	Et	Et	**2c** : 79	**3c** : 13
3	^{n}Pr	^{n}Pr	**2a** : 82	**3a** : 14
4	^{n}Bu	^{n}Bu	**2d** : 76	**3d** : 14
5	^{i}Pr	Me	**2e** : 77 [2.2:1][b]	**3e** : 9
6	TMS	Me	**2f** : 34 [5.5:1][b]	**3f** : trace
7	Ph	Me	**2g** : 33 [>99:1][b]	**3g** : 9

[a]The reaction was undertaken in the presence of [Ni(cod)$_2$] (5.0 mol%), cyclic carbonate **1a** (1.2 mmol), alkyne (1.0 mmol), and Me$_2$Al(OMe) (1.2 mmol) in DMSO (3.0 mL) at 60 °C under nitrogen atmosphere for 24 h. [b]The ratios show the regioselectivities with respect to the alkyne substitutents.

The results of treating 4-substitited cyclic carbonates (**1a**, **1h**-**1l**) with 3-hexyne are shown in **Table 3**. Unsymmetrical 5-disubstituted carbonate **1h** (R^1=Et, R^2=Me) gave unsymmetrical α-disubstituted β-keto acid **2h** as the major product, as well as ketone **3h** (Entry 2, **Table 3**). Phenyl and methyl substituted cyclic carbonate **1i** was transformed into β-keto acid **2i** in lower yield as a mixture with ketone **3i** as a major product (Entry 3, **Table 3**). Unsubstituted cyclic carbonate **1j** (R^1=H, R^2=H) underwent a similar coupling reaction, giving rise to a mixture of β-keto acid **2j** and ketone **3j** as a minor product (Entry 4, **Table 3**). In the case of mono-substituted carbonate **1k** (R^1=Me, R^2=H), a mixture of regioisomers α-methyl-β-keto acid **2k** and γ-methyl-β-keto acid **2'k** were produced in 63% yield in a ca. 3:1 ratio, along with a small amount of ketone **3k** and **3'k** in 20% yield (Entry 5, **Table 3**). Seemingly, 5-phenyl substituted carbonates undergo the decarboxylation as a side reaction (Entry 6, **Table 3**). The ratios of β-keto acid **2** and ketone **3** might depend on the stability of the metal enolates as key intermediates, in addition to the steric bulk of the R^1 and R^2 groups.

The structures of the products **2f**, **2g**, **2k**, and **2'k** were determined based on coupling constants from ^{1}H NMR, ^{13}C NMR, HMBC, HMQC spectral data and NOE experiment. The selected data for the NOE observed by the irradiation at the bold face protons are illustrated in **Figure 1**.

Table 3. Ni-Catalyzed Coupling of Various Cyclic Carbonate **1** with 3-hexyne and Me$_2$Al(OMe)^a
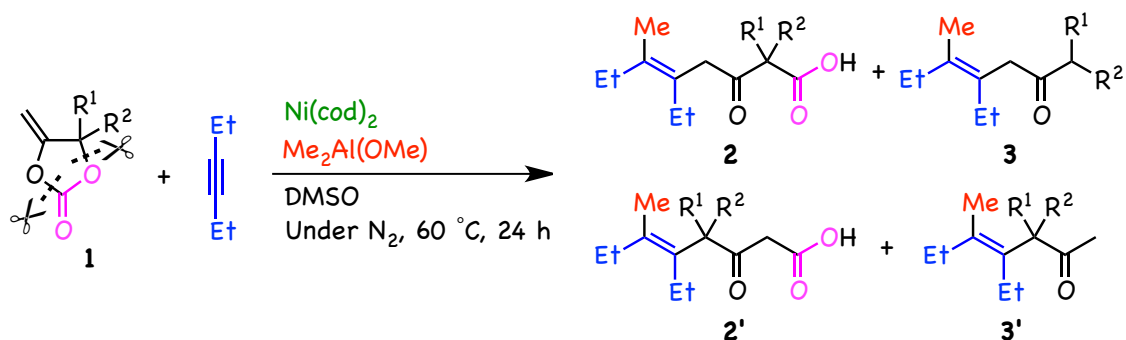
Entry	R^1	R^2	1	Isolated Yield [%]	
				2	3
1	Me	Me	1a	2c : 79	3c : 13
2	Et	Me	1h	2h : 52	3h : 35
3^b	Ph	Me	1i	2i : 15	3i : 72
4^b	H	H	1j	2j : 60	3j : 25
5^b	Me	H	1k	2k : 45, **2'k** : 18	3k : 11, **3'k** : 9
6^b	Ph	H	1l	2l : 38, **2'k** : 12	3l : 36, **3'l** : 5

^{a}The reaction was undertaken in the presence of [Ni(cod)$_2$] (5.0 mol%), cyclic carbonate **1** (1.2 mmol), 3-hexyne (1.0 mmol), and Me$_2$Al(OMe) (1.2 mmol) in DMSO (3.0 mL) at 60 °C under nitrogen atmosphere for 24 h. ^{b}β-Ketocarboxylic acids **2** and **2'** were isolated as methyl ester by treatment of products with trimethylsilyldiazomethane.
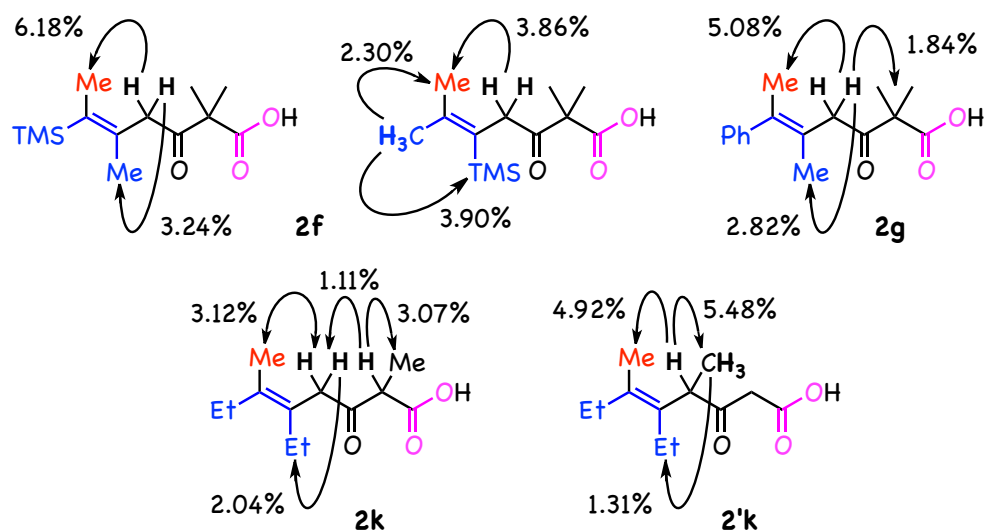
Figure 1. Structure Determination for NOE Data of β-Ketocarboxylic Acids **2f**, **2g**, **2k**, and **2'k**

Next, the reaction of a stoichiometric amount of Ni(cod)$_2$, alkyne, and cyclic carbonate without Me$_2$Al(OMe) was conducted (**Scheme 3**).   In the absence of Me$_2$Al(OMe), the mixture of Ni(cod)$_2$ (0.5 mmol), 4-octyne (0.5 mmol), and cyclic carbonate (0.5 mmol) did not provide the expected β-keto acid **2m** and the corresponding decarboxylated ketone **3m**.   In this case, the reaction was not proceed at all and the almost carbonate was recovered.   This result shows Me$_2$Al(OMe) is indispensable to carry out the reaction even in DMSO solvent.[12]   That is, we believe that Me$_2$Al(OMe) acts as a Lewis acid and promotes the oxidative addition in the first step.
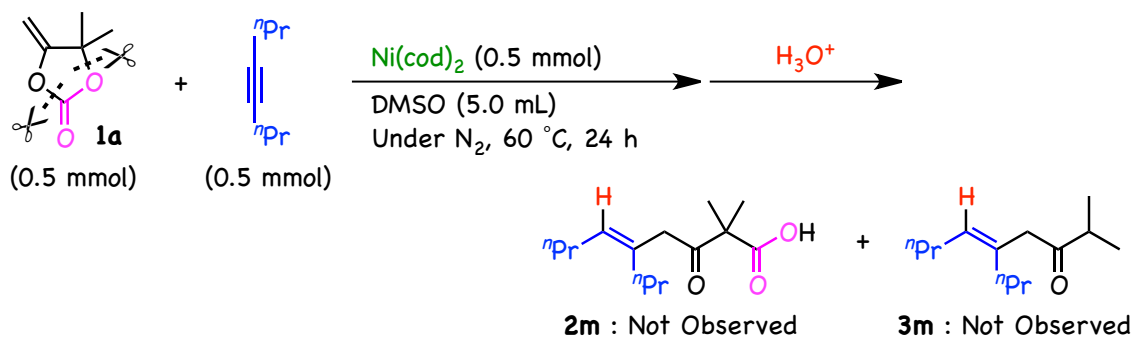
**Scheme 3**. Stoichiometric Reaction in the Absence of Me$_2$Al(OMe)

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Although it would be premature to provide a complete explanation of the reactivities and selectivities described herein, a plausible mechanism for the multicomponent coupling reaction of 5-substituted 4-methylene-1,3-dioxolan- 2-ones with alkynes promoted by the Ni catalyst and Me$_2$Al(OMe) is proposed in **Scheme 4**. Thus, oxidative addition of the cyclic carbonate to the Ni(0) catalyst, promoted by Me$_2$Al(OMe) as a Lewis acid, at the allylic moiety proceeds to form the oxanickelacycle intermediate **I**. The stability of metallacycle **I** seems to depend on the type of 5-substituents, and readily isomerizes to the more stabilized nickelacycle **III** *via* σ-π-σ allylnickel interconversions.[13] The insertion of additional alkyne proceeds to form eight-membered oxanickelacycle intermediate **V**, which then undergoes transmetallation with Me$_2$Al(OMe) to form enolative aluminum carbonate **VII**.[14] This enol metal carbonate **VII** readily undergoes [1,3]-rearrangement to afford β-ketocarboxylic acid,[15] followed by reductive elimination resulting in the generation of catalytically active Ni(0) species.
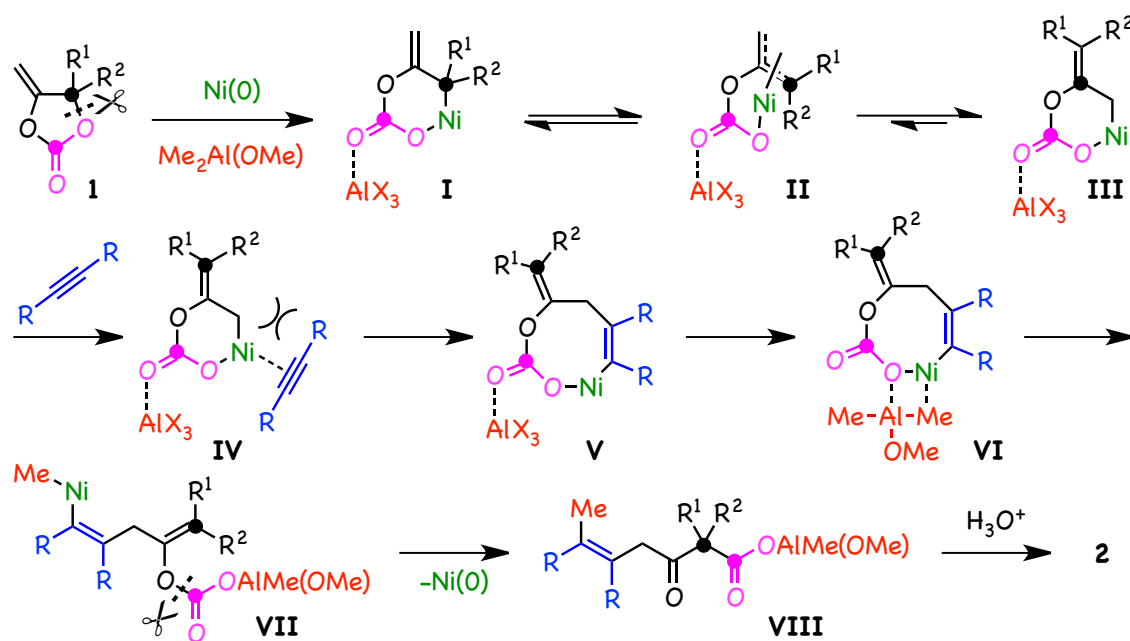
Scheme 4. Plausible Reaction Mechanism for the Multicomponent Coupling Reaction of Cyclic Carbonate and Alkyne with Me$_2$Al(OMe)

In the case of mono-substituted cyclic carbonate, the coupling reaction proceeds to give γ-substituted β-keto acid **2'** as a by-product, and the plausible reaction mechanism shown in **Scheme 5**. Oxidative addition of the cyclic carbonate to the Ni(0) catalyst, promoted by Me$_2$Al(OMe) as a Lewis acid, at the allylic moiety proceeds to form the oxanickelacycle intermediate **I**. The insertion of additional alkyne proceeds to form eight-membered oxanickelacycle intermediate **V'**, which then undergoes transmetallation with Me$_2$Al(OMe) to form enolative aluminum carbonate **VII'**. This enol metal carbonate **VII'** readily undergoes [1,3]-rearrangement to afford γ-substituted β-ketocarboxylic acid **2'**, followed by reductive elimination resulting in the generation of catalytically active Ni(0) species.
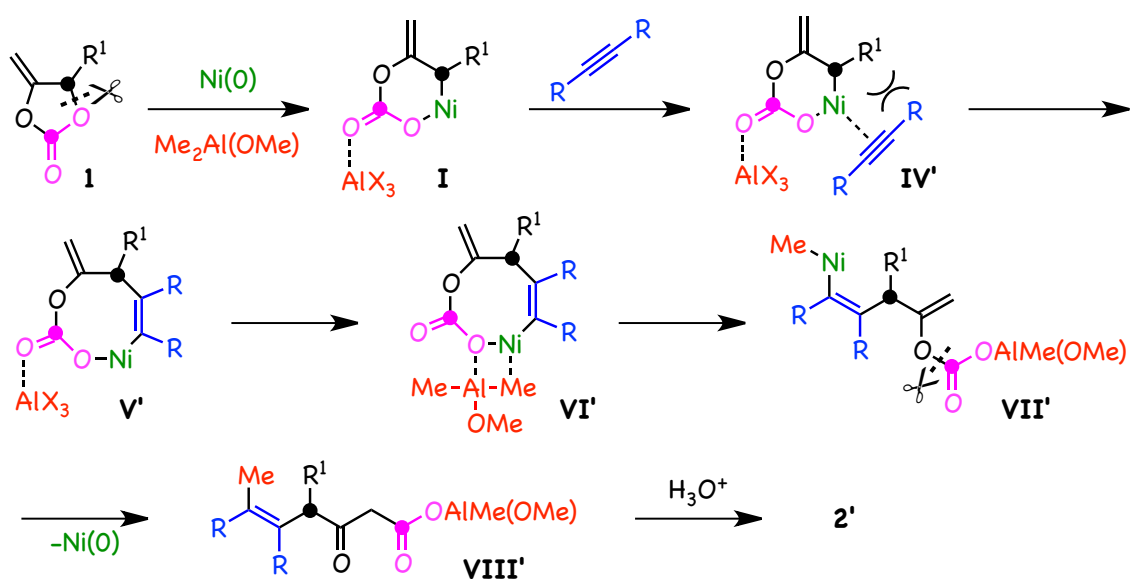
Scheme 5. Plausible Reaction Mechanism for the Multicomponent Coupling Reaction of Mono-Substituted Cyclic Carbonate and Alkyne with Me$_2$Al(OMe)

Conclusion

In conclusion, we developed an efficient first synthesis of β-ketocarboxylic acids from 4-methylene-1,3-dioxolan-2-one *via* oxidative addition of Ni(0) catalyst in the presence of $Me_2Al(OMe)$ and alkynes.   [1,3]-Rearrangement of enolative aluminum carbonate proceeds to form δ,ε-unsaturated β-ketocarboxylic acids with high regio- and stereoselectivities.   This protocol contributes to the efficient fixation of CO_2 for the carbon resource utilization, as in the CAM process in biological photosynthesis.

Reactions employed oven-dried glassware unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator (Merck, Silica gel 60F$_{254}$). Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. Proton and carbon NMR data were obtained with a JEOL-GX400 and Varian-500PS-SN with tetramethylsilane as an internal standard. Chemical shift values were given in ppm downfield from the internal standard. Infrared spectra were recorded with a JASCO A-100 FT-IR spectrophotometer. High resolution mass spectra (HRMS) were measured with a JEOL JMS-700N.

Solvents and Reagents

Anhydrous hexane, toluene, DME, dioxane, THF, DMA, DMF, DMSO were purchased (Wako) and used without further purification. Ni(cod)$_2$, Me$_2$Zn (1.0 M hexane solution), Me$_3$Al (1.0 M hexane solution), Et$_3$Al (1.0 M hexane solution), Et$_2$Al(OEt) (1.0 M hexane solution) (Kanto Kagaku) were purchased and used without further purification. Me$_2$Al(OMe) was prepared by adding an equimolar amount of MeOH to a hexane solution of Me$_3$Al before used. Me$_3$B was prepared from BCl$_3$ (1.0 M heptane solution, Aldrich) and 3-equivalents of MeLi (1.17 M dietylether solution, Kanto Kagaku). 2-Butyne, 3-hexyne, 4-octyne, 5-decyne, 4-methyl-2-pentyne, 1-trimethylsilyl-1-propyne, and 1-phenyl-1-propyne (Tokyo Kasei Kogyo Co., Ltd) were purchased and distilled prior to use.

Preparation of Me₂Al(OMe) Reagent

A 25 mL two-necked round-bottomed flask equipped with a rubber septum was charged with Me₃Al solution (2.0 mL of 1.0 M in hexane, 2 mmol, Kanto Kagaku) under argon atmosphere. Anhydrous MeOH (2.0 mmol, Wako) was added to the Me₃Al solution via syringe at 0 °C for 30 min.

Preparation of Me₃B Reagent

A 100 mL Schlenk tube equipped with a rubber septum was charged with BCl_3 solution (2.0 mL of 1.0 M in heptane, 2.0 mmol, Aldrich) under argon atmosphere. A solution of MeLi (5.1 mL of 1.17 M in diethylether, 6.0 mmol, Kanto Kagaku) was added to the BCl_3 solution via syringe at 0 °C to room temperature for 12 hours.

Preparation of 1a

The reaction of 2-methyl-3-butyn-2-ol with CO_2 was carried out in a 100 mL stainless steel autoclave equipped with a stirring bar in high pressure. The autoclave containing 2-methyl-3-butyn-2-ol (1.95 mL, 20 mmol) was purged with argon gas to remove oxygen. $^nBu_3P$ (0.25 mL, 1.0 mmol) was introduced into the autoclave with a syringe while the vessel was purged with argon. After the vessel was filled with carbon dioxide (5.0 MPa) and stirred for 16 hours at 100 °C. The crude product were purified by column chromatography on silica gel (hexane/ethyl acetate = 4/1 v/v) to yield 5,5-dimethyl-4-methylene-1,3-dioxolan-2-one **1a** (86%).

Preparation of 1k

To a solution of propargyl *tert*-butyl carbonate in dichloromethane (0.5 M) at room temperature was added the $(PPh_3)AuNTf_2$ catalyst (0.01 equiv). After the reaction, dichloromethane was evaporated in vacuo, and then the residue was purified by column chromatography over silica gel (hexane/ethyl acetate = 4/1 v/v) to yield 5-methyl-4-methylene-1,3-dioxolan-2-one **1k** (85%).

General Procedure: Formation of β-Ketocarboxylic Acid 2 from 4-Methylene-1,3-dioxolan-2-one by Ni-catalyst (Entry 7, **Table 1**)

To a solution of $Ni(cod)_2$ (13.8 mg, 0.05 mmol) in anhydrous DMSO (3.0 mL) were successively added 5,5-dimethyl-4-methylene-1,3-dioxolan-2-one **1a** (153.8 mg, 1.2 mmol), 4-octyne (110.2 mg, 1.0 mmol), and $Me_2Al(OMe)$ (1.2 mmol, 1.0 M hexane solution) via syringe under nitrogen atmosphere.   The mixture was stirred at 60 °C for 24 h.   The mixture was diluted with ethyl acetate (30 mL) and washed with 2 M HCl, and brine, and then dried ($MgSO_4$) and concentrated in vacuo.   The residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 1/1 v/v) to give **2a** (208.6 mg, 82%, R_f = 0.50; hexane/EtOAc = 1/1 v/v) along with **3a** (29.4 mg, 14%, R_f = 0.73; hexane/EtOAc = 4/1 v/v).

Typical Procedure for Isolation as Methyl Ester by Treatment of β-Ketocarboxylic Acid with Trimethylsilyldiazomethane (Entry 4, **Table 3**)

To a crude mixture of the products dissolved in Et_2O (20.0 mL) and MeOH (5.0 mL), and was added $TMSCHN_2$ (2.0 M in Et_2O) at 0 °C and stirred for 1 hour.   AcOH (2.0 mL) was added at 0 °C and stirred for 5 min, and sat. $NaHCO_3$ was added.   The mixture was extracted with ethyl acetate (30 mL) and washed with brine, and then dried ($MgSO_4$) and concentrated in vacuo.   The

residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 20/1 v/v) to give **2j** (127.4 mg, 60%, R_f = 0.60; hexane/EtOAc = 4/1 v/v) along with **3j** (38.3 mg, 25%, R_f = 0.73; hexane/EtOAc = 4/1 v/v).

2a
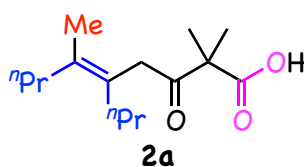
(*E*)-2,2,6-Trimethyl-3-oxo-5-propylnon-5-enoic acid (2a)

IR (neat) 3153 (br), 2961 (s), 2934 (s), 2872 (s), 1717 (s), 1701 (s), 1466 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.87 (t, *J* = 7.3 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 1.28 (sext, *J* = 7.3 Hz, 2 H), 1.42 (sext, *J* = 7.3 Hz 2 H), 1.44 (s, 6 H), 1.53 (s, 3 H), 1.97 (t, *J* = 7.3 Hz, 2 H), 2.06 (t, *J* = 7.3 Hz, 2 H), 3.33 (s, 2H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.0, 14.2, 18.5, 21.6, 21.8, 22.4, 35.0, 36.2, 41.5, 55.5, 125.4, 133.7, 179.5, 205.8 ; High-resolution MS, calcd for C$_{15}$H$_{26}$O$_3$: 254.1882. Found *m/z* (relative intensity): 254.1874 (M$^+$, 51.6), 210 (100).

3a
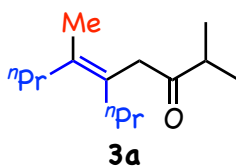
(*E*)-2,6-Dimethyl-5-propylnon-5-en-3-one (3a)

IR (neat) 2961 (s), 2932 (s), 2872 (s), 1709 (s), 1466 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, *J* = 7.3 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 1.08 (d, *J* = 6.8 Hz, 6 H), 1.32 (sext, *J* = 7.3 Hz, 2 H), 1.42 (sext, *J* = 7.3 Hz, 2 H), 1.60 (s, 3 H), 1.99 (t, *J* = 7.3 Hz, 2 H), 2.06 (t, *J* = 7.3 Hz, 2 H), 2.69 (sept, *J* = 6.8 Hz, 1H), 3.19 (s, 2H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.1, 14.2, 18.6, 18.7, 21.6,

21.8, 35.1, 36.3, 39.7, 44.9, 126.5, 133.1, 213.3 ; High-resolution MS, calcd for $C_{14}H_{26}O$: 210.1984.

Found *m/z* (relative intensity): 210.1984 (M$^+$, 100), 167 (65).

2b
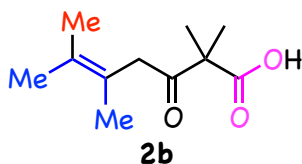
2,2,5,6-Tetramethyl-3-oxohept-5-enoic acid (2b)

IR (neat) 3167 (br), 2984 (s), 2918 (s), 2876 (m), 1713 (s), 1705 (s), 1470 (m) cm^{-1}; ^{1}H NMR (400

MHz, CDCl$_3$) δ 1.44 (s, 6 H), 1.60 (s, 3 H), 1.62 (s, 3 H), 1.71 (s, 3 H), 3.34 (s, 2 H); ^{13}C NMR (100

MHz, CDCl$_3$) δ 19.1, 20.6, 20.6, 22.2, 43.7, 55.5, 120.5, 128.9, 179.5, 206.0; High-resolution MS,

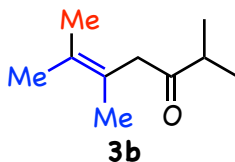calcd for $C_{11}H_{18}O_3$: 198.1256. Found *m/z* (relative intensity): 198.1255 (M$^+$, 100), 180 (3).

3b

2,5,6-Trimethylhept-5-en-3-one (3b)

IR (neat) 2968 (s), 2926 (s), 2874 (s), 1711 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.09 (d, *J* = 6.8

Hz, 6 H), 1.65 (s, 3 H), 1.66 (s, 3 H), 2.67 (sept, *J* = 6.8 Hz, 1H), 3.20 (s, 2H); ^{13}C NMR (100 MHz,

CDCl$_3$) δ 18.4, 19.2, 20.6, 20.7, 39.8, 46.7, 121.3, 128.2, 213.3; High-resolution MS, calcd for

$C_{10}H_{18}O$: 154.1358. Found *m/z* (relative intensity): 154.1361 (M$^+$, 20.8), 135 (100).
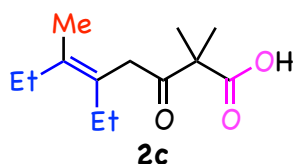
(*E*)-5-Ethyl-2,2,6-trimethyl-3-oxooct-5-enoic acid (2c)

IR (neat)   2968 (s), 2936 (m), 2874 (m), 1717 (s), 1705 (s), 1456 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H), 1.44 (s, 6 H), 1.55 (s, 3 H), 2.02 (q, J = 7.3 Hz, 2 H), 2.09 (q, J = 7.3 Hz, 2 H), 3.33 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.2, 13.2, 18.1, 22.4, 25.7, 27.1, 41.1, 55.5, 126.1, 134.8, 179.8, 205.8; High-resolution MS, calcd for C$_{13}$H$_{22}$O$_3$: 226.1569. Found *m/z* (relative intensity): 226.1566 (M$^+$, 38.4), 197 (12), 182 (100).
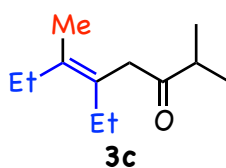

(*E*)-5-Ethyl-2,6-dimethyloct-5-en-3-one (3c)

IR (neat) 2968 (s), 2934 (s), 2874 (s), 1713 (s), 1462 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.92 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H), 1.08 (d, J = 6.8 Hz, 6 H), 1.61 (s, 3 H), 2.04 (q, J = 7.3 Hz, 2 H), 2.09 (q, J = 7.3 Hz, 2 H), 2.69 (sept, J = 6.8 Hz, 1H), 3.18 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.2, 13.3, 18.3, 18.6, 25.8, 27.1, 39.7, 44.5, 127.2, 134.2, 213.4; High-resolution MS, calcd for C$_{12}$H$_{22}$O: 182.1671. Found *m/z* (relative intensity): 183 (M$^+$+1, 28), 182.1669 (M$^+$, 100), 139 (95).

2d
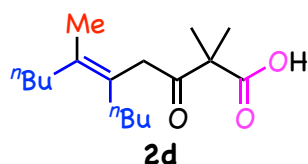
(*E*)-5-Butyl-2,2,6-trimethyl-3-oxodec-5-enoic acid (2d)

IR (neat) 2959 (s), 2930 (s), 2870 (m), 2860 (m), 1718 (s), 1703 (s), 1470 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (t, *J* = 7.3 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 1.19-1.39 (m, 8 H), 1.44 (s, 6 H), 1.53 (s, 3 H), 1.97 (t, *J* = 7.3 Hz, 2 H), 2.07 (t, *J* = 7.3 Hz, 2 H), 3.33 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.0, 14.1, 18.5, 22.3, 22.7, 22.8, 30.7, 30.8, 32.6, 33.9, 41.5, 55.5, 125.2, 133.7, 179.8, 205.7; High-resolution MS, calcd for C$_{17}$H$_{30}$O$_3$: 282.2195. Found *m/z* (relative intensity): 282.2199 (M$^+$, 16.9), 238 (100).

3d
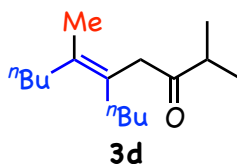
(*E*)-5-Butyl-2,6-dimethyldec-5-en-3-one (3d)

IR (neat) 2959 (s), 2930 (s), 2860 (s), 1709 (s), 1466 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (t, *J* = 7.3 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 1.08 (d, *J* = 6.8 Hz, 6 H), 1.22-1.41 (m, 8 H), 1.60 (s, 3 H), 2.00 (t, *J* = 7.3 Hz, 2 H), 2.06 (t, *J* = 7.3 Hz, 2 H), 2.68 (sept, *J* = 6.8 Hz, 1H), 3.18 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 14.0, 14.1, 18.6, 18.7, 22.8, 22.8, 30.8, 30.9, 32.7, 34.0, 39.6, 44.9, 126.3, 133.1, 213.3; High-resolution MS, calcd for C$_{16}$H$_{30}$O: 238.2297. Found *m/z* (relative intensity): 238.2298(M$^+$, 85.7), 195 (100).
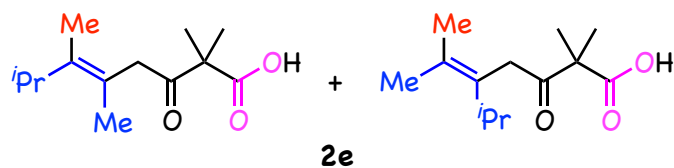
(E)-2,2,5,6,7-Pentamethyl-3-oxooct-5-enoic acid (2e, major isomer) and

5-Isopropyl-2,2,6-trimethyl-3-oxohept-5-enoic acid (minor isomer): (a mixture of regioisomers

in a 2.2 : 1 ratio)

IR (neat) 3194 (br), 2964 (s), 2932 (s), 2870 (m), 1720 (s), 1709 (s), 1703 (s), 1691 (s), 1468 (s)

cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, major isomer) δ 0.95 (d, J = 6.8 Hz, 6 H), 1.44 (s, 6 H), 1.45 (s, 3

H), 1.63 (s, 3 H), 2.90 (sept, J = 6.8 Hz, 1 H), 3.33 (s, 2 H); ^{1}H NMR (400 MHz, CDCl$_3$, minor

isomer) δ 0.83 (d, J = 6.8 Hz, 6 H), 1.47 (s, 6 H), 1.48 (s, 3 H), 1.75 (s, 3 H), 2.90 (sept, J = 6.8 Hz,

1 H), 3.30 (s, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$, a mixture of regioisomers) δ 12.2, 18.4, 19.8, 20.5,

20.6, 21.2, 22.3, 22.8, 29.8, 30.0, 36.4, 44.1, 55.4, 55.5, 119.3, 128.5, 129.1, 137.9, 179.8, 179.9,

205.4, 205.9; High-resolution MS, calcd for C$_{13}$H$_{22}$O$_3$: 226.1569. Found m/z (relative intensity):

226.1575 (M$^+$, 64.8), 182 (100).
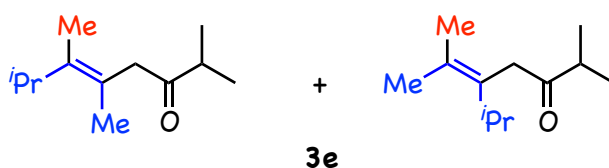
(E)-2,5,6,7-Tetramethyloct-5-en-3-one (3e, major isomer) and

5-Isopropyl-2,6,6,-trimethylhept-5-en-3-one (minor isomer): (a mixture of regioisomers in a 2.3 :

1 ratio)

IR (neat) 2964 (s), 2934 (s), 2872 (m), 1713 (s), 1466 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, major

isomer) δ 0.95 (d, J = 6.8 Hz, 6 H), 1.08 (d, J = 6.8 Hz, 6 H), 1.53 (s, 3 H), 1.63 (s, 3 H), 2.67 (sept,

J = 6.8 Hz, 1 H), 2.90 (sept, J = 6.8 Hz, 1 H), 3.18 (s, 2 H); ^{1}H NMR (400 MHz, CDCl$_3$, minor

isomer) δ 0.86 (d, J = 6.8 Hz, 6 H), 1.12 (d, J = 6.8 Hz, 6 H), 1.53 (s, 3 H), 1.75 (s, 3 H), 2.71 (sept,

J = 6.8 Hz, 1 H), 2.90 (sept, J = 6.8 Hz, 1 H), 3.16 (s, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$, a mixture

of regioisomers) δ ; 12.4, 18.6, 18.6, 18.9, 19.9, 20.5, 20.8, 21.5, 29.9, 30.1, 39.4, 39.6, 40.3, 47.5,

120.1, 127.6, 130.5, 137.5, 212.8, 213.4; High-resolution MS, calcd for C$_{12}$H$_{22}$O : 182.1671. Found

m/z (relative intensity): 182.1660 (M$^+$, 10.8), 163 (12), 139 (57), 121 (100).
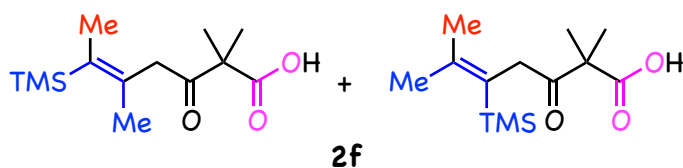
(*E*)-2,2,5-Trimethyl-6-(trimethylsilyl)-3-oxohept-5-enoic   acid   (2f,   major   isomer) and

2,2,6-trimethyl-5-(trimethylsilyl)-3-oxohept-5-enoic   acid   (minor   isomer):   (a   mixture   of

regioisomers in a 5.5 : 1 ratio)

IR (neat) 3209 (br), 2976 (s), 2957 (s), 2912 (m), 1713 (s), 1703 (s), 1470 (s) cm^{-1}; ^{1}H NMR (400

MHz, CDCl$_3$, major isomer) δ 0.15 (s, 9H), 1.44 (s, 6 H), 1.59 (s, 3 H), 1.77 (s, 3 H), 3.42 (s, 2 H);

^{1}H NMR (400 MHz, CDCl$_3$, minor isomer) δ 0.11 (s, 9H), 1.45 (s, 6 H), 1.60 (s, 3 H), 1.89 (s, 3 H),

3.47 (s, 2 H); ^{13}C NMR (100 MHz, CDCl$_3$, major isomer) δ ; 0.3, 18.2, 22.2, 23.8, 44.0, 55.7, 132.5,

137.6, 179.8, 205.2; ^{13}C NMR (100 MHz, CDCl$_3$, minor isomer) δ 0.1, 21.2, 22.6, 25.4, 41.3, 55.3,

124.9, 146.7, 179.9, 207.0; High-resolution MS, calcd for C$_{13}$H$_{24}$O$_3$Si : 256.1495. Found m/z

(relative intensity): 256.1499 (M$^+$, 6.9), 212 (24), 195 (100).
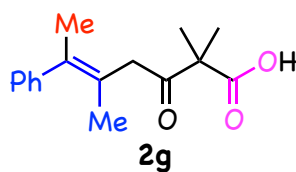
(E)-2,2,5-Trimethyl-3-oxo-6-phenylhept-5-enoic acid (2g)

IR (neat) 3061 (br), 2984 (m), 2937 (m), 1703 (s), 1470 (m), 1443 (m), 1265 (s) cm^{-1}; ^{1}H NMR (400 MHz, C$_5$D$_5$N) δ 1.68 (s, 6 H), 1.76 (s, 3 H), 2.01 (s, 3 H), 3.77 (s, 2 H), 7.24-7.38 (m, 5 H); ^{13}C NMR (100 MHz, C$_5$D$_5$N) δ 21.2, 21.2, 22.8, 43.9, 56.3, 125.7, 126.6, 128.6, 128.8, 134.4, 145.1, 176.5, 206.6; High-resolution MS, calcd for C$_{16}$H$_{20}$O$_3$: E.M.:260.1412. Found m/z (relative intensity): 260.1412 (M$^+$, 8.0), 216 (100).
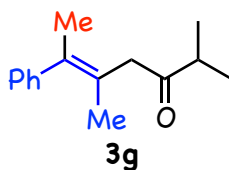
(E)-2,5-Dimethyl-6-phenylhept-5-en-3-one (3g)

IR(neat); 2970 (s), 2930 (s), 2872 (s), 1709 (s), 1437 (s) cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.15 (d, J = 6.9 Hz, 6 H), 1.57 (q, J = 1.5 Hz, 3 H), 1.96 (q, J = 1.5 Hz, 3 H), 2.76 (sept, J = 6.9 Hz, 1H), 3.36 (s, 2H), 7.14-7.33 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.5, 20.9, 21.1, 40.1, 46.7, 124.8, 126.1, 128.0, 128.2, 134.3, 144.5, 212.5; High-resolution MS, calcd for C$_{15}$H$_{20}$O: 216.1514. Found m/z (relative intensity): 217 (M$^+$+1, 16), 216.1514 (M$^+$, 100), 173 (10).
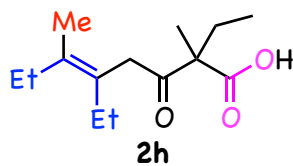
(E)-2,5-Diethyl-2,6-dimethyl-3-oxooct-5-enoic acid (2h)

IR (neat) 3090 (br), 2968 (s), 2936 (s), 2874 (m), 1701 (s), 1695 (s), 1458 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (t, J = 7.3 Hz, 3 H), 0.90 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H), 1.40 (s, 3 H), 1.54 (s, 3 H), 1.85-2.12 (m, 6 H), 3.32 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 8.8, 13.2, 13.2, 18.1, 18.8, 25.7, 27.1, 28.4, 41.5, 59.8, 126.1, 134.8, 179.1, 206.1; High-resolution MS, calcd for C$_{14}$H$_{24}$O$_3$: 240.1725. Found m/z (relative intensity): 240.1730 (M$^+$, 100), 211 (48).
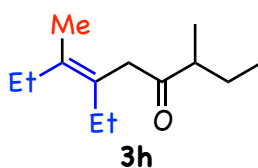
(E)-6-Ethyl-3,7-dimethylnon-6-en-4-one (3h)

IR (neat) 2964 (s), 2934 (s), 2874 (s), 1709 (s), 1456 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.86 (t, J = 7.1 Hz, 3 H), 0.92 (t, J = 7.1 Hz, 3 H), 0.99 (t, J = 7.1 Hz, 3 H), 1.05 (d, J = 7.1 Hz, 3 H), 1.35 (dquint, J = 14.2, 7.1 Hz, 1 H), 1.62 (s, 3 H), 1.68 (dquint, J = 14.2, 7.1 Hz, 1 H), 2.03 (q, J = 7.1 Hz, 2 H), 2.09 (q, J = 7.1 Hz, 2 H), 2.53 (sext, J = 7.1 Hz, 1H), 3.17 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 11.8, 13.2, 13.3, 16.4, 18.3, 25.8, 26.2, 27.1, 45.4, 46.7, 127.0, 134.2, 213.1; High-resolution MS, calcd for C$_{13}$H$_{24}$O : 196.1827. Found m/z (relative intensity): 196.1925 (M$^+$, 100), 181 (43), 167 (93).
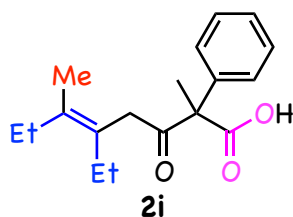
(*E*)-Methyl-5-ethyl-2,6-dimethyl-3-oxo-2-phenyloct-5-enoate (2i)

IR (neat) 2964 (s), 2934 (m), 2872 (m), 1744 (s), 1720 (s), 1447 (m), 1252 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.77 (t, *J* = 7.3 Hz, 3 H), 0.95 (t, *J* = 7.3 Hz, 3 H), 1.42 (s, 3 H), 1.83 (s, 3 H), 1.87-1.99 (m, 2 H), 2.04 (q, *J* = 7.3 Hz, 2 H), 3.09 (d, *J* = 18.3 Hz, 1 H), 3.23 (d, *J* = 18.3 Hz, 1 H), 3.80 (s, 3 H), 7.29-7.40 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.2, 13.2, 17.9, 21.5, 25.4, 27.0, 42.0, 52.6, 64.5, 126.6, 127.5, 127.7, 128.6, 134.6, 138.5, 172.7, 205.0; High-resolution MS, calcd for C$_{17}$H$_{24}$O : 302.1882. Found *m/z* (relative intensity): 302.1885(M$^+$, 100), 300 (18), 271 (10).
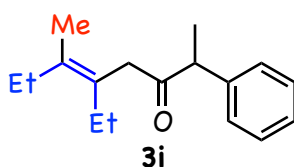
(*E*)-5-Ethyl-6-methyl-2-phenyloct-5-en-3-one (3i)

IR (neat) 2966 (s), 2932 (s), 2872 (s), 1709 (s), 1452 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.81 (t, *J* = 7.3 Hz, 3 H), 0.96 (t, *J* = 7.3 Hz, 3 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.45 (s, 3 H), 1.85-2.00 (m, 2 H), 2.05 (q, *J* = 7.3 Hz, 2 H), 3.06 (d, *J* = 16.1 Hz, 1 H), 3.13 (d, *J* = 16.1 Hz, 1 H), 3.83 (q, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.1, 13.2, 18.0, 18.1, 25.5, 27.1, 45.0, 51.8, 127.0, 127.0, 127.9, 128.8, 134.4, 140.9, 209.4; High-resolution MS, calcd for C$_{17}$H$_{24}$O: 244.1827. Found *m/z* (relative intensity): 244.1829(M$^+$, 100), 215 (9).
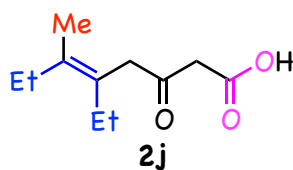
(*E*)-Methyl-5-ethyl-6-methyl-3-oxooct-5-enoate (2j)

IR (neat) 2964 (s), 2936 (s), 2874 (s), 1751 (s), 1717 (s), 1437 (m), 1317 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.93 (t, *J* = 7.3 Hz, 3 H), 1.00 (t, *J* = 7.3 Hz, 3 H), 1.65 (s, 3 H), 2.06 (q, *J* = 7.3 Hz, 2 H), 2.10 (q, *J* = 7.3 Hz, 2 H), 3.24 (s, 2 H), 3.45 (s, 2H), 3.73 (s, 3 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.1, 13.2, 18.4, 25.7, 27.1, 47.0, 47.7, 52.3, 126.4, 135.6, 167.8, 201.7; High-resolution MS, calcd for C$_{12}$H$_{20}$O$_3$: 212.1412. Found *m/z* (relative intensity): 212.1404 (M$^+$, 96.0), 194 (100), 183 (37), 165 (34).
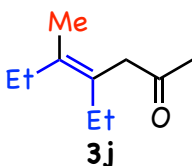
(*E*)-4-Ethyl-5-methylhept-4-en-2-one (3j)

IR (neat) 2964 (s), 2934 (s), 2874 (s), 17012 (s), 1456 (m), 1354 (s) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.94 (t, *J* = 7.3 Hz, 3 H), 0.99 (t, *J* = 7.3 Hz, 3 H), 1.66 (s, 3 H), 2.06 (q, *J* = 7.3 Hz, 2 H), 2.11 (q, *J* = 7.3 Hz, 2 H), 2.11 (s, 3 H), 3.12 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.1, 13.2, 18.3, 25.7, 27.1, 28.9, 47.7, 127.4, 134.5, 208.2; High-resolution MS, calcd for C$_{10}$H$_{18}$O: 154.1358 Found *m/z* (relative intensity): 154.1361 (M$^+$, 81), 125 (100).
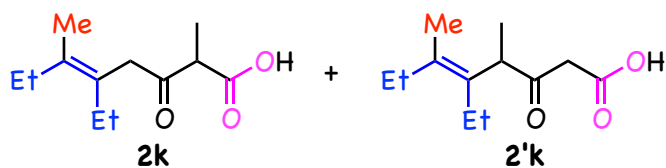
(*E*)-Methyl-5-ethyl-2,6-dimethyl-3-oxooct-5-enoate (2k, major isomer) and **(*E*)-Methyl 5-ethyl-4,6-dimethyl-3-oxooct-5-enoate (2'k, minor isomer)**: (a mixture of regioisomers in a 2.5 : 1 ratio)

IR (neat) 2966 (s), 2936 (s), 2874 (m), 1755 (s), 1748 (s), 1718 (s), 1715 (s), 1456 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$, major isomer) δ 0.92 (t, J = 7.3 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H), 1.33 (d, J = 6.8 Hz, 3 H), 1.61 (s, 3 H), 1.99-2.12 (m, 4 H), 3.28 (d, J = 17.1 Hz, 1 H), 3.29 (d, J = 17.1 Hz, 1 H), 3.63 (q, J = 6.8 Hz, 1 H), 3.72 (s, 3 H); ^{1}H NMR (400 MHz, CDCl$_3$, minor isomer) δ 0.96 (t, J = 7.3 Hz, 3 H), 1.01 (t, J = 7.3 Hz, 3 H), 1.16 (d, J = 6.8 Hz, 3 H), 1.71 (s, 3 H), 1.80-1.89 (m, 1 H), 2.02-2.14 (m, 3H), 3.40 (d, J = 15.4 Hz, 1 H), 3.48 (d, J = 15.4 Hz, 1 H), 3.58 (q, J = 6.8 Hz, 1 H), 3.72 (s, 3 H); ^{13}C NMR (100 MHz, CDCl$_3$, major isomer) δ ; 13.1, 13.1, 13.2, 18.3, 25.6, 27.1, 45.5, 51.2, 52.4, 126.3, 135.3, 171.1, 204,5; ^{13}C NMR (100 MHz, CDCl$_3$, minor isomer) δ ; 12.8, 13.8, 14.8, 17.9, 23.0, 27.6, 46.7, 51.0, 52.2, 132.1, 135.7, 168.0, 204.6; High-resolution MS, calcd for C$_{13}$H$_{22}$O$_3$: 226.1569. Found *m/z* (relative intensity): 226.1570 (M$^+$, 67.4), 197 (100).
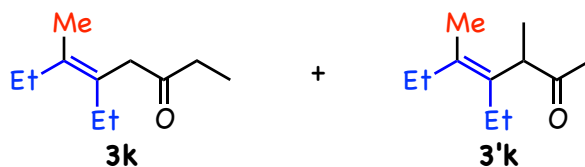
(*E*)-5-Ethyl-6-methyloct-5-en-3-one (3k, major isomer) and **(*E*)-4-Ethyl-3,5-dimethylhept-4-en-2-one (3'k, minor isomer)**: (a mixture of regioisomers in a 1.2 : 1 ratio)

IR (neat) 2964 (s), 2934 (s), 2874 (m), 1713 (s), 1458 (m), 1261 (m) cm^{-1}; ^{1}H NMR (500 MHz,

CDCl$_3$, major isomer) δ 0.93 (t, J = 7.6 Hz, 3 H), 0.99 (t, J = 7.6 Hz, 3 H), 1.03 (t, J = 7.3 Hz, 3 H),

1.65 (s, 3 H), 2.05 (q, J = 7.6 Hz, 2 H), 2.09 (q, J = 7.6 Hz, 2 H), 2.43 (q, J = 7.3 Hz, 2 H), 3.12 (s,

2 H); ^{1}H NMR (500 MHz, CDCl$_3$, minor isomer) δ 0.96 (t, J = 7.6 Hz, 3 H), 1.01 (t, J = 7.6 Hz, 3

H), 1.12 (d, J = 6.9 Hz, 3 H), 1.71 (s, 3 H), 1.83-1.89 (m, 1 H), 2.03-2.13 (m, 3H), 2.07 (s, 3 H),

3.43 (q, J = 6.9 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$, major isomer) δ 7.9, 13.1, 13.3, 18.4, 25.8,

27.1, 34.7, 46.5, 127.5, 134.2, 210.6; ^{13}C NMR (100 MHz, CDCl$_3$, minor isomer) δ 12.8, 13.9, 14.9,

17.9, 23.0, 27.5, 28.1, 51.2, 133.0, 134.3, 210.9; High-resolution MS, calcd for C$_{11}$H$_{20}$O: 168.1514.

Found m/z (relative intensity): 168.1514(M$^+$, 40.0), 153 (55), 139 (100).
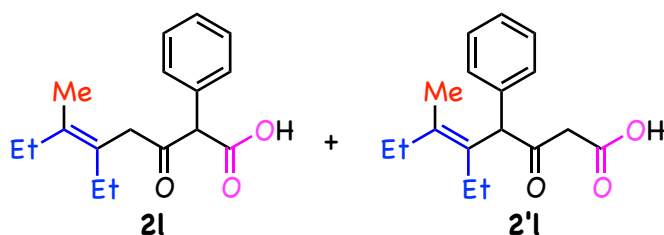
(E)-Methyl 5-ethyl-6-methyl-3-oxo-2-phenyloct-5-enoate (2l)

IR (neat) 2964 (s), 2934 (s), 2872 (m), 1755 (s), 1720 (s), 1641 (m), 1601 (m), 1456 (m), 1435 (m)

cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.84 (t, J = 7.3 Hz, 3 H), 0.98 (t, J = 7.3 Hz, 3 H), 1.48 (s, 3 H),

1.96 (q, J = 7.3 Hz, 2 H), 2.06 (q, J = 7.3 Hz, 2 H), 3.20 (s, 2 H), 3.73 (s, 2 H), 4.82 (s, 1 H),

7.31-7.38 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.1, 13.1, 18.2, 25.5, 27.1, 45.6, 52.5, 63.3,

126.3, 128.2, 128.8, 129.5, 132.6, 135.6, 169.1, 202.2; High-resolution MS, calcd for C$_{18}$H$_{24}$O$_3$:

288.1725. Found m/z (relative intensity): 288.1730 (M$^+$, 100), 259 (6), 231 (28).

(E)-Methyl 5-ethyl-6-methyl-3-oxo-4-phenyloct-5-enoate (2'l)

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.76 (t, J = 7.3 Hz, 3 H), 1.07 (t, J = 7.3 Hz, 3 H), 1.72 (s, 3 H),

2.01-2.23 (m, 4 H), 3.52 (d, J = 15.6 Hz, 1 H), 3.63 (d, J = 15.6 Hz, 1 H), 3.73 (s, 3 H), 4.92 (s, 1

H), 7.18-7.36 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 12.9, 14.2, 18.6, 24.4, 27.8, 48.0, 52.3, 61.5, 127.0, 128.3, 129.2, 130.2, 136.7, 137.4, 167.9, 201.9.
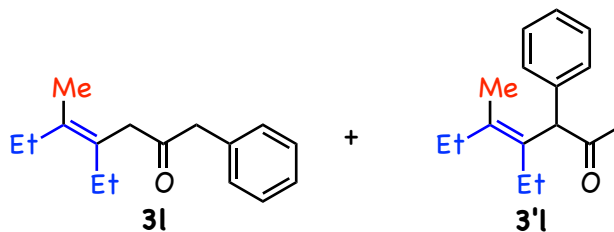

(*E*)-4-Ethyl-5-methyl-1-phenylhept-4-en-2-one (3l)

IR (neat) 2964 (s), 2934 (s), 2872 (m), 1715 (s), 1497 (m), 1454 (m) cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.89 (t, *J* = 7.3 Hz, 3 H), 0.99 (t, *J* = 7.3 Hz, 3 H), 1.58 (s, 3 H), 2.02 (q, *J* = 7.3 Hz, 2 H), 2.09 (q, *J* = 7.3 Hz, 2 H), 3.17 (s, 2 H), 3.69 (s, 2 H), 7.18-7.34 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 13.1, 13.2, 18.3, 25.7,0 27.1, 46.0, 48.8, 126.8, 127.0, 128.6, 129.4, 134.4, 134.7, 207.0; High-resolution MS, calcd for C$_{16}$H$_{22}$O: 230.1671. Found *m/z* (relative intensity): 230.1671 (M$^+$, 100), 201 (65).

(*E*)-4-Ethyl-5-methyl-3-phenylhept-4-en-2-one (3'l, minor isomer)

^{1}H NMR (400 MHz, CDCl$_3$) δ 0.77 (t, *J* = 7.3 Hz, 3 H), 1.06 (t, *J* = 7.3 Hz, 3 H), 1.71 (s, 3 H), 2.00-2.21 (m, 4 H), 2.23 (s, 3 H), 4.72 (s, 1 H), 7.17-7.33 (m, 5 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 12.9, 14.2, 18.6, 24.6, 27.7, 29.8, 62.2, 126.7, 128.2, 129.2, 131.1, 136.1, 137.6, 208.0.

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13. In entries 5 and 6 of **Table 3**, a regioisomeric mixture of b-ketocarboxylic acids **2** and **2'** were produced. Both nickelacycles **I** and **III** through the s-p-s allylnickel interconversion would participate in the alkyne insertion to form a regioisomeric mixture of nickelacycle intermediates providing **2** along with **2'** (**Scheme 4** and **5**). However, the alternative reaction mechanism involving decarboxylation-carboxylation sequences can never be ruled out.

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15. Enol zinc carbonate undergoes [1,3]-rearrangement to provide β-ketocarboxylic acid, see: a) K. Kataoka, T. Tsuruta, *Polymer J.* **1977**, *9*, 595-604.

Chapter 3

Nickel-Catalyzed Three-Component Coupling of 4-Methylene-2-oxazolidinone, Alkyne, and Trimethylaluminum
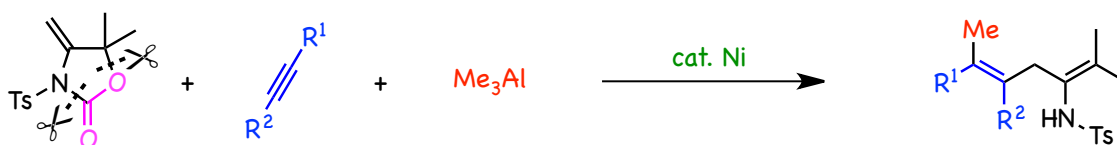
Summary: In the presence of Ni(0) catalyst, the regio- and stereoselective three-component coupling reaction of 4-methylene-2-oxazolidinone, alkynes, and Me_3Al accompanied by extrusion of carbon dioxide to furnish 2-amino-1,4-hexadiene in good yields.

Introduction

Nickelacycles are one of the most attractive and efficient active species for C−C bond transformation in modern organic chmistry.[1]   In particularly, multi-component coupling reactions promoted by Ni-catalyst are extremely straightforward and convenient methods for construction of complicated molecules in material science and medicinal chemistry.[2]   The research of our group is mainly directed towards the development of novel transformation for the nickel-catalyzed multicomponent coupling reaction *via* nickelacycle as a key intermediate.[3]

Recently, we have reported the Ni-catalyzed three-component coupling reactions of Me_2Zn, alkynes with vinylepoxides and vinylcyclopropanes to afford dienyl alcohols and α-heptadienyl dimethyl malonates, respectively (**Scheme 1**).[4]
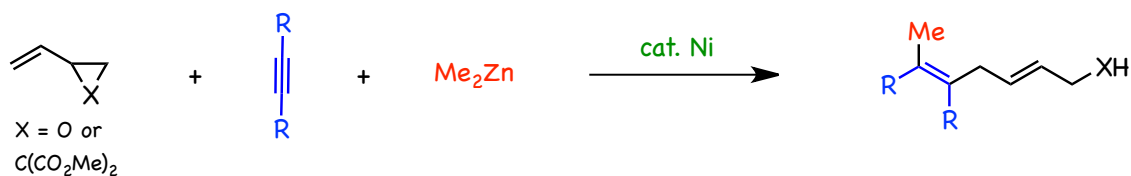
Scheme 1. Ni-Catalyzed Three-Component Coupling Reaction of Me_2Zn, alkynes with vinylepoxides and vinylcyclopropanes

More recently, we have developed the Ni-catalyzed three-component coupling reaction of 4-methylene-1,3-dioxolan-2-one, alkyne, and $Me_2Al(OMe)$ proceeded to give δ,ε-unsaturated β-ketocarboxylic acids with high regio- and stereoselectivities (**Scheme 2**).[5]   The reaction proceeds *via* [1,3]-rearrangement of an enolative metal carbonate intermediate and the formal reinsertion of CO_2 for efficient construction of the β-ketocarboxylic acid framework.
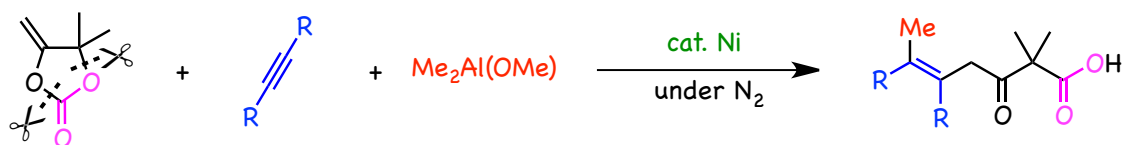
Scheme 2. Ni-Catalyzed Three-Component Coupling Reaction of 4-Methylene-1,3-dioxolan-2-one, alkyne, and Me$_2$Al(OMe)

In this research, we have focused on a 4-methylene-2-oxazolidinone as a starting material for the efficient formation of oxanickelacycle species.   Previously, we could succeed in the efficient formation of 4-methylene-2-oxazolidinones from propargyl alcohols with isocyanate followed by intramolecular addition of nitrogen atom to C-C triple bond promoted by Cu and Ag catalysts (**Scheme 3**).[6]   4-Methylene-2-oxazolidinones are densely functionalized useful and competent molecules possesing stereochemically defined enamine and protected allylic alcohols moieties. For examples, 4-methylene-2-oxazolidinones could serve as an aza-trimethylene methane intermediate to undergo the amphiphilic addition towards α,β-unsaturated enones and active alkenes.   The versatile heterocylic compounds have potential for the important synthon of physiologically active molecules and pharmaceutical products.
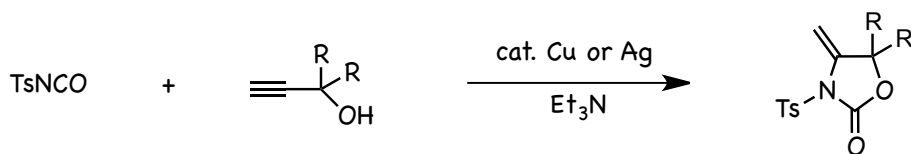
Scheme 3. Synthesis of 4-methylene-2-oxazolidinone from propargyl alcohol and isocyanate

Herein, we would like to disclose that *N-p*-toluenesulfonyl-4-methylene-2-oxazolidinone can serve as an allylic aza-nickelacycle species to undergo the three-component coupling reactions with alkynes and trimethylaluminum accompanying extrusion of carbon dioxide (**Scheme 4**).   This

protocol is an useful and efficient synthetic methodology of nitrogen containing compounds such as

β-amino acids and unsaturated dienyl amines.
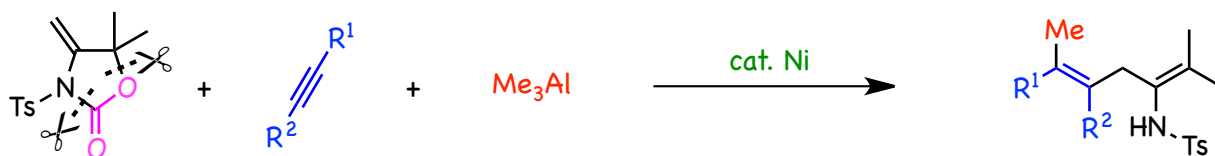
Scheme 4. Ni-Catalyzed Three-Component Coupling Reaction of 4-Methylene-2-oxazolidinone,

Alkyne, and Me₃Al

Results and Discussion

The optimization of the reaction conditions are summarized in **Table 1**. At first, we examined a variety of organometallic reagents. In the presence of 5 mol% of Ni(cod), the reaction of 5,5-dimethyl-4-methylene-2-oxazolidinone **1a**, 4-octyne, and Me$_3$Al proceeded at 60 °C in toluene to give the corresponding 2-amino-1,4-hexadiene in 64% yield (Entry 1, **Table 1**). However, in the case of Me$_2$Al(OMe), which was effective for the synthesis of β-ketocarboxylic acid (Chapter 2), did not work well in this case (Entry 2, **Table 1**). Under similar conditions, complex mixtures were produced using Et$_3$Al, and DIBAL-H (Entries 3 and 4, **Table 1**). Organozinc reagent, such as Me$_2$Zn and Et$_2$Zn, were not effective to promote the coupling reactions (Entries 5 and 6, **Table 1**). Next, we investigated the solvent effects in the multi-component coupling reaction. As the results of using non-polar and aprotic polar solvents, toluene is the best solvent for the expected reaction (Entries 1 and 7-14, **Table 1**). Aprotic polar solvents such as DMA, DMF, and DMSO provided the isomerized dienyl enamine **3a** as by-product. Especially, NMP gave the conjugated diene **3a** as major product (Entry 12, **Table 1**). As the unconjugated diene **2a** did not convert to conjugated diene **3a** in the similar conditions, aprotic solvents might accelerate to isomerize from **2a** to **3a** in situ during the coupling reaction. We have further examined ligands for the coupling reaction, and the results are shown in entries 15-19. Irrespective of the kinds of phosphine ligands, the yields of the products were diminished and, instead, no ligand resulted in the formation of the desired product in better yields.

Table 1. Optimization of the Reaction Conditions for Nickel-Catalyzed Three-Component Coupling of 4-Methylene-2-oxazolidinone, Alkyne, and Me_3Al[a]
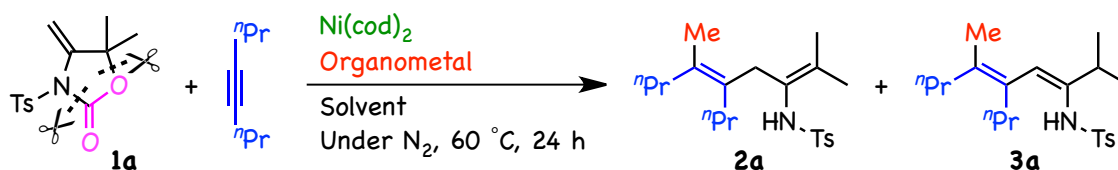
Entry	Organometal	Solvent	Ligand	Isolated Yield [%]	
				2a	3a
1	*Me_3Al*	*Toluene*	*None*	*64*	*0*
2	$Me_2Al(OMe)$	Toluene	None	5	0
3	Et_3Al	Toluene	None	Complex Mixture	
4	DIBAL–H	Toluene	None	Complex Mixture	
5	Me_2Zn	Toluene	None	No Reaction	
6	Et_2Zn	Toluene	None	No Reaction	
7	Me_3Al	Hexane	None	37	0
8	Me_3Al	CPME	None	6	0
9	Me_3Al	1,4–Dioxane	None	8	0
10	Me_3Al	THF	None	33	0
11	Me_3Al	DMA	None	34	36
12	Me_3Al	NMP	None	39	54
13	Me_3Al	DMF	None	30	26
14	Me_3Al	DMSO	None	22	23
15	Me_3Al	Toluene	PPh_3	23	0
16	Me_3Al	Toluene	PCy_3	33	0
17	Me_3Al	Toluene	$P(OPh)_3$	23	0
18	Me_3Al	Toluene	DPPE	55	0
19	Me_3Al	Toluene	Xantphos	29	0

[a]The reaction was undertaken in the presence of $[Ni(cod)_2]$ (5.0 mol%), cyclic carbamate **1a** (1.0 mmol), 4-octyne (2.0 mmol), and organometallic reagent (1.2 mmol) in solvent (5.0 mL) at 60 °C under nitrogen atmosphere for 24 h.

Next, we investigated the reactions of 5,5-dimethyl-4-methylene-3-tosyloxazolidin-2-one **1a** with a various kinds of alkynes and Me$_3$Al, and the results summarized in **Table 2**. Symmetrical alkynes, such as 2-butyne, 3-hexyne, 4-octyne, and diphenylacetylene reacted smoothly with cyclic carbamate **1a** in the presence of Me$_3$Al to provide corresponding 2-amino-1,4-hexadiene **2a**-**2d** in moderate yields (Entries 1-4, **Table 2**). In the case of unsymmetrical alkynes, such as 4-methyl-2-pentyne and 1-trimethylsilyl-1-propyne, the corresponding 2-amino-1,4-hexadiene **2e**-**2f** were obtained in low to modest yields as a mixture of regioisomers in ratios of 1.8:1 to 4.0:1 (Entries 5 and 6, **Table 2**).

Table 2. Ni-Catalyzed Coupling of Cyclic Carbamate **1a** with Various Alkyne and Me$_3$Al^a
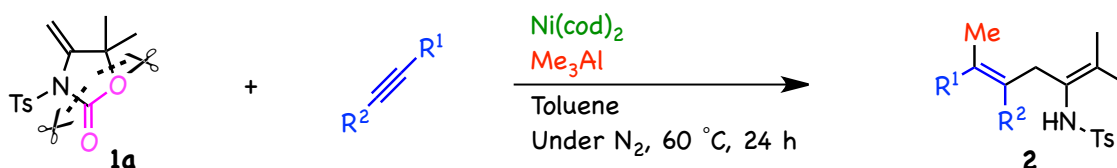
Entry	R^1	R^2	Isolated Yield of **2** [%]
1	Me	Me	**2b** : 64
2	Et	Et	**2c** : 57
3	^{n}Pr	^{n}Pr	**2a** : 64
4	Ph	Ph	**2d** : 37
5	^{i}Pr	Me	**2e** : 38 [1.8:1]^b
6	TMS	Me	**2f** : 25 [4.0:1]^b

^{a}The reaction was undertaken in the presence of [Ni(cod)$_2$] (5.0 mol%), cyclic carbamate **1a** (1.0 mmol), alkyne (2.0 mmol), and Me$_3$Al (1.2 mmol) in toluene (5.0 mL) at 60 °C under nitrogen atmosphere for 24 h.

^{b}The ratios show the regioselectivities with respect to the alkyne substitutents.

The stereochemistry of the product **2a** was unequivocally determined as *E*-isomer on the basis of NOE experiment. The result of irradiation at the bold face protons are illustrated in **Figure 1**.
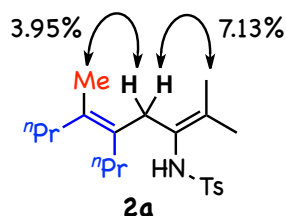
Figure 1. NOE Data for Irradiation of Bold Face Protons in Dienylamine **2a**

Next, the reaction of a stoichiometric amount of Ni(cod)$_2$, alkyne, and cyclic carbonate without Me$_3$Al was conducted (**Scheme 5**). In the absence of Me$_3$Al, the mixture of Ni(cod)$_2$ (1.0 mmol), 4-octyne (2.0 mmol), and 5,5-dimethyl-4-methylene-3-tosyloxazolidin-2-one **1a** (1.0 mmol) did not provide the expected 2-amino-1,4-hexadiene **2g**. In this case, the reaction was not proceed at all and the almost cyclic carbamate was recovered. This result shows Me$_3$Al is indispensable to carry out the reaction, and we believe that Me$_3$Al acts as a Lewis acid and promotes the oxidative addition in the first step.
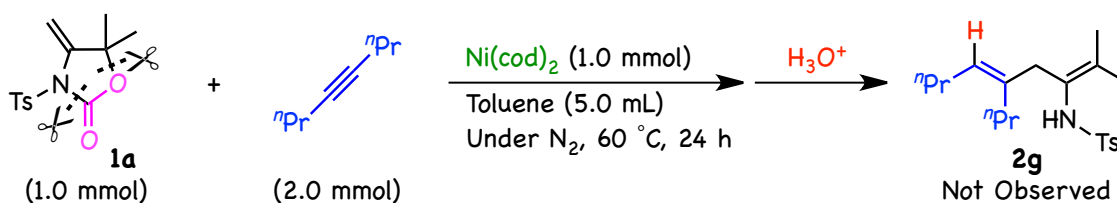
Scheme 5. Stoichiometric Reaction in the Absence of Me$_3$Al

In the absence of alkyne, the mixture of Ni(cod)$_2$ catalyst, 5,5-dimethyl-4-methylene-3-tosyloxazolidin-2-one **1a**, and Me$_3$Al proceeded to give the corresponding enylamine **4a** in low yield (**Scheme 6**). That is, oxidative addition of 5,5-dimethyl-4-methylene-3-tosyloxazolidin-2-one **1a** toward Ni(0) catalyst proceeds accompanying extrusion of carbon dioxide promoted by Me$_3$Al as Lewis acid. Aza-trimethylenemethane nickel intermediate **II** can participate in the formation of azanickelcycle species **III** to undergo the transmetallation with Me$_3$Al proceeds to afford enylamine **4a**.
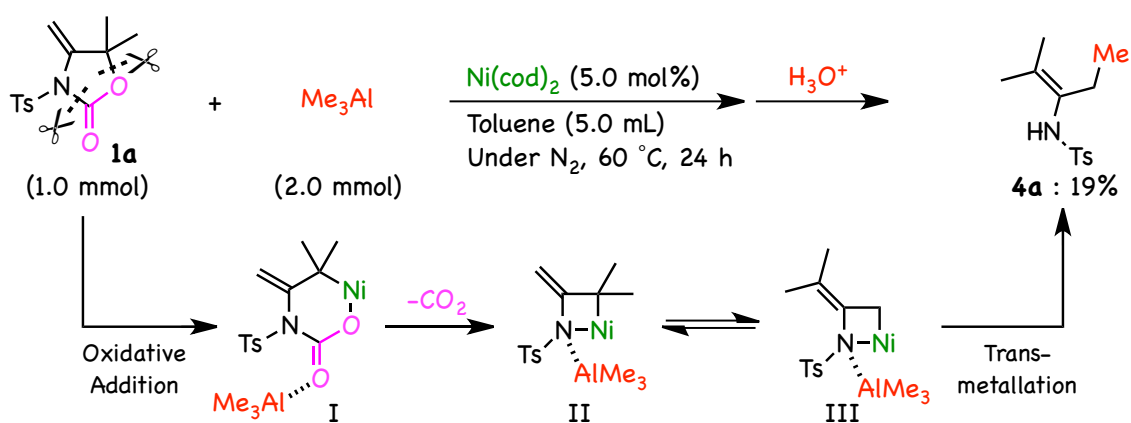
Scheme 6. Control Experiment in the Absence of Alkyne

A plausible reaction mechanism for three-component coupling reaction with 4-methylene-2-oxazolidinone in the presence of Ni-catalyst, alkyne, and Me_3Al is shown in **Scheme 6**. Oxidative addition of 4-methylene-2-oxazolidinone toward Ni(0) catalyst proceeds accompanying extrusion of carbon dioxide promoted by Me_3Al as Lewis acid. Aza-trimethylenemethane nickel intermediate **II** can participate in the formation of azanickelcycle species **III** to undergo the insertion of alkyne in *syn* addition manner to form six-membered azanickelacycle **V**. Transmetallation with Me_3Al proceeds to afford methyl vinyl nickel intermediate **VI** following reductive elimination to afford dienylamine **2**. Ni(0) catalyst can be generated as an active species to promote the multi-component coupling reaction.
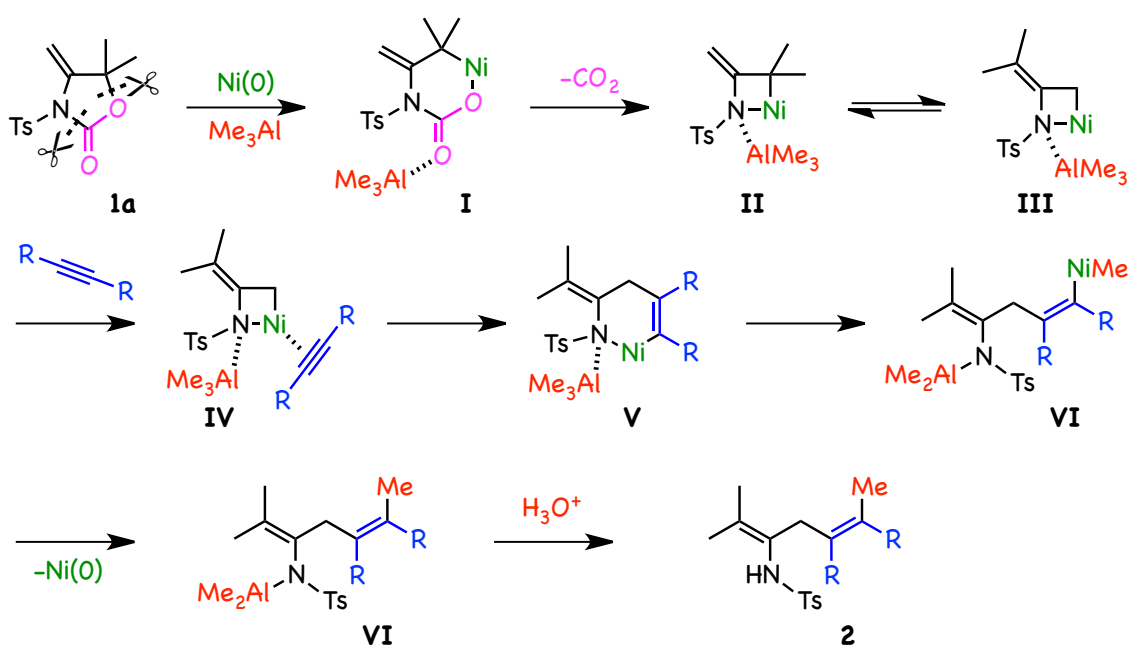
Scheme 6. Plausible Reaction Mechanism for Ni-Catalyzed Three-Component Coupling of 4-methylene-2-oxazolidinone, alkyne, and Me_3Al

Conclusion

In conclusion, we developed Ni-catalyzed three-component coupling reactions of 4-methylene-2-oxazolidinone, alkyne, and Me_3Al accompanied by extrusion of carbon dioxide to furnish 2-amino-1,4-hexadiene with high regio- and stereoselectivities.   The products are useful as the synthetic enamine key intermediates for the preparation of nitrogen containing compounds. The study is in progress to apply our protocol to the synthesis of physiologically active molecules, such as unsaturated amines and amino acids.

Distillation were carried out in a Kugelrohr apparatus (SIBATA glass tube oven GTO-350RG). Boiling points are meant to refer to the oven temperature (± 1 °C). Microanalyses were performed by the Instrumental Analysis Center of Nagasaki University. Analysis agreed with the calculated values within ± 0.4%. High resolution mass spectra (HRMS) were measured with JEOL JMSDX303. Infrared spectra were recorded with a JASCO A-100 or SHIMAZU FTIR-8700 infrared spectrophotometer. 1H and 13C magnetic resonance spectra were measured on JEOL-GX400 instrument with tetramethylsilane as an internal standard. Chemical shift values were given in ppm downfield from the internal standard.

Solvents and Reagents

Toluene was dried and distilled from sodium immediately prior to use under nitrogen atmosphere. Tetrahydrofuran, 1,4-dioxane, DMSO, CPME, n-hexane, DMA, NMP, and DMF were purchased and used without further purification. Me_3Al, Me_2Zn, Et_3Al, Et_2Zn, DIBAL-H were purchased and used without further purification. $Me_2Al(OMe)$ was prepared by reacting Me_3Al (1.0 M hexane solution) and methanol (Wako). $Ni(cod)_2$, PPh_3, $P(c-Hex)_3$, $P(OPh)_3$, dppe, and Xantphos were purchased and used without further purification. 5,5-Dimethyl-4-methylene-2-oxazolidinone was prepared from according to the literature.[6]

Preparation of Me₂Al(OMe)

A 25 mL of two-necked round-bottomed flask, equipped with a magnetic stir bar, a rubber septum and an air condenser at the top of which is attached a three-way stopcock fitted a nitrogen

balloon.　Me$_3$Al (1.0 M hexane solution, 2.0 mL, 2.0 mmol) are placed in the flask under nitrogen atmosphere.　The stirring solution are cooled 0 °C and methanol (64.3 mg, 2.0 mmol) are dropwised over 5 min.　This reaction completes for 30 min.

General procedure for multi-component coupling reaction (Entry 1, **Table 1**)

A 25 mL of two-necked round-bottomed flask, equipped with a rubber septum and an air condenser at the top of which is attached a three-way stopcock fitted a nitrogen balloon. *N-p*-Toluenesulfonyl-5,5-dimethyl-4-methylene-2-oxazolidinone (281.3 mg, 1 mmol) and Ni(cod)$_2$ (13.8 mg, 0.05 mmol) are placed in the flask and purged with nitrogen.　Freshly distilled toluene (5 mL), 4-octyne (220.4 mg, 2.0 mmol), and Me$_3$Al (1.2 mL of 1 M hexane solution; 1.2 mmol) are successively added while stirring the solution with a magnetic stirrer.　The stirring is continued for 24 h at 60°C.　After the reaction completes, the reaction mixture is diluted with ethyl acetate (20 mL).　The organic phase is washed with sat. NaHCO$_3$ (2 x 20 mL) and brine (2 x 20 mL), and then dried over magnesium sulfate, filtered, and concentrated.　The organic phase was dried (MgSO$_4$) and concentrated in vacuo to give a pale yellow oil, which was subjected to column chromatography over silica gel (hexane/EtOAc = 11/1 v/v) to give 1a (232.5 mg, 64%).

2a
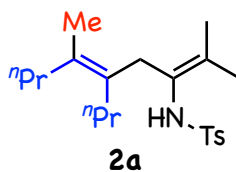
16. (5E)-N-(2,6-Dimethyl-5-propyl-2,5-nonadienyl)-p-toluenesulfonamide (2a)

17. IR (neat) 3277 (br), 2959 (s), 2930 (m), 2870 (m), 2343 (w), 1599 (w), 1456 (m), 1381 (m), 1325 (m), 1165 (s), 1092 (m), 665 (m) cm^{-1}; ^{1}H NMR (C$_6$D$_6$, 400 MHz) δ 0.85 (t, J = 7.3 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H), 1.26-1.41 (m, 4 H), 1.48 (s, 3 H), 1.54 (s, 3 H), 1.67 (s, 3 H), 1.87 (s, 3 H), 1.88 (t, J = 7.3 Hz, 2 H), 1.98 (t, J = 7.3, 2 H), 3.03 (s, 2 H), 5.32 (s, 1 H), 6.75 (d, J = 8.3 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 14.2, 14.4, 18.1, 20.3, 21.0, 21.5, 21.7, 22.4, 32.9, 33.8, 36.6, 125.4, 127.4, 128.8, 129.4, 132.2, 133.4, 138.0, 143.3; High-resolution MS, calcd for C$_{21}$H$_{33}$NO$_2$S: 363.2232. Found m/z (relative intensity): 363.2226 (M$^+$, 100), 361 (2), 348 (2).

2b
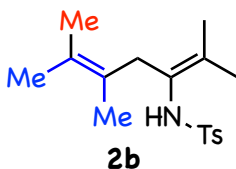
2,5,6-Trimethyl-N-p-toluenesulfonylhepta-2,5-dien-3-amine (2b): IR (neat) 3296 (w), 3055 (w), 2920 (w), 2862 (w), 1599 (w), 1494 (w), 1373 (m), 1323 (m), 1265 (s), 1165 (s), 1092 (m), 739 (s), 706 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.44 (s, 3 H), 1.46 (t, 3 H), 1.58 (s, 3 H), 1.62 (s, 3 H), 1.74 (s, 3 H), 2.42 (s, 3 H), 2.77 (s, 2 H), 5.21 (s, 1 H), 7.28 (d, J = 8.3 Hz, 2 H), 7.72 (d, J = 8.3 Hz, 2 H); 13C NMR (CDCl$_3$, 100 MHz) δ 17.2, 20.3, 20.4, 20.84, 20.87, 21.5, 35.8, 123.6, 125.3, 127.3, 128.2, 129.4, 132.2, 137.9, 143.3; High-resolution MS, calcd for C$_{17}$H$_{25}$NO$_2$S: 307.1606. Found m/z (relative intensity): 307.1608 (M+, 100), 305(1), 292 (13).
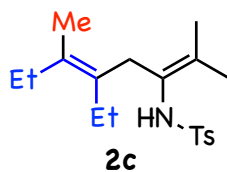
(*E*)-5-Ethyl-2,6-dimethyl-*N*-*p*-toluenesulfonylocta-2,5-dien-3-amine (2c)

IR (neat) 3275 (s), 2964 (s), 2934 (s), 2874 (m), 1598 (w), 1454 (w), 1373 (m), 1325 (m), 1165 (s), 1092 (m), 814 (m), 739 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.84 (t, *J* = 7.3 Hz, 3 H), 0.94 (t, *J* = 7.3 Hz, 3 H), 1.45 (s, 3 H), 1.58 (s, 3 H), 1.75 (s, 3 H), 1.82 (q, *J* =7.3 Hz, 2 H), 2.00 (q, *J* = 7.3 Hz, 2 H), 2.42 (s, 3 H), 2.77 (s, 2 H), 5.19 (s, 1 H), 7.28 (d, *J* = 8.3 Hz, 2 H), 7.73 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 13.3, 13.8, 17.7, 20.4, 21.0, 21.5, 23.5, 27.3, 33.4, 125.5, 127.4, 129.5, 129.6, 132.3, 134.4, 137.9, 143.4; High-resolution MS, calcd for C$_{19}$H$_{29}$NO$_2$S: 335.1919. Found m/z (relative intensity): 335.1911 (M+, 100), 333 (2).
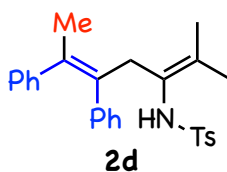
(Z)-2-Methyl-5,6-diphenyl-*N*-*p*-toluenesulfonylhepta-2,5-dien-3-amine (2d)

IR (neat) 3277 (s), 3045 (m), 2918 (m), 2866 (m), 2363 (w), 1744 (w), 1599 (s), 1491 (s), 1445 (s), 1367 (s), 920 (m), 812 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.29 (s, 3 H), 1.45 (s, 3 H), 2.09 (s, 3 H), 2.44 (s, 3 H), 3.39 (s, 2 H), 5.09 (s, 1 H), 6.76-7.07 (m, 10 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.68 (d, *J* = 8.3, 2 H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 20.1, 20.2, 21.2, 21.5, 36.4, 124.4, 125.7, 125.8, 126.5, 127.2, 127.5, 128.8, 129.5, 131.4, 134.05, 134.12, 135.9, 137.9, 142.0, 143.2, 144.1; High-resolution MS, calcd for C$_{27}$H$_{29}$NO$_2$S: 431.1919. Found m/z (relative intensity): 431.1934 (M+, 100), 429 (1), 416 (4).
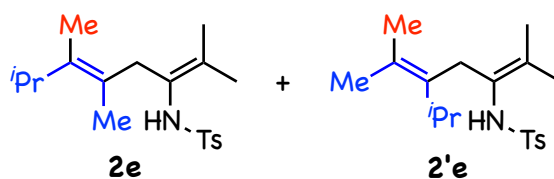
(*E*)-2,5,6,7-Tetramethyl-*N*-*p*-toluenesulfonylocta-2,5-dien-3-amine (**2e**, major isomer) and

5-isopropyl-2,6-dimethyl-*N*-*p*-toluenesulfonylhepta-2,5-dien-3-amine (**2'e**, minor isomer): (a

mixture of regioisomers in a 1.8 : 1 ratio)

IR (neat) 3275 (w), 2963 (m), 2932 (m), 2930 (m), 2870 (w), 1599 (w), 1323 (m), 1265 (m), 1165

(s), 1092 (m), 814 (w), 739 (s) cm^{-1}; ^{1}H NMR (C$_6$D$_6$, 400 MHz, major isomer) δ 0.92 (d, *J* = 6.8 Hz,

6 H), 1.47 (s, 3 H), 1.50 (s, 3 H), 1.50 (s, 3 H), 1.55 (s, 3 H), 1.89 (s, 3 H), 2.81 (sept, *J* = 6.8 Hz, 1

H), 3.00 (s, 2 H), 5.48 (s, 1 H), 6.78 (d, *J* = 8.3 Hz, 2 H), 7.82 (d, *J* = 8.3 Hz, 2 H); ^{1}H NMR (C$_6$D$_6$,

400 MHz, minor isomer) δ 0.91 (d, *J* = 6.8 Hz, 6 H), 1.47 (s, 3 H), 1.58 (s, 3 H), 1.58 (s, 3 H), 1.74

(s, 3 H), 1.87 (s, 3 H), 2.70 (sept, *J* = 6.8 Hz, 1 H), 3.05 (s, 2 H), 5.56 (s, 1 H), 6.75 (d, *J* = 8.3 Hz, 2

H), 7.28 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (CDCl$_3$, 100 MHz, major isomer) δ 11.9, 16.5, 20.4, 20.6,

20.9, 21.5, 30.3, 36.2, 122.4, 125.3, 127.4, 129.5, 132.3, 137.7, 138.0, 143.3; ^{13}C NMR (CDCl$_3$, 100

MHz, minor isomer) δ 20.6, 20.9, 21.2, 21.4, 21.5, 21.6, 30.5, 31.2, 126.1, 127.5, 129.4, 129.6,

130.0, 132.7, 138.2, 143.3; High-resolution MS (major isomer), calcd for C$_{19}$H$_{29}$NO$_2$S: 335.1919.

Found m/z (relative intensity): 335.1922 (M+, 100), 333 (1), 320 (3); High-resolution MS (minor

isomer), calcd for C$_{19}$H$_{29}$NO$_2$S: 335.1919. Found m/z (relative intensity): 335.1930 (M+, 100), 333

(1), 320 (3).

2f   **+**   **2'f**
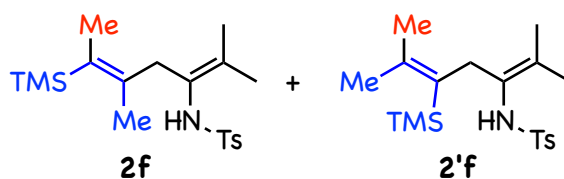
(*E*)-Dimethyl-6-(trimethylsilyl)-*N*-*p*-toluenesulfonylhepta-2,5-dien-3-amine (**2f**, major isomer)

and **2,6-dimethyl-5-(trimethylsilyl)- *N*-*p*-toluenesulfonylhepta-2,5-dien-3-amine** (**2'f**, minor

isomer): (a mixture of regioisomers in a 4.0 : 1 ratio)

IR (KBr, major isomer) 3260 (s), 3252 (s), 2953 (s), 2862 (s), 2719 (m), 1904 (w), 1601 (s), 1402

(s), 1157 (s), 953 (m), 754 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz, major isomer) δ 0.10 (s, 9 H),

1.49 (s, 3 H), 1.55 (s, 3 H), 1.62 (s, 3 H), 1.73 (s, 3 H), 2.42 (s, 3 H), 2.90 (s, 2 H), 5.20 (s, 1 H),

7.28 (d, *J* = 8.3 Hz, 2 H), 7.72 (d, *J* = 8.3 Hz, 2 H); ^{1}H NMR (CDCl$_3$, 400 MHz, minor isomer) δ

0.08 (s, 9 H), 1.43 (s, 3 H), 1.61 (s, 3 H), 1.71 (s, 3 H), 1.87 (s, 3 H), 2.42 (s, 3 H), 3.00 (s, 2 H),

5.36 (s, 1 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.72 (d, *J* = 8.3 Hz, 2 H); ^{13}C NMR (CDCl$_3$, 100 MHz,

major isomer) δ 0.4, 17.9, 20.4, 20.7, 21.5, 22.0, 36.4, 125.1, 127.4, 129.5, 131.8, 132.4, 137.8,

141.3, 143.4; 13C NMR (CDCl$_3$, 100 MHz, minor isomer) δ 0.8, 20.7, 21.3, 21.5, 21.8, 26.1, 34.7,

125.8, 127.5, 128.2, 129.4, 129.8, 138.4, 143.2, 149.2; High-resolution MS (major isomer), calcd

for C$_{19}$H$_{31}$NO$_2$SSi: 365.1845. Found m/z (relative intensity): 365.1856 (M+, 100), 363 (35), 350

(47); High-resolution MS (minor isomer), calcd for C$_{19}$H$_{31}$NO$_2$SSi: 365.1845. Found m/z (relative

intensity): 365.1856 (M+, 100), 350 (37).

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Chapter 4

Reconstruction of Carbon Bond Frameworks *via* Oxapalladacycle Promoted by Synergistic Effect of Palladium Catalyst and Triethylborane
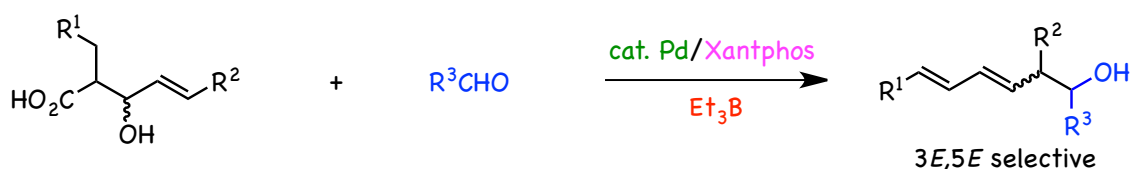
Summary: Pd-catalyzed β-carbon elimination of 3-hydroxy-4-pentenoic acid derivatives promoted by triethylborane proceeded to form conjugated dienes *via* a decarboxylation process. The formed conjugated dienes underwent the Prins reaction with aldehydes in situ to afford conjugated homoallylic alcohols. These sequential transformations enabled conversion of a diastereomeric mixture of 3-hydroxy-4-pentenoic acids, which were readily prepared from the simple crossed aldol reaction of esters and α,β-unsaturated aldehydes, to 3,5-hexadienyl alcohols with high regio- and stereoselectivities in a single manipulation.

Introduction

C-C bond cleavage reactions are convenient and powerful tools for the transformations of functional groups and expansion of the carbon bond frameworks of cyclic compounds.[1] Although C-C bond cleavage reactions have received less attention than C-C bond formation, they still have considerable synthetic utility for efficient chemical transformations.[2]

We previously reported the transition metal-catalyzed Grob-type decarboxylative ring-opening reaction of vinyl cyclic carbonates into ω-dienyl aldehydes by β-carbon elimination via an oxapalladacyclopentane intermediate (**Scheme 1**).[3] 4-Pentene-1,3-diols also underwent the dehydrative β-carbon elimination of oxapalladacycles promoted by Pd(0) catalyst and organoboran reagent (**Scheme 2**).[4] In this case, the combination of Pd(0) catalyst with *B*-Ph-9-BBN readily promoted the oxidative addition of an allylic alcohol moiety to form an oxapalladacyclopentane, followed by b-carbon elimination to efficiently provide a w-dienyl aldehyde. Organoborane can serve as a Lewis acid to assist the oxidative addition of allylic alcohols to the Pd(0) catalyst to produce oxapalladacycle intermediates.[5]
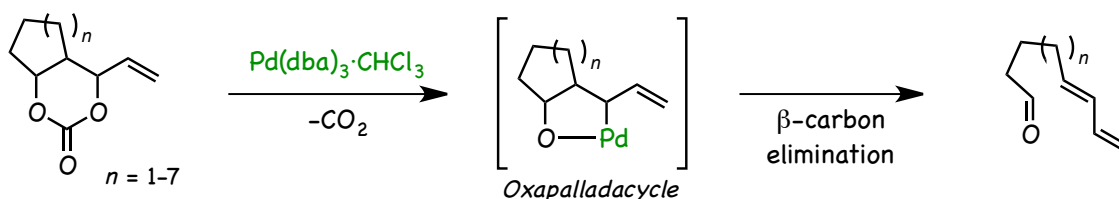
Scheme 1. Pd-Catalyzed C–C Bond Cleavage of Vinyl Cyclic Carbonates *via* Oxapalladacycle
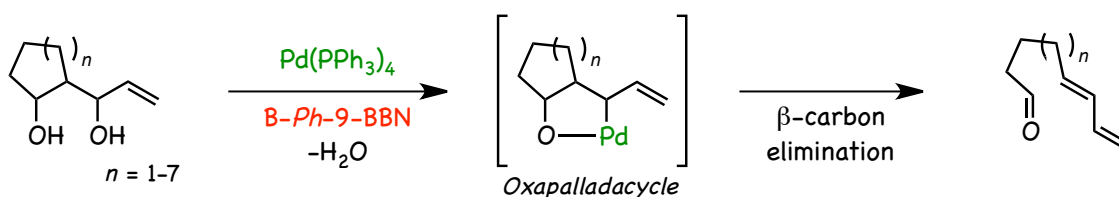
Scheme 2. Pd-Catalyzed C–C Bond Cleavage of 4-Pentene-1,3-diol *via* Oxapalladacycle

Furthermore, we have previously demonstrated that 3-hydroxy-4-pentenoic acids underwent C–C bond cleavage in the presence of Pd catalyst and Et$_3$B *via* oxapalladacycle intermediates proceeds to provide conjugated dienes in good yields with excellent stereoselectivities (**Scheme 3**).[6] This methodology is useful for the stereodefined construction of conjugated dienes from readily available esters and α,β-unsaturated aldehydes.
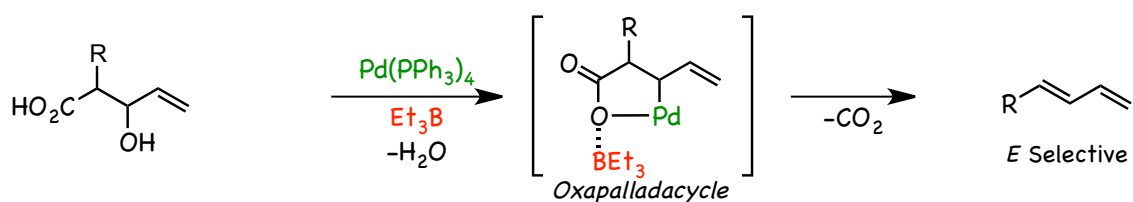
Scheme 3. Pd-Catalyzed C–C Bond Cleavage of 3-Hydroxy-4-pentenoic Acid *via* Oxapalladacycle

C–C bond formation using conjugated dienes and carbonyl compounds is also an attractive strategy in modern organic synthesis.[7] Transition metal-catalyzed reductive couplings of conjugated dienes and carbonyls mediated by organometallic reagents such as hydrosilane, trialkylborane, and dialkylzinc can provide allyl alcohols, homoallyl alcohols, and bis-homoallyl alcohols with exceptionally high regio- and stereoselectivities.[8] Most of these reactions proceed through the oxidative cyclization of low-valent transition metals across the conjugated dienes and carbonyls, followed by transmetallation with organometallic reagents *via* the oxametallacycles. Thus, the oxametallacycles formed in situ can serve as common important intermediates for C–C bond coupling as well as β-carbon elimination.

Regarding C–C bond coupling, the ene-type coupling reaction (Prins reaction) can occur in the presence of a Pd catalyst and Xantphos ligand.[9] Et$_3$B promotes the allylation of aldehydes with conjugated dienes to provide homoallyl alcohols. The reaction takes place smoothly at the C–C

double bond of the conjugated diene bearing higher electron density through the oxapalladacycle intermediate (**Scheme 4**).
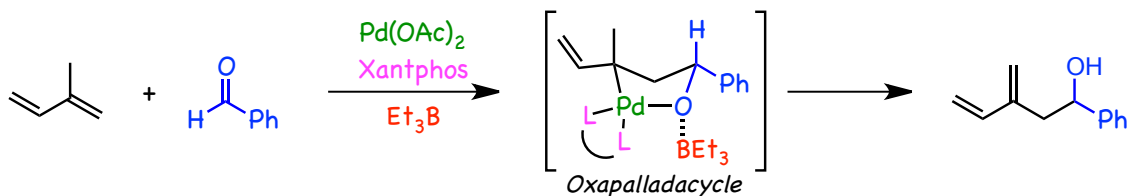
Scheme 4. Pd-Catalyzed C–C Bond Formation of Conjugated Diene and Aldehyde *via* Oxapalladacycle

Based on these findings, 3-hydroxy-4-pentenoic acid was regarded as a conjugated diene equivalent and planned to be utilized as a synthetic intermediate. Herein, we disclose the Pd-catalyzed β-carbon elimination of 3-hydroxy-4-pentenoic acids with accompanying decarboxylation promoted by Et$_3$B to form 1,3-pentadiene derivatives, which is followed by Prins reactions with aldehydes in situ to afford the conjugated homoallylic alcohols (**Scheme 5**). These sequential transformations enable conversion of a diastereomeric mixture of 3-hydroxy-4-pentenoic acids to a 3,5-hexadienyl framework in a single manipulation irrespective of the steric nature of the starting materials.
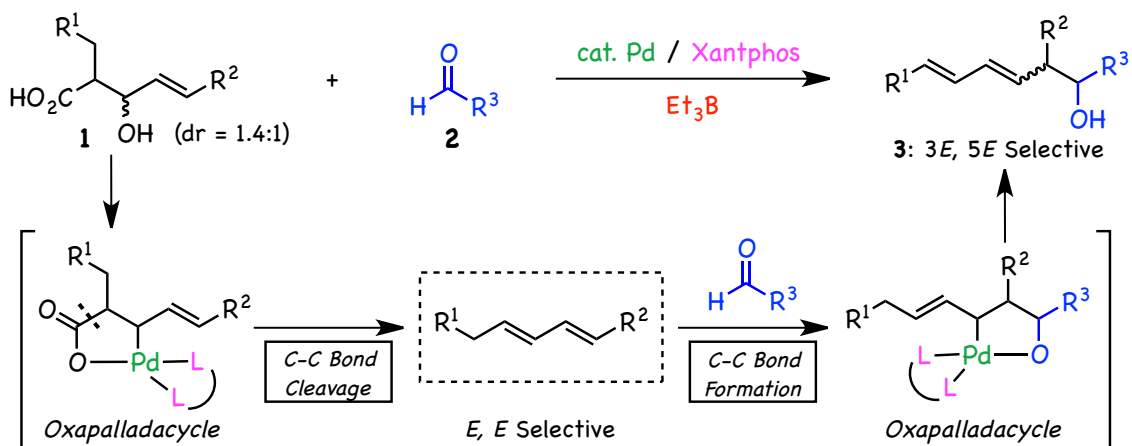
Scheme 5. Pd-Catalyzed C–C Bond Formation Utilizing 3-Hydroxy-4-pentenoic Acids as an Equivalent of Conjugated Diene with Aldehyde

Results and Discussion

The optimization of the reaction conditions are summarized in **Table 1**. In the presence of Pd(OAc)$_2$ (10 mol%), Xantphos (10 mol%), and Et$_3$B (1.5 mmol, 1.0 M in THF), the coupling reaction of 3-hydroxy-4-pentenoic acid **1a** (0.5 mmol) with benzaldehyde **2a** (1.5 mmol) proceeded at 67 °C to give the corresponding (3*E*,5*E*)- and (3*Z*,5*E*)-3,5-hexadien-1-ol **3a** in 91% yield in a 10:1 ratio (Entry 1, **Table 1**). When 1.0 mmol and 0.5 mmol of **2a** were used, the desired product **3a** was obtained in 85% and 72% yields, respectively (Entries 2 and 3, **Table 1**). Pd(acac)$_2$ was also effective for this reaction (Entry 4, **Table 1**). On the other hand, PdCl$_2$ was not effective to promote the desired reaction (Entry 5, **Table 1**). Using Pd(dba)$_2$ significantly reduced the yield (Entry 6, **Table 1**). Next, we investigated the ligand effects in this coupling reaction, and the results are summarized in entries 1, 7-16. In the case of Cy-Xantphos as a ligand, the desired product obtained in low yield along with diene **4'a** as major product (Entry 7, **Table 1**). When *N*-Xantphos and DPEphos were used as ligand instead of Xantphos, the reactions proceeded to give **3a** in 75% and 72% yields, respectively (Entries 8 and 9, **Table 1**). However, by use of DPPF and *rac*-BINAP, the yield decreased to 50% and 32%, respectively (Entries 10 and 11, **Table 1**). In the case of DPPE and DPPP, the desired reaction did not proceed (Entries 12 and 13, **Table 1**). Mono-dentate ligand, such as PPh$_3$ and Xphos, the corresponding products were obtained in low to moderate yields (Entries 14 and 15, **Table 1**). Bathophenanthroline did not work well (Entry 16, **Table 1**). We have further examined organometallic reagents for the coupling reaction, and the results are shown in entries 17-19. However, Et$_3$Al, Et$_2$Zn, and Ph$_3$B were not effective to promote the coupling reactions. As expected, control experiments revealed no product formation when Palladium catalyst or Xantphos

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was omitted from the mixture (Entries 20-21, **Table 1**).   On the other hand, when Et_3B was

excluded from the mixture, desired product formation was not observed, but the diene **4'a** was

observed in moderate yield (Entry 22, **Table 1**).   That is, Et_3B is indispensable for the C–C bond

formation reaction, and accelerates the C–C bond cleavage reaction.
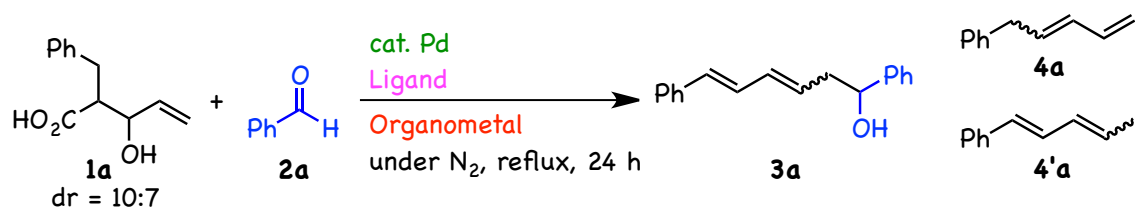
Table 1. Optimization of the Reaction Conditions for Palladium-Catalyzed C–C Bond Formation
Utilizing 3-Hydroxy-4-pentenoic Acids as an Equivalent of Conjugated Diene with Aldehyde[a]

| Entry | cat. Pd | Ligand (mol%) | Organometal | Isolated Yield [%] | | |
				3a [(3E,5E):(3Z,5E)]	4a [E:Z]	4'a [E:Z]
1	Pd(OAc)₂	Xantphos (10)	Et₃B	91 [10:1]	0	0
2[b]	Pd(OAc)₂	Xantphos (10)	Et₃B	85 [9:1]	Trace	Trace
3[c]	Pd(OAc)₂	Xantphos (10)	Et₃B	72 [8:1]	Trace	13 [4:1]
4	Pd(acac)₂	Xantphos (10)	Et₃B	89 [10:1]	0	0
5	PdCl₂	Xantphos (10)	Et₃B	0	19 [3:1]	2 [7:1]
6	Pd(dba)₂	Xantphos (10)	Et₃B	43 [9:1]	6 [4:1]	18 [5:1]
7	Pd(OAc)₂	Cy–Xantphos[d] (10)	Et₃B	28 [6:1]	0	65 [7:1]
8	Pd(OAc)₂	N–Xantphos[e] (10)	Et₃B	75 [9:1]	0	0
9	Pd(OAc)₂	DPEphos[f] (10)	Et₃B	72 [10:1]	0	0
10	Pd(OAc)₂	DPPF (10)	Et₃B	50 [8:1]	6 [2:1]	32 [6:1]
11	Pd(OAc)₂	rac-BINAP (10)	Et₃B	32 [36:1]	1 [2:1]	39 [8:1]
12	Pd(OAc)₂	DPPE (10)	Et₃B	0	1 [2:1]	26 [7:1]
13	Pd(OAc)₂	DPPP (10)	Et₃B	0	3 [1:2]	39 [9:1]
14	Pd(OAc)₂	PPh₃ (20)	Et₃B	18 [8:1]	0	0
15	Pd(OAc)₂	Xphos[g] (20)	Et₃B	42 [8:1]	0	0
16	Pd(OAc)₂	Bathophen (10)	Et₃B	0	0	19 [5:1]

17[h]	Pd(OAc)$_2$	Xantphos (10)	Et$_3$Al	0	0	0
18[h]	Pd(OAc)$_2$	Xantphos (10)	Et$_2$Zn	0	5 [2.5:1]	1 [2.3:1]
19[i]	Pd(OAc)$_2$	Xantphos (10)	Ph$_3$B	0	0	0
20	None	Xantphos (10)	Et$_3$B	0	0	0
21	Pd(OAc)$_2$	None	Et$_3$B	0	0	0
22[j]	Pd(OAc)$_2$	Xantphos (10)	None	0	0	57 [4.5:1]

Xantphos (112°)[k]   Cy-Xantphos   N-Xantphos (114°)[k]   DPEphos (102°)[k]   DPPF (96°)[k]

rac-BINAP (92°)[k]   DPPE (85°)[k]   DPPP (91°)[k]   Xphos   Bathophen
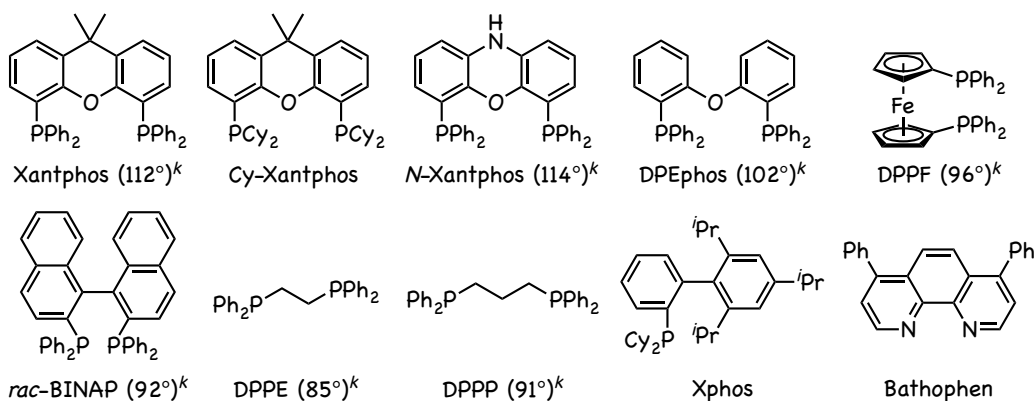
[a]3-Hydroxy-4-pentenoic acid **1a** (0.5 mmol) and benzaldehyde **2a** (1.5 mmol), in the presence of Pd catalyst (10 mol%), Ligand (10-20 mol%), and organometallic reagent (1.5 mmol, 1.0 M in THF) at 67 °C for 24 h under nitrogen atmosphere. [b]1.0 mmol of **2a** was used. [c]0.5 mmol of **2a** was used. [d]Cy-Xantphos: 4,5-Bis(dicyclohexylphosphino)-9,9-dimethylxanthene. [e]N-Xantphos: 4,6-Bis(diphenylphosphino)phenoxazine. [f]DPEphos: Bis[2-(diphenylphosphino)phenyl] Ether. [g]Xphos: 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. [h]THF (1.5 mL) and hexane (1.5 mL) were used. [i]THF (1.5 mL), hexane (1.1 mL), Bu$_2$O (3.2 mL) were used. [j]THF (1.5 mL) was used. [k]Bite angle (P-M-P).

With the optimal conditions in hand, we next explored the substrate scope of the coupling reactions of a variety of 3-hydroxy-4-pentenoic acids **1a** with benzaldehyde **2a** under the Pd(OAc)$_2$/Xantphos/Et$_3$B system, and the results are summarized in **Table 2**.   In the presence of Pd(OAc)$_2$ (10 mol%), Xantphos (10 mol%), and Et$_3$B (1.5 mmol, 1.0 M in THF), the coupling reaction of 3-hydroxy-4-pentenoic acid **1a** with benzaldehyde **2a** to provide (3*E*,5*E*)- and (3*Z*,5*E*)-3,5-hexadien-1-ol **3a** in 91% yield in a 10:1 ratio (Entry 1, **Table 2**).   The 3-hydroxy-4-pentenoic acids bearing a tolyl and *p*-methoxyphenyl group at R^1 position provided the desired products in moderate to good yields (Entries 2 and 3, **Table 2**).   In the case of 5-substituted 3-hydroxy-4-pentenoic acids **1d** and **1e** (R^1=Ph, R^2=Ph or Me), the desired reactions proceeded to give the corresponding 3*E*,5*E*-hexadien-1-ol in good yields with excellent stereoselectivities as a mixture of diastereomers (Entries 4 and 5, **Table 2**).   The 3-hydroxy-4-pentenoic acid bearing a benzyl group at R^1 position also provided the desired product in moderate yield (Entry 6, **Table 2**).   Cyclohexyl substituted 3-hydroxy-4-pentenoic acid **1g** was transformed into 3,5-hexadien-1-ol **3g** in moderate yield (Entry 7, **Table 2**).   Thus, aromatic substituents on R^1 are not necessary to trigger a carbonyl–ene-type coupling reaction with an aldehyde to provide conjugated dienyl alcohols.

Table 2. Palladium-Catalyzed C–C Bond Formation Utilizing Various 3-Hydroxy-4-pentenoic Acids **1** as an Equivalent of Conjugated Diene with Benzaldehyde **2a**[a]
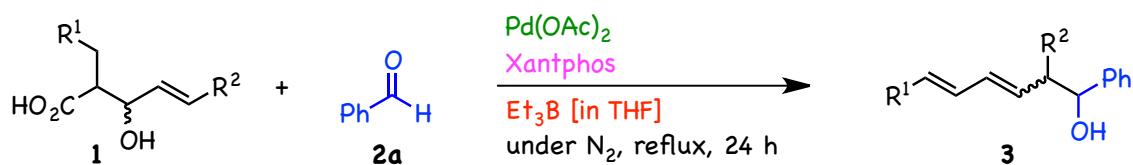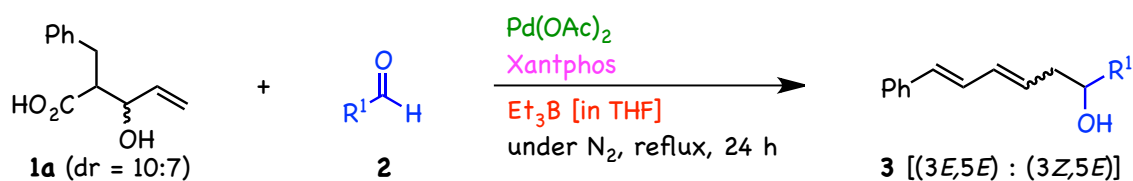

Entry	**1** [dr]	Isolated Yield of **3** [(3*E*,5*E*) : (3*Z*,5*E*)] [%]
1	**1a** : R^1 = Ph, R^2 = H [1.4:1]	**3a** : 91 [10:1]
2	**1b** : R^1 = (*p*–Me)Ph, R^2 = H [1.3:1]	**3b** : 84 [10:1]
3	**1c** : R^1 = (*p*–OMe)Ph, R^2 = H [1.8:1]	**3c** : 60 [8:1]
4	**1d** : R^1 = Ph, R^2 = Ph [2.0:1]	**3d** : 79 [single, dr = 2.3:1]
5	**1e** : R^1 = Ph , R^2 = Me [1.3:1]	**3e** : 82 [single, dr = 1.5:1]
6	**1f** : R^1 = Bn , R^2 = H [1.4:1]	**3f** : 52 [8:1]
7	**1g** : R^1 = Cy , R^2 = H [1.4:1]	**3g** : 48 [7:1]

[a]3-Hydroxy-4-pentenoic acid **1** (0.5 mmol) and benzaldehyde **2a** (1.5 mmol), in the presence of Pd(OAc)$_2$ (10 mol%), Xantphos (10 mol%), and Et$_3$B (1.5 mmol, 1.0 M in THF) at 67 °C for 24 h under nitrogen atmosphere.

Next, we examined the reactions of a variety of aldehydes **2** with 3-hydroxy-4-pentenoic acid **1a**, and the results are summarized in **Table 3**. As expected, a host of aldehydes substituted with either aromatic (Entries 1-15, **Table 3**) or aliphatic backbones (Entries 16-19, **Table 3**) reacted equally well with the Pd(OAc)$_2$/Xantphos/Et$_3$B system. Notably, the outcome of the latter was found to be insensitive to whether electron-rich or electron-poor arenes were employed, even in the presence of *ortho-*, *meta-*, or *para*-substituents (**2b-2l**). In the case of 1-naphthaldehyde, the desired product was obtained in good yield (Entry 13, **Table 3**). Likewise, the reaction could be applied in the presence of heterocyclic cores (Entries 14 and 15, **Table 3**).

Table 3. Palladium-Catalyzed C–C Bond Formation Utilizing 3-Hydroxy-4-pentenoic Acid **1a** as an Equivalent of Conjugated Diene with Various Aldehyde **2**[a]

Entry	2	Isolated Yield of 3 [(3*E*,5*E*) : (3*Z*,5*E*)] [%]
1	**2a** : R = Ph	**3a** : 91 [10:1]
2	**2b** : R = (*o*–Me)Ph	**3h** : 92 [11:1]
3	**2c** : R = (*o*–Cl)Ph	**3i** : 73 [12:1]
4	**2d** : R = (*m*–OMe)Ph	**3j** : 51 [9:1]
5	**2e** : R = (*m*–Cl)Ph	**3k** : 66 [13:1]
6	**2f** : R = (*m*–OPiv)Ph	**3l** : 69 [16:1]
7	**2g** : R = (*p*–OMe)Ph	**3m**: 84 [11:1]
8	**2h** : R = (*p*–SMe)Ph	**3n** : 86 [12:1]
9	**2i** : R = (*p*–Cl)Ph	**3o** : 73 [9:1]
10	**2j** : R = (*p*–F)Ph	**3p** : 71 [9:1]
11	**2k** : R = (*p*–CN)Ph	**3q** : 54 [10:1]
12	**2l** : R = (*p*–NO$_2$)Ph	**3r** : 37 [9:1]
13	**2m**: R = 1–naphthyl	**3s** : 87 [7:1]
14	**2n** : R = 2–furyl	**3t** : 44 [>20:1]
15	**2o** : R = 3–benzothiophenyl	**3u** : 79 [12:1]
16	**2p** : R = –CH$_2$CH$_2$Ph	**3v** : 33 [>99:1]
17	**2q** : R = Et	**3w**: 75 [>99:1]
18	**2r** : R = *tert*–Bu	**3x** : 67 [>20:1]
19	**2s** : R = Cy	**3y** : 71 [9:1]

[a]3-Hydroxy-4-pentenoic acid **1a** (0.5 mmol) and aldehyde **2** (1.5 mmol), in the presence of Pd(OAc)$_2$ (10 mol%), Xantphos (10 mol%), and Et$_3$B (1.5 mmol, 1.0 M in THF) at 67 °C for 24 h under nitrogen atmosphere.

To shed light on the reaction mechanism, we studied the coupling reactions of conjugated dienes as the major intermediates with PhCHO in the formation of the coupling products (**Scheme 6**). Isolated conjugated dienes **4a** and **4'a**, which were independently prepared from **1a** *via* decarboxylation, were treated with a mixture of Pd catalyst and Et$_3$B in the presence of Xantphos. Diene **4a** provided the desired homoallylic alcohol **3a** with high 3*E*,5*E* selectivity (Eq. (a), **Scheme 6**), whereas diene **4'a** afforded the completely different allylic alcohol **5a** as the sole product (Eq. (b), **Scheme 6**). These results suggest that the sequential coupling of 1a with PhCHO proceeds in situ *via* 5-phenyl-1,3-pentadiene **4a** as an important intermediate in the final step of the C−C bond coupling reaction and isomerization from **4a** to **4'a** is irreversible.
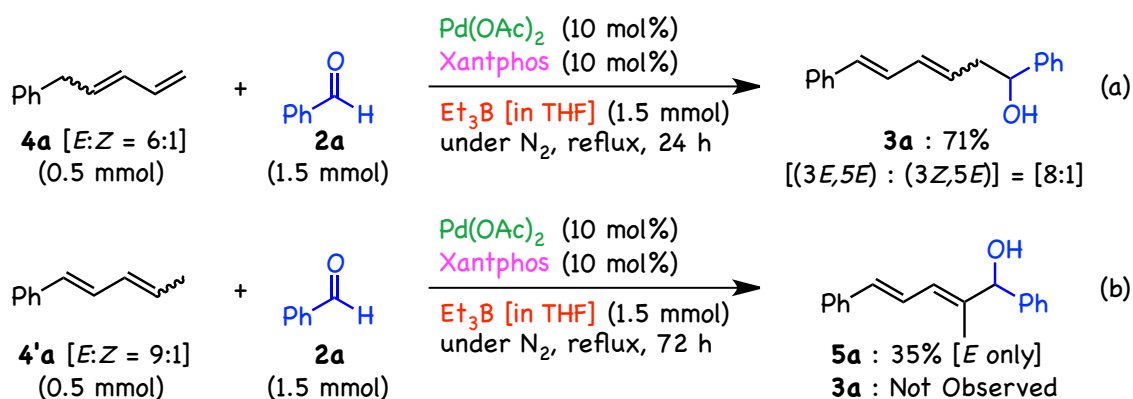
Scheme 6. Pd-Catalyzed C–C Bond Formation Utilizing Conjugated Diene with Aldehyde

The structure of the product **5a** was determined based on coupling constants from ¹H NMR, ¹³C NMR, HMBC, HMQC spectral data and NOE experiment. The selected data for the NOE observed by the irradiation at the bold face protons are illustrated in **Figure 1**.
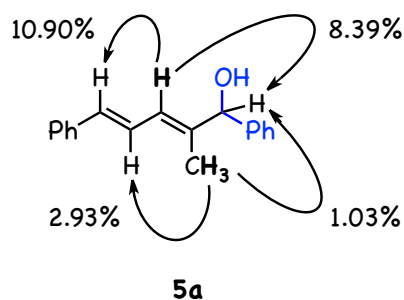
Figure 1. Structure Determination for NOE Data of Dienyl Alcohol **5a**

Next, a plausible reaction mechanism for the coupling reactions of 3-hydroxy-4-pentenoic acid and aldehyde promoted by a palladium catalyst, Xantphos, and Et$_3$B are illustrated in **Scheme 7**. We propose that *anti*-oxapalladacycle-**I** is generated by oxidative addition of the Pd/Xantphos complex to the allylic position of *syn*-**1** activated by Et$_3$B with inversion of configuration. Similarly, *syn*-oxapalladacycle-**I'** is generated from *anti*-**1**. The intermediate *syn*-oxapalladacycle-**I'** then isomerizes to the sterically more stable *anti*-oxapalladacycle-**I** from by σ-π-σ interconversion.[10] Then, the *anti*-oxapalladacycle-**I** could undergo the C3-C4 bond fission with evolution of carbon dioxide to provide (*E*)-conjugated diene **4a**. Next, in the presence of Pd and Xantphos catalyst with Et$_3$B, promotes conjugated diene **4a** to undergo the oxidative cyclization with aldehyde to form the oxapalladacycle-**II**. The intermediates **II** undergo transmetallation with Et$_3$B to form allylpalladium species **III**. This allylpalladium species **III** readily undergoes σ-π-σ interconversion to afford allylpalladium species **V** and **V'**, followed by β-hydride elimination resulting in the generation of (3*E*, 5*E*)- and (3*Z*, 5*E*)-dienyl alcohol **3** and is accompanied with the formation of the Pd/Xantphos complex as the key catalytic species.[11] Despite use of a diastereomeric mixture of **1a** as starting materials, stereocontrolled homoallylic alcohols were obtained because of the stability of the oxidative cyclization.
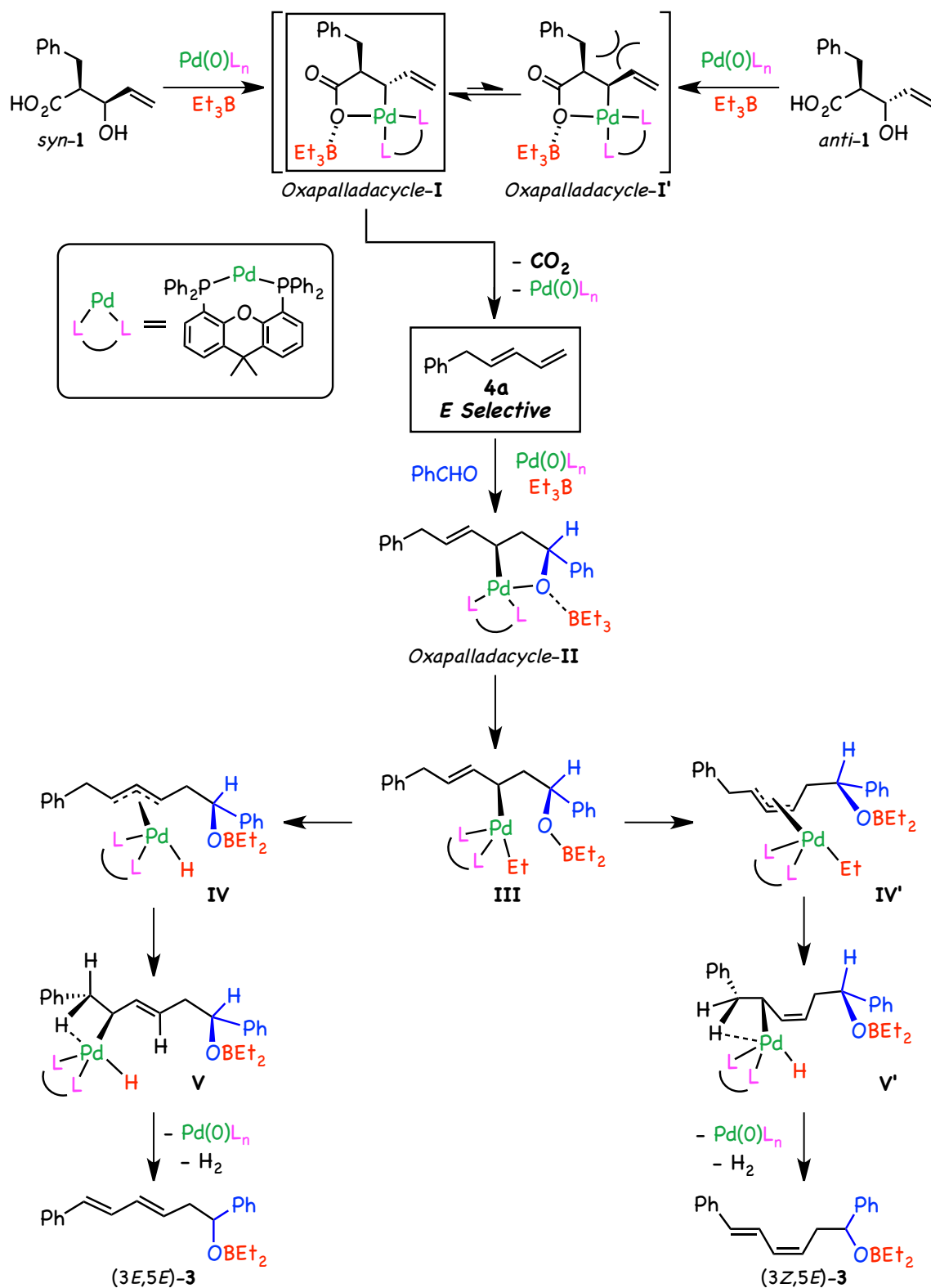
Scheme 7. Plausible Reaction Mechanism for Palladium-Catalyzed C–C Bond Formation Utilizing 3-Hydroxy-4-pentenoic Acids as an Equivalent of Conjugated Diene with Aldehyde

Conclusion

In conclusion, we developed the Pd-catalyzed β-carbon elimination of 3-hydroxy-4-pentenoic acid derivatives accompanied by a decarboxylation process promoted by Et$_3$B to form pentadiene derivatives as *E,E* isomers. The formed conjugated dienes can serve as major intermediates to undergo the Prins reaction with a wide variety of aldehydes in situ to afford conjugated homoallylic alcohols. These sequential transformations enabled transformation of a diastereomeric mixture of 3-hydroxy-4-pentenoic acids, which was readily prepared by a crossed aldol reaction of esters and acrolein and their derivatives, to 3,5-hexadienyl alcohols in a single manipulation. This consecutive cascade synthesis is a useful strategy for the stereodefined controlled reconstruction of carbon bond frameworks irrespective of the steric nature of the starting materials.

Experimental Section

Reactions employed oven-dried glassware unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator (Merck, Silica gel 60F$_{254}$). Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL-GX400 and Varian-500PS-SN. All ^{1}H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for CHCl$_3$ (7.26 ppm) or acetone-d$_5$ (2.05 ppm). All ^{13}C NMR spectra were reported in ppm relative to residual CHCl$_3$ (77.16 ppm) or acetone-d$_5$ (29.84 ppm) and were obtained with ^{1}H decoupling. Chemical shift values were given in ppm downfield from the internal standard. Infrared spectra were recorded with a JASCO A-100 FT-IR spectrophotometer. High resolution mass spectra (HRMS) were measured with a JEOL JMS-700N. Melting points were measured using open glass capillaries in a Stuart^{TM} melting point apparatus SMP3.

Solvent and Reagents

Dehydrated THF, Pd(OAc)$_2$, Pd(acac)$_2$, PdCl$_2$, Pd(dba)$_2$, Xantphos, Cy-Xantphos, *N*-Xantphos, DPEphos, DPPF, *rac*-BINAP, DPPE, DPPP, PPh$_3$, Xphos, Bathophenanthroline, Et$_3$B (1.0 M in THF), Et$_2$Zn (1.0 M in hexane), Et$_3$Al (1.0 M in hexane), *n*-BuLi (1.6 M in hexane), diisopropylamine, 3-phenylpropionic acid, 3-(4-tolyl)propionic acid, 3-(4-methoxyphenyl)propionic acid, benzenebutanoic acid, 3-cyclohexylpropionic acid, aldehyde **2i**, **2k**, **2l**, **2o** and 3-hydroxybenzaldehyde were purchased and used without further purification. Aldehyde **2a**-**2e**, **2g**-**2h**, **2j**, **2m**-**2n**, **2p**-**2s**, acrolein, crotonaldehyde, and trans-cinnamaldehyde were purchased and

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distilled prior to use by Kugelrohr apparatus. Ph_3B was prepared from BCl_3 (1.0 M in heptane) and 3-equivalents of PhLi (1.6 M in butyl ether).

Procedure for Preparing 3-Hydroxy-4-pentenoic Acids via Cross-Aldol Reaction:

General Procedure A: A solution of lithium diisopropylamide (LDA) was prepared by the slow addition of *n*-BuLi (30 mL, 48 mmol, 1.6 M in hexane) to a solution of diisopropylamine (6.8 mL, 48 mmol) in THF (30 mL) at -78 °C for 30 minutes.   Then, the corresponding carboxylic acid (20 mmol dissolved in 30 mL of THF) was added dropwise at -78 °C.   The reaction mixture was stirred for 30 minutes at room temperature and then the corresponding aldehyde (24 mmol) was added dropwise at -78 °C.   The reaction mixture was stirred for 10 minutes at room temperature. After this time, it was quenched with a 2 M HCl and extracted 3 times with chloroform.   The combined organic phases were washed with brine, dried over $MgSO_4$ and filtered.   The solvent was then removed under reduced pressure and it was purified by column chromatography (hexane/EtOAc = 4/1 to 1/1 v/v) to obtain the corresponding 3-hydroxy-4-pentenoic acid in good yield.

General Procedure for the Pd-Catalyzed C−C Bond Formation Utilizing 3-Hydroxy-4-pentenoic Acid 1a (Entry 3, Table 1):

General Procedure B: An oven-dried reactor vessel containing $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), Xantphos (28.9 mg, 0.05mmol), and 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.5 mg, 0.5 mmol) were purged with nitrogen gas to remove oxygen. Et_3B (1.5 mmol, 1.0 M in THF) and benzaldehyde (**2a**, 155 μL, 1.5 mmol) were introduced into the reactor vessel with a syringe.   The mixture was stirred at 67 ℃ for 24 h.   After this time, it was quenched with a 2 M HCl and

extracted 3 times with Et_2O. The combined organic phases were washed with sat. $NaHCO_3$ and brine, and then dried over $MgSO_4$ and filtered. Then, the solvent was then removed under reduced pressure, and the crude product was subjected to column chromatography over silica gel (hexane/EtOAc = 10/1 v/v) to give **3a** (114.6 mg, 91% yield, R_f = 0.33; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 10:1). White solid (m.p. 89.3-90.3 °C).

Spectroscopic Data

1a
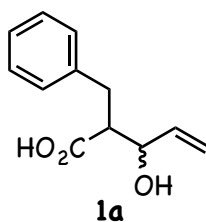
2-benzyl-3-hydroxypent-4-enoic acid (1a). Following the general procedure A using 3-phenylpropionic acid (3.00 g, 20 mmol) and acrolein (1.6 mL, 24 mmol), afford **1a** (3.78 g, 92% yield, R_f = 0.40; hexane/EtOAc = 1/1 v/v) as a mixture of diastereoisomers (1.4:1). White solid (m.p. 77.7-78.5 °C).

^{1}H NMR (500 MHz, Acetone-d_6, major isomer) δ 7.27-7.15 (m, 5 H), 5.98 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.32 (ddd, J = 17.0, 1.5, 1.5 Hz, 1 H), 5.17 (ddd, J = 10.5, 1.5, 1.5 Hz, 1 H), 4.30 (dddd, J = 6.5, 6.5, 1.5, 1.5 Hz, 1 H), 2.92-2.78 (m, 3 H) ppm.
^{1}H NMR (500 MHz, Acetone-d_6, minor isomer) δ 7.27-7.14 (m, 5 H), 5.99 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.31 (ddd, J = 17.0, 1.5, 1.5 Hz, 1 H), 5.14 (ddd, J = 10.5, 1.5, 1.5 Hz, 1 H), 4.33 (dddd, J = 6.5, 6.5, 1.5, 1.5 Hz, 1 H), 3.08-2.76 (m, 3 H) ppm.

^{13}C NMR (126 MHz, Acetone-d_6, major isomer) δ 175.26, 140.51, 139.94, 129.63, 128.99, 126.85, 116.25, 73.98, 54.53, 34.92 ppm.
^{13}C NMR (126 MHz, Acetone-d_6, minor isomer) δ 174.88, 140.87, 139.87, 129.63, 128.96, 126.76, 115.84, 73.86, 54.92, 34.65 ppm.

IR (KBr, cm^{-1}): 3265, 3067, 3055, 3028, 2953, 2939, 2677, 2646, 2320, 1705, 1456, 1393, 1265, 1221, 1167, 1045, 1016, 961, 874, 826, 698, 648.

High-resolution MS, ($C_{12}H_{14}O_3$) *calculated* 206.0943, *found* 206.0943.

1b

2-(4-methylbenzyl)-3-hydroxypent-4-enoic acid (1b). Following the general procedure A using

3-(4-tolyl)propionic acid (1.64 g, 10 mmol) and acrolein (1.0 mL, 15 mmol), afford **1b** (1.98 g, 90% yield, R_f = 0.33; hexane/EtOAc = 1/1 v/v) as a mixture of diastereoisomers (1.3:1). White solid (m.p. 94.9-95.6 °C).

¹H NMR (500 MHz, Acetone-d_6, major isomer) δ 7.11 (d, J = 8.0 Hz, 2 H), 7.05 (d, J = 8.0 Hz, 2 H), 5.97 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.31 (ddd, J = 17.0, 1.5, 1.5 Hz, 1 H), 5.16 (ddd, J = 10.5, 1.5, 1.5 Hz, 1 H), 4.28 (dddd, J = 6.5, 6.5, 1.5, 1.5 Hz, 1 H), 2.92-2.75 (m, 3 H), 2.25 (s, 3 H) ppm.
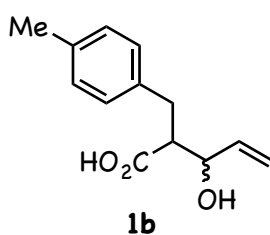
¹H NMR (500 MHz, Acetone-d_6, minor isomer) δ 7.11 (d, J = 8.0 Hz, 2 H), 7.05 (d, J = 8.0 Hz, 2 H), 5.98 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.31 (ddd, J = 17.0, 1.5, 1.5 Hz, 1 H), 5.13 (ddd, J = 10.5, 1.5, 1.5 Hz, 1 H), 4.32 (dddd, J = 6.5, 6.5, 1.5, 1.5 Hz, 1 H), 3.03-2.74 (m, 3 H), 2.25 (s, 3 H) ppm.

¹³C NMR (126 MHz, Acetone-d_6, major isomer) δ 175.23, 140.12, 137.36, 136.14, 129.67, 129.58, 116.21, 74.03, 54.62, 34.69, 20.99 ppm.

¹³C NMR (126 MHz, Acetone-d_6, minor isomer) δ 174.80, 139.95, 137.73, 136.03, 129.64, 129.58, 115.84, 73.88, 54.98, 34.29, 20.99 ppm.

IR (KBr, cm⁻¹): 3252, 3047, 3022, 2997, 2953, 2939, 2878, 2652, 1908, 1707, 1516, 1447, 1396, 1269, 1236, 1159, 1109, 1018, 949, 806, 694, 648.

High-resolution MS, ($C_{13}H_{16}O_3$) *calculated* 220.1099, *found* 220.1099.

1c
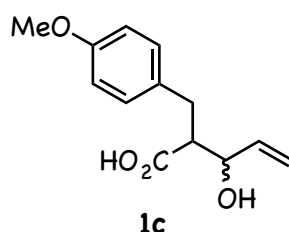
2-(4-methoxybenzyl)-3-hydroxypent-4-enoic acid (1c). Following the general procedure A using 3-(4-methoxyphenyl)propionic acid (1.80 g, 10 mmol) and acrolein (1.0 mL, 15 mmol), afford **1c** (1.96 g, 83% yield, R_f = 0.20; hexane/EtOAc = 1/1 v/v) as a mixture of diastereoisomers (1.8:1). White solid (m.p. 57.4-58.4 °C).

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.11 (d, J = 8.5 Hz, 2 H), 6.81 (d, J = 8.5 Hz, 2 H),

5.87 (ddd, J = 17.0, 11.0, 6.0 Hz, 1 H), 5.30 (d, J = 17.0 Hz, 1 H), 5.21 (d, J = 11.0 Hz, 1 H), 4.20 (dd, J = 6.0, 6.0 Hz, 1 H), 3.76 (s, 3 H), 2.98-2.73 (m, 3 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 7.09 (d, J = 8.5 Hz, 2 H), 6.80 (d, J = 8.5 Hz, 2 H), 5.91 (ddd, J = 17.0, 10.5, 6.0 Hz, 1 H), 5.33 (d, J = 17.0 Hz, 1 H), 5.24 (d, J = 10.5 Hz, 1 H), 4.36 (dd, J = 6.0, 6.0 Hz, 1 H), 3.76 (s, 3 H), 2.98-2.73 (m, 3 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 179.31, 158.38, 138.10, 130.05, 129.95, 117.08, 114.08, 72.54, 55.30, 34.14, 32.30 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 178.77, 158.26, 136.87, 130.86, 130.25, 117.60, 114.04, 72.98, 53.10, 34.14, 31.68 ppm.

IR (KBr, cm⁻¹): 3395, 3082, 3013, 2953, 2935, 2835, 2365, 2341, 2247, 2058, 1713, 1612, 1582, 1514, 1445, 1248, 1178, 1036, 910, 839, 756, 734.

High-resolution MS, (C₁₃H₁₆O₄) *calculated* 236.1049, *found* 236.1049.
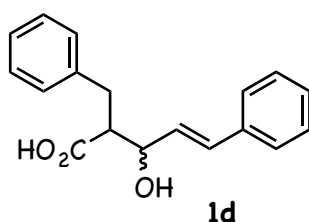
2-benzyl-3-hydroxy-5-phenylpent-4-enoic acid (1d). Following the general procedure A using 3-phenylpropionic acid (2.25 g, 15 mmol) and *trans*-cinnamaldehyde (2.9 mL, 22.5 mmol), afford **1d** (3.26 g, 77% yield, R_f = 0.40; hexane/EtOAc = 1/1 v/v) as a mixture of diastereoisomers (2.0:1). White solid (m.p. 145.8-146.6 °C).

¹H NMR (500 MHz, Acetone-d_6, major isomer) δ 7.45 (d, J = 7.0 Hz, 2 H), 7.32 (t, J = 7.0 Hz, 2 H), 7.26-7.22 (m, 5 H), 7.19-7.14 (m, 1 H), 6.70 (d, J = 15.5 Hz, 1 H), 6.41 (dd, J = 15.5, 6.5 Hz, 1 H), 4.52-4.50 (m, 1 H), 3.03-2.91 (m, 3 H) ppm.

¹H NMR (500 MHz, Acetone-d_6, minor isomer) δ 7.42 (d, J = 7.0 Hz, 2 H), 7.31 (t, J = 7.0 Hz, 2 H), 7.26-7.21 (m, 5 H), 7.19-7.14 (m, 1 H), 6.68 (d, J = 15.5 Hz, 1 H), 6.42 (dd, J = 15.5, 6.5 Hz, 1 H), 4.54-4.50 (m, 1 H), 3.16-2.88 (m, 3 H) ppm.

^{13}**C NMR** (126 MHz, Acetone-d_6, major isomer) δ 175.03, 140.60, 137.82, 131.99, 131.51, 129.74, 129.38, 129.05, 128.37, 127.32, 126.91, 74.04, 54.98, 35.31 ppm.

^{13}**C NMR** (126 MHz, Acetone-d_6, minor isomer) δ 174.61, 140.97, 137.86, 131.60, 131.36, 129.74, 129.38, 129.05, 128.33, 127.28, 126.84, 73.82, 55.20, 34.88 ppm.

IR (KBr, cm^{-1}): 3240, 3086, 3061, 3028, 2953, 2934, 2881, 2652, 2359, 2340, 1707, 1495, 1456, 1396, 1269, 1196, 993, 968, 824, 745, 692.

High-resolution MS, (C$_{18}$H$_{18}$O$_3$) *calculated* 282.1256, *found* 282.1256.
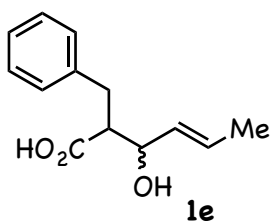
2-benzyl-3-hydroxyhex-4-enoic acid (1e). Following the general procedure A using 3-phenylpropionic acid (3.00 g, 20 mmol) and crotonaldehyde (2.0 mL, 24 mmol), afford **1e** (1.75 g, 40% yield, R_f = 0.33; hexane/EtOAc = 1/1 v/v) as a mixture of diastereoisomers (1.3:1). White solid (m.p. 138.1-139.0 °C).

^{1}**H NMR** (500 MHz, Acetone-d_6, major isomer) δ 10.59 (brs, 1 H), 7.24 (d, *J* = 7.0 Hz, 2 H), 7.22 (d, *J* = 7.0 Hz, 2 H), 7.16 (t, *J* = 7.0 Hz, 1 H), 5.73 (dq, *J* = 15.5, 6.5 Hz, 1 H), 5.58 (dd, *J* = 15.5, 7.5 Hz, 1 H), 4.23 (dd, *J* = 7.5, 7.5 Hz, 1 H), 4.10 (brs, 1 H), 2.89-2.73 (m, 3 H), 1.69 (d, *J* = 6.5 Hz, 3 H) ppm.

^{1}**H NMR** (500 MHz, Acetone-d_6, minor isomer) δ 10.59 (brs, 1 H), 7.26 (d, *J* = 7.0 Hz, 2 H), 7.22 (d, *J* = 7.0 Hz, 2 H), 7.16 (t, *J* = 7.0 Hz, 1 H), 5.72 (dq, *J* = 15.5, 6.5 Hz, 1 H), 5.60 (dd, *J* = 15.5, 7.5 Hz, 1 H), 4.23 (dd, *J* = 7.5, 7.5 Hz, 1 H), 4.10 (brs, 1 H), 3.07-2.73 (m, 3 H), 1.67 (d, *J* = 6.5 Hz, 3 H) ppm.

^{13}**C NMR** (126 MHz, Acetone-d_6, major isomer) δ 175.14, 140.73, 133.30, 129.71, 129.03, 128.18, 126.87, 74.12, 54.95, 35.36, 17.84 ppm.

^{13}**C NMR** (126 MHz, Acetone-d_6, minor isomer) δ 174.63, 141.10, 132.96, 129.71, 129.03, 127.68, 126.80, 73.75, 55.20, 34.99, 17.84 ppm.

IR (KBr, cm^{-1}): 3265, 3028, 2978, 2953, 2939, 2926, 2652, 2365, 1965, 1886, 1709, 1495, 1450, 1433, 1393, 1269, 1204, 1042, 968, 880, 824, 746, 702, 654, 554.

High-resolution MS, (C$_{13}$H$_{16}$O$_3$) *calculated* 220.1099, *found* 220.1099.
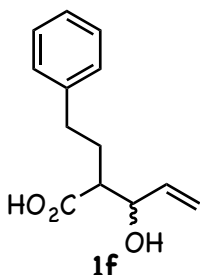
(1-Hydroxy-2-propen-1-yl)benzenebutanoic acid (1f). Following the general procedure A using benzenebutanoic acid (3.29 g, 20 mmol) and acrolein (1.6 mL, 24 mmol), afford **1f** (4.26 g, 97% yield, R_f = 0.25; hexane/EtOAc = 1/1 v/v) as a mixture of diastereoisomers (1.4:1). Yellowish Oil.

^{1}H NMR (500 MHz, Acetone-d_6, major isomer) δ 7.25 (d, J = 7.5 Hz, 2 H), 7.19 (d, J = 7.5 Hz, 2 H), 7.15 (t, J = 7.5 Hz, 1 H), 5.87 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.27 (dd, J = 17.0, 1.5 Hz, 1 H), 5.12 (dd, J = 10.5, 1.5 Hz, 1 H), 4.32 (dd, J = 6.5, 6.5 Hz, 1 H), 2.78-2.54 (m, 3 H), 2.05-1.81 (m, 2 H) ppm.

^{1}H NMR (500 MHz, Acetone-d_6, minor isomer) δ 7.26 (d, J = 7.5 Hz, 2 H), 7.20 (d, J = 7.5 Hz, 2 H), 7.15 (t, J = 7.5 Hz, 1 H), 5.93 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.28 (dd, J = 17.0, 1.5 Hz, 1 H), 5.10 (dd, J = 10.5, 1.5 Hz, 1 H), 4.36 (dd, J = 6.5, 6.5 Hz, 1 H), 2.78-2.54 (m, 3 H), 2.05-1.81 (m, 2 H) ppm.

^{13}C NMR (126 MHz, Acetone-d_6, major isomer) δ 176.14, 142.48, 139.82, 129.03, 129.00, 126.53, 116.32, 74.33, 51.98, 34.11, 31.09 ppm.

^{13}C NMR (126 MHz, Acetone-d_6, minor isomer) δ 175.73, 142.66, 139.84, 129.03, 128.99, 126.48, 115.65, 73.79, 51.88, 34.26, 30.45 ppm.

IR (neat, cm^{-1}): 3354, 3086, 3067, 3022, 2989, 2953, 2939, 2862, 2646, 2359, 2332, 1707, 1603, 1497, 1456, 1261, 1217, 1043, 991, 932, 700.

High-resolution MS, (C$_{13}$H$_{16}$O$_3$) *calculated* 220.1099, *found* 220.1099.

1g
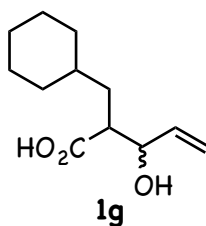
2-cyclohexyl-3-hydroxyhex-4-enoic acid (1g). Following the general procedure A using cyclohexanepropionic acid (2.4 mL, 15 mmol) and acrolein (1.5 mL, 22.5 mmol), afford **1g** (3.00 g, 92% yield, R_f = 0.40; hexane/EtOAc = 1/1 v/v) as a mixture of diastereoisomers (1.4:1). White solid (m.p. 51.2-52.0 °C).

^{1}H NMR (500 MHz, CDCl$_3$, major isomer) δ 6.64 (brs, 1 H), 5.85 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.31 (d, J = 17.0 Hz, 1 H), 5.22 (d, J = 10.5 Hz, 1 H), 4.19 (dd, J = 6.5, 6.5 Hz, 1 H), 2.64-2.60 (m, 1 H), 1.84-0.79 (m, 13 H) ppm.
^{1}H NMR (500 MHz, CDCl$_3$, minor isomer) δ 6.64 (brs, 1 H), 5.88 (ddd, J = 17.0, 10.5, 6.5 Hz, 1 H), 5.32 (d, J = 17.0 Hz, 1 H), 5.22 (d, J = 10.5 Hz, 1 H), 4.37 (dd, J = 6.5, 6.5 Hz, 1 H), 2.72-2.68 (m, 1 H), 1.84-0.79 (m, 13 H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 180.43, 138.28, 117.29, 74.29, 48.79, 36.73, 35.54, 33.90, 32.64, 26.56, 26.26, 26.16 ppm.
^{13}C NMR (126 MHz, CDCl$_3$, minor isomer) δ 180.06, 137.15, 117.07, 73.61, 48.21, 35.68, 34.40, 33.93, 32.64, 26.59, 26.31, 26.20 ppm.

IR (KBr, cm^{-1}): 3207, 2926, 2853, 2671, 2365, 2332, 1705, 1450, 1288, 1252, 1196, 1123, 1045, 1020, 926, 820, 696.

High-resolution MS, (C$_{12}$H$_{20}$O$_3$) *calculated* 212.1412, *found* 212.1412.

3a
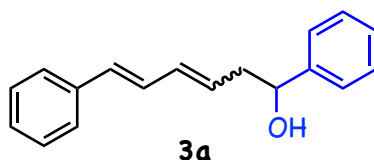
(*3E*, *5E*)-1,6-diphenylhexa-3,5-dien-1-ol (3a, major isomer) and (*3Z*, *5E*)-1,6-diphenylhexa-3,5-dien-1-ol (3a, minor isomer). Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.5 mg, 0.5 mmol) and benzaldehyde (**2a**, 155 μL, 1.5 mmol), afford **3a** (114.6 mg, 91% yield, R_f = 0.33; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 10:1). White solid (m.p. 89.3-90.3 °C).

^{1}H NMR (500 MHz, CDCl$_3$, major isomer) δ 7.40-7.35 (m, 6 H), 7.32-7.28 (m, 3 H), 7.21 (tt, *J* = 7.5, 1.5 Hz, 1 H), 6.75 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.48 (d, *J* = 15.5 Hz, 1 H), 6.32 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.79 (dt, *J* = 15.5, 7.0 Hz, 1 H), 4.77 (t, *J* = 7.0 Hz, 1 H), 2.65-2.56 (m, 2 H), 2.03 (brs, 1 H) ppm.

^{1}H NMR (500 MHz, CDCl$_3$, minor isomer) δ 7.40-7.28 (m, 9 H), 7.22-7.19 (m, 1 H), 7.05 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.55 (d, *J* = 15.5 Hz, 1 H), 6.35-6.30 (m, 1 H), 5.54 (dt, *J* = 10.5, 7.5 Hz, 1 H), 4.79 (t, *J* = 7.5 Hz, 1 H), 2.85-2.77 (m, 1 H), 2.74-2.68 (m, 1 H), 2.03 (brs, 1 H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 143.98, 137.44, 134.11, 131.54, 130.34, 128.86, 128.71, 128.59, 127.74, 127.52, 126.39, 125.93, 73.86, 43.01 ppm.

^{13}C NMR (126 MHz, CDCl$_3$, minor isomer) δ 133.51, 131.89, 130.12, 129.03, 128.36, 127.82, 127.56, 126.58, 125.97, 124.03, 74.04, 37.98 ppm.

IR (KBr, cm^{-1}): 3416, 3061, 3026, 2930, 2880, 1952, 1682, 1603, 1495, 1454, 1337, 1213, 989, 752, 700.

High-resolution MS, (C$_{18}$H$_{18}$O) *calculated* 250.1358, *found* 250.1356.

3b
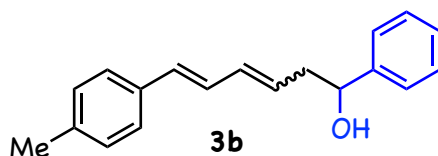
(*3E*, *5E*)-6-(4-methylphenyl)-1-phenylhexa-3,5-dien-1-ol (3b, major isomer) and (*3Z*, *5E*)-6-(4-methylphenyl)-1-phenylhexa-3,5-dien-1-ol (3b, minor isomer). Following the general

procedure B using 2-(4-methylbenzyl)-3-hydroxypent-4-enoic acid (**1b**, dr = 1.3:1, 110.3 mg, 0.5 mmol) and benzaldehyde (**2a**, 155 μL, 1.5 mmol), afford **3b** (110.8 mg, 84% yield, R_f = 0.33; hexane/EtOAc = 4/1 v/v m.p.) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 10:1). White solid (76.4-77.0 °C).

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.35-7.32 (m, 4 H), 7.28-7.24 (m, 3 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 6.68 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.43 (d, *J* = 15.5 Hz, 1 H), 6.27 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.72 (dt, *J* = 15.5, 7.5 Hz, 1 H), 4.72-4.69 (m, 1 H), 2.60-2.51 (m, 2 H), 2.31 (s, 3 H), 2.23 (brs, 1 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 7.38-7.31 (m, 4 H), 7.29-7.24 (m, 3 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 6.94 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.50 (d, *J* = 15.5 Hz, 1 H), 6.29-6.24 (m, 1 H), 5.47 (dt, *J* = 10.5, 7.5 Hz, 1 H), 4.74-4.72 (m, 1 H), 2.81-2.74 (m, 1 H), 2.70-2.64 (s, 1 H), 2.32 (s, 3 H), 2.23 (brs, 1 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 144.00, 137.32, 134.63, 134.16, 131.45, 129.70, 129.40, 128.52, 127.90, 127.64, 126.27, 125.91, 73.81, 42.96, 21.31 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 137.57, 133.42, 131.93, 129.03, 128.97, 128.93, 127.71, 126.95, 126.48, 125.96, 123.09, 73.98, 37.90, 21.31 ppm.

IR (KBr, cm⁻¹): 3406, 3082, 3017, 2924, 2405, 2365, 1965, 1944, 1607, 1510, 1456, 1217, 1042, 1028, 989, 812, 700, 667.

High-resolution MS, (C₁₉H₂₀O) *calculated* 264.1514, *found* 264.1514.
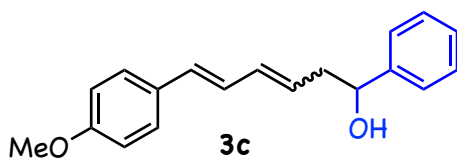
(3*E*, 5*E*)-6-(4-methoxyphenyl)-1-phenylhexa-3,5-dien-1-ol (**3c**, major isomer) and (3*Z*, 5*E*)-6-(4-methoxyphenyl)-1-phenylhexa-3,5-dien-1-ol (**3c**, minor isomer). Following the general procedure B using 2-(4-methoxybenzyl)-3-hydroxypent-4-enoic acid (**1c**, dr = 1.8:1, 117.7 mg, 0.5 mmol) and benzaldehyde (**2a**, 155 μL, 1.5 mmol), afford **3c** (83.7 mg, 60% yield, R_f = 0.40; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 8:1). White solid (m.p. 97.6-98.0 °C).

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.39-7.25 (m, 7 H), 6.85-6.81 (m, 2 H), 6.60 (dd, J = 15.5, 10.5 Hz, 1 H), 6.41 (d, J = 15.5 Hz, 1 H), 6.27 (dd, J = 15.5, 10.5 Hz, 1 H), 5.70 (dt, J = 15.5, 7.5 Hz, 1 H), 4.73-4.71 (m, 1 H), 3.77 (s, 3 H), 2.61-2.52 (m, 2 H), 2.23 (brs, 1 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 7.39-7.25 (m, 7 H), 6.87 (dd, J = 15.5, 10.5 Hz, 1 H), 6.86-6.81 (m, 2 H), 6.48 (d, J = 15.5 Hz, 1 H), 6.29-6.24 (m, 1 H), 5.45 (dt, J = 10.5, 7.5 Hz, 1 H), 4.76-4.73 (m, 1 H), 3.78 (s, 3 H), 2.81-2.75 (m, 1 H), 2.70-2.66 (s, 1 H), 2.23 (brs, 1 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 159.18, 144.02, 134.25, 131.05, 130.24, 129.08, 128.52, 127.63, 127.55, 126.87, 125.92, 114.15, 73.83, 55.36, 42.98 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 159.35, 133.02, 132.03, 128.62, 127.78, 127.71, 127.05, 126.35, 125.96, 122.08, 113.78, 74.00, 55.36, 37.93 ppm.

IR (KBr, cm⁻¹): 3404, 3017, 2959, 2930, 2895, 2835, 2399, 2359, 4950, 1879, 1605, 1574, 1510, 1454, 1300, 1254, 1215, 1175, 1045, 1028, 984, 827, 700, 667.

High-resolution MS, (C₁₉H₂₀O₂) *calculated* 280.1463, *found* 280.1465.
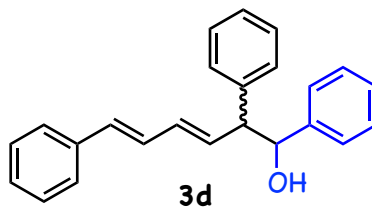
(3E, 5E)-1,2,6-triphenylhexa-3,5-dien-1-ol (3d, major isomer). Following the general procedure B using 2-benzyl-3-hydroxy-5-phenyl-4-pentenoic acid (**1d**, dr = 2.0:1, 141.2 mg, 0.5 mmol) and benzaldehyde (**2a**, 155 μL, 1.5 mmol), afford **3d** (128.9 mg, 79% yield, R_f = 0.40; hexane/EtOAc = 4/1 v/v) as a mixture of diastereoisomers (2.3:1). Colorless oil.

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.36-7.23 (m, 14 H), 7.15 (t, J = 7.5 Hz, 1 H), 6.62 (dd, J = 15.5, 10.5 Hz, 1 H), 6.31 (d, J = 15.5 Hz, 1 H), 5.97 (dd, J = 15.5, 10.5 Hz, 1 H), 5.85 (dd, J = 15.5, 8.0 Hz, 1 H), 4.91 (d, J = 8.0 Hz, 1 H), 3.71 (dd, J = 8.0, 8.0 Hz 1 H), 2.01 (brs, 1 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 7.37-7.07 (m, 15 H), 6.80 (dd, J = 15.5, 10.5 Hz, 1 H), 6.47 (d, J = 15.5 Hz, 1 H), 6.33 (dd, J = 15.5, 10.5 Hz, 1 H), 6.21 (dd, J = 15.5, 8.0 Hz, 1 H), 4.88 (d, J = 8.0 Hz, 1 H), 3.64 (dd, J = 8.0, 8.0 Hz 1 H), 2.30 (brs, 1 H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 141.95, 140.46, 137.34, 133.77, 132.89, 131.77, 128.96, 128.87, 128.83, 128.63, 128.30, 127.93, 127.46, 127.22, 127.12, 126.30, 77.80, 57.62 ppm.

^{13}C NMR (126 MHz, CDCl$_3$, minor isomer) δ 142.05, 140.96, 137.34, 134.01, 133.45, 132.25, 128.71, 128.68, 128.53, 128.50, 128.09, 127.60, 126.76, 126.43, 77.81, 58.29 ppm.

IR (neat, cm^{-1}): 3445, 3086, 3061, 3026, 2964, 2905, 2403, 2313, 1946, 1869, 1595, 1495, 1454, 1387, 1339, 1313, 1217, 1186, 1026, 989, 914, 756, 700, 584.

High-resolution MS, (C$_{24}$H$_{22}$O) *calculated* 326.1671, *found* 326.1671.
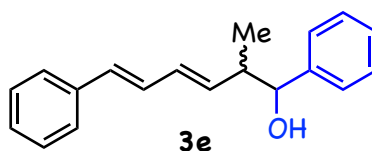
(3*E*, 5*E*)-2-methyl-1,6-diphenylhexa-3,5-dien-1-ol (3e). Following the general procedure B using 2-benzyl-3-hydroxy-5-methyl-4-pentenoic acid (**1e**, dr = 1.3:1, 110.3 mg, 0.5 mmol) and benzaldehyde (**2a**, 155 μL, 1.5 mmol), afford **3e** (108.3 mg, 82% yield, R_f = 0.40; hexane/EtOAc = 4/1 v/v) as a mixture of diastereoisomers (1.5:1). Colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$, major isomer) δ 7.37-7.15 (m, 10 H), 6.76 (dd, J = 15.6, 10.4 Hz, 1 H), 6.48 (d, J = 15.6 Hz, 1 H), 6.31 (dd, J = 15.6, 10.4 Hz, 1 H), 5.76 (dd, J = 15.6, 7.2 Hz, 1 H), 4.36 (d, J = 7.6 Hz, 1 H), 2.55 (ddt, J = 7.6, 7.2, 6.8 Hz 1 H), 2.25 (brs, 1 H), 0.89 (d, J = 6.8 Hz, 3 H) ppm.

^{1}H NMR (400 MHz, CDCl$_3$, minor isomer) δ 7.37-7.15 (m, 10 H), 6.69 (dd, J = 15.6, 10.4 Hz, 1 H), 6.42 (d, J = 15.6 Hz, 1 H), 6.18 (dd, J = 15.6, 10.4 Hz, 1 H), 5.69 (dd, J = 15.6, 7.2 Hz, 1 H), 4.58 (d, J = 5.6 Hz, 1 H), 2.64 (dtd, J = 7.2, 6.8, 5.6 Hz 1 H), 2.17 (brs, 1 H), 1.03 (d, J = 6.8 Hz, 3 H) ppm.

^{13}C NMR (101 MHz, CDCl$_3$, mixture of diastereoisomers) δ 142.60, 137.48, 137.43, 136.63, 136.57, 132.40, 131.59, 131.28, 131.19, 129.17, 128.90, 128.68, 128.63, 128.33, 128.16, 127.74, 127.47, 127.37, 126.89, 126.62, 126.35, 126.29, 78.38, 77.70, 77.16, 45.38, 44.01, 16.93, 14.79 ppm.

IR (neat, cm^{-1}): 3481, 3061, 3024, 2966, 2930, 2874, 2359, 2336, 1948, 1873, 1805, 1747, 1637, 1595, 1495, 1454, 1373, 1304, 1217, 1192, 1070, 991, 941, 700, 667.

High-resolution MS, (C$_{19}$H$_{20}$O) *calculated* 264.1514, *found* 264.1513.

3f

(3*E*, 5*E*)-1,7-diphenylhepta-3,5-dien-1-ol (3f, major isomer**)** and **(3*Z*, 5*E*)-1,7-diphenylhepta-3,5-dien-1-ol (3f**, minor isomer**)**. Following the general procedure B using (1-Hydroxy-2-propen-1-yl)benzenebutanoic acid (**1f**, dr = 1.4:1, 110.3 mg, 0.5 mmol) and benzaldehyde (**2a**, 155 μL, 1.5 mmol), afford **3f** (68.8 mg, 52% yield, R_f = 0.33; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 8:1). Yellow oil.
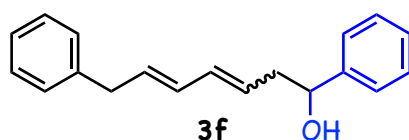
^{1}H NMR (500 MHz, CDCl$_3$, major isomer) δ 7.37-7.17 (m, 10 H), 6.16 (dd, J = 15.0, 10.5 Hz, 1 H), 6.07 (dd, J = 15.0, 10.5 Hz, 1 H), 5.78 (dt, J = 15.0, 7.0 Hz, 1 H), 5.58 (dt, J = 15.0, 7.0 Hz, 1 H), 4.71 (ddd, J = 7.0, 5.0, 2.5 Hz, 1 H), 3.40 (d, J = 7.0 Hz 2 H), 2.60-2.38 (m, 2 H), 2.00 (d, J = 2.5 Hz, 1 H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 144.05, 140.31, 133.82, 132.19, 131.18, 128.71, 128.55, 128.09, 127.65, 126.22, 125.90, 73.76, 42.87, 39.06 ppm.

IR (neat, cm^{-1}): 3383, 3082, 3061, 3026, 2924, 2897, 2365, 2336, 2247, 1950, 1879, 1657, 1603, 1495, 1454, 1429, 1290, 1200, 1047, 1028, 989, 910, 735, 698.

High-resolution MS, (C$_{19}$H$_{20}$O) *calculated* 264.1514, *found* 264.1513.

3g
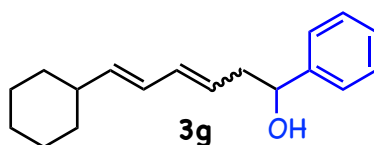
(3*E*, 5*E*)-6-cyclohexyl-1-phenylhexa-3,5-dien-1-ol (3g, major isomer**)** and **(3*Z*, 5*E*)-6-cyclohexyl-1-phenylhexa-3,5-dien-1-ol (3g**, minor isomer**)**. Following the general procedure B using 2-cyclohexyl-3-hydroxy-4-pentenoic acid (**1g**, dr = 1.4:1, 107.6 mg, 0.5 mmol)

and benzaldehyde (**2a**, 155 μL, 1.5 mmol), afford **3g** (61.8 mg, 48% yield, R_f = 0.50; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 7:1). Yellow oil.

^{1}H NMR (500 MHz, CDCl$_3$, major isomer) δ 7.36-7.26 (m, 5 H), 6.13 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.98 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.59 (dd, *J* = 15.5, 7.0 Hz, 1 H), 5.54 (dt, *J* = 15.5, 7.5 Hz, 1 H), 4.71 (ddd, *J* = 7.5, 5.0, 3.0 Hz, 1 H), 2.56-2.44 (m, 2 H), 2.05-1.95 (m, 2 H), 1.74-1.62 (m, 5 H), 1.31-1.03 (m, 5 H), ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 144.11, 140.08, 134.58, 128.50, 127.59, 127.36, 126.99, 125.89, 73.74, 42.95, 40.77, 32.93, 26.26, 26.11 ppm.

IR (neat, cm^{-1}): 3360, 3088, 3065, 3024, 2924, 2851, 2665, 2359, 1948, 1877, 1805, 1657, 1603, 1493, 1448, 1200, 1049, 1030, 988, 949, 758, 700.

High-resolution MS, (C$_{18}$H$_{24}$O) *calculated* 256.1827, *found* 256.1827.

3h
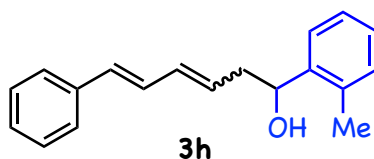
(3*E*, 5*E*)-1-(2-methylphenyl)-6-phenylhexa-3,5-dien-1-ol (3h, major isomer) and **(3*Z*, 5*E*)-1-(2-methylphenyl)-6-phenylhexa-3,5-dien-1-ol (3h, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.2 mg, 0.5 mmol) and *o*-tolualdehyde (**2b**, 175 μL, 1.5 mmol), afford **3h** (121.5 mg, 92% yield, R_f = 0.40; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 11:1). Colorless oil.

^{1}H NMR (500 MHz, CDCl$_3$, major isomer) δ 7.53 (d, *J* = 7.5 Hz, 1 H), 7.38 (d, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.26-7.14 (m, 4 H), 6.76 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.49 (d, *J* = 15.5 Hz, 1 H), 6.34 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.84 (dt, *J* = 15.5, 7.5 Hz, 1 H), 5.01 (dd, *J* = 7.5, 5.0 Hz, 1 H), 2.62-2.50 (m, 2 H), 2.35 (s, 3 H), 1.94 (brs, 1 H) ppm.

^{1}H NMR (500 MHz, CDCl$_3$, minor isomer) δ 7.55 (d, *J* = 7.5 Hz, 1 H), 7.40-7.38 (m, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.26-7.14 (m, 4 H), 7.03 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.56 (d, *J* = 15.5 Hz, 1 H), 6.35-6.30 (m, 1 H), 5.59 (dt, *J* = 10.5, 7.5 Hz, 1 H), 5.07-5.02 (m, 1 H), 2.81-2.66 (m, 2 H), 2.37 (s, 3 H), 1.88 (brs, 1 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 142.07, 137.45, 134.46, 133.91, 131.50, 130.67, 130.49, 128.86, 128.69, 127.49, 127.40, 126.41, 126.37, 125.27, 70.23, 41.78, 19.20 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 134.52, 133.45, 131.78, 130.29, 129.02, 128.58, 127.87, 127.71, 127.63, 126.55, 125.33, 124.01, 70.35, 36.82, 19.26 ppm.

IR (neat, cm⁻¹): 3341, 3076, 3059, 3022, 2930, 2365, 2336, 1668, 1595, 1489, 1462, 1447, 1217, 1042, 988, 754, 691, 667.

High-resolution MS, (C₁₉H₂₀O) *calculated* 264.1514, *found* 264.1512.

3i
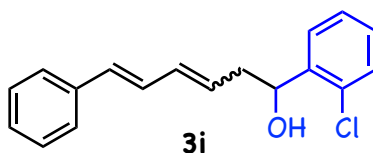
(3*E*, 5*E*)-1-(2-chlorophenyl)-6-phenylhexa-3,5-dien-1-ol (3i, major isomer) and **(3*Z*, 5*E*)-1-(2-chlorophenyl)-6-phenylhexa-3,5-dien-1-ol (3i, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.1 mg, 0.5 mmol) and 2-chlorobenzaldehyde (**2c**, 170 μL, 1.5 mmol), afford **3i** (104.3 mg, 73% yield, R_f = 0.50; hexane/EtOAc = 4/1 v/v m.p.) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 12:1). White solid (87.1-87.7 °C).

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.58 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.38 (dd, *J* = 8.0, 1.5 Hz, 2 H), 7.34-7.29 (m, 4 H), 7.21 (td, *J* = 8.0, 1.5 Hz, 2 H), 6.77 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.49 (d, *J* = 15.5 Hz, 1 H), 6.33 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.85 (dt, *J* = 15.5, 7.5 Hz, 1 H), 5.20-5.18 (m, 1 H), 2.73-2.68 (m, 1 H), 2.51-2.45 (m, 1 H), 2.16 (brs, 1 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 7.62 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.39 (dd, *J* = 8.0, 1.5 Hz, 2 H), 7.34-7.29 (m, 4 H), 7.21 (td, *J* = 8.0, 1.5 Hz, 2 H), 6.55 (d, *J* = 15.5 Hz, 1 H), 6.38-6.31 (m, 1 H), 5.62 (dt, *J* = 10.5, 7.5 Hz, 1 H), 5.23-5.20 (m, 1 H), 2.85-2.80 (m, 1 H), 2.70-2.64 (m, 1 H), 2.16 (brs, 1 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 141.31, 137.45, 134.37, 131.82, 131.71, 130.09, 129.55, 128.81, 128.74, 128.64, 127.56, 127.21, 127.18, 126.43, 70.23, 41.22 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 133.59, 132.31, 132.22, 130.37, 129.94, 129.21,

129.06, 128.38, 127.75, 127.29, 127.03, 126.61, 124.02, 70.64, 36.20 ppm.

IR (KBr, cm^{-1}): 3242, 3082, 3018, 2935, 2918, 2359, 2336, 1961, 1938, 1892, 1595, 1574, 1495, 1472, 1447, 1410, 1348, 1123, 1032, 984, 885, 750.3, 691.

High-resolution MS, (C$_{18}$H$_{17}$ClO) *calculated* 284.0968, *found* 284.0969.
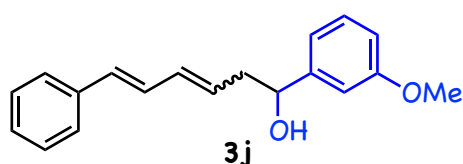
(3*E*, 5*E*)-1-(3-methoxyphenyl)-6-phenylhexa-3,5-dien-1-ol (3j, major isomer) and **(3*Z*, 5*E*)-1-(3-methoxyphenyl)-6-phenylhexa-3,5-dien-1-ol (3j, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 109.4 mg, 0.5 mmol) and 3-anisaldehyde (**2d**, 185 μL, 1.5 mmol), afford **3j** (76.0 mg, 51% yield, R_f = 0.23; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 9:1). Yellowish oil.

^{1}H NMR (500 MHz, CDCl$_3$, major isomer) δ 7.37-7.35 (m, 2 H), 7.30-7.24 (m, 3 H), 7.22-7.17 (m, 1 H), 6.93-6.92 (m, 2 H), 6.81 (ddd, *J* = 7.5, 2.0, 0.5 Hz, 1 H), 6.73 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.46 (d, *J* = 15.5 Hz, 1 H), 6.29 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.76 (dt, *J* = 15.5, 7.5 Hz, 1 H), 4.71 (t, *J* = 7.5 Hz, 1 H), 3.79 (s, 3 H), 2.60-2.53 (m, 2 H), 2.20 (brs, 1 H) ppm.

^{1}H NMR (500 MHz, CDCl$_3$, minor isomer) δ 7.38-7.36 (m, 2 H), 7.31-7.24 (m, 3 H), 7.22-7.17 (m, 1 H), 6.98 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.96-6.94 (m, 2 H), 6.83-6.79 (m, 1 H), 6.53 (d, *J* = 15.5 Hz, 1 H), 6.36-6.30 (m, 1 H), 5.52 (dt, *J* = 10.5, 7.5 Hz, 1 H), 4.75-4.72 (m, 1 H), 3.79 (s, 3 H), 2.80-2.75 (m, 1 H), 2.71-2.66 (m, 1 H), 2.20 (brs, 1 H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 159.83, 145.74, 137.43, 134.01, 131.48, 130.34, 129.57, 128.85, 128.68, 127.47, 126.36, 118.23, 113.14, 111.41, 73.73, 55.32, 42.91 ppm.

^{13}C NMR (126 MHz, CDCl$_3$, minor isomer) δ 133.43, 131.79, 130.02, 129.00, 128.32, 127.69, 127.55, 126.55, 124.04, 118.23, 113.14, 111.41, 73.90, 55.32, 37.87 ppm.

IR (neat, cm^{-1}): 3423, 3018, 2947, 2839, 2359, 2336, 1940, 1730, 1672, 1599, 1485, 1456, 1258, 1157, 1047, 988, 866, 785, 748, 692.

High-resolution MS, ($C_{19}H_{20}O_2$) *calculated* 280.1463, *found* 280.1463.

3k
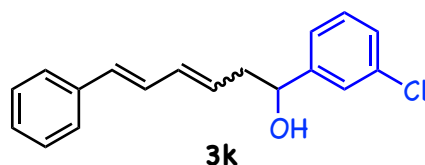
(3*E*, 5*E*)-1-(3-chlorophenyl)-6-phenylhexa-3,5-dien-1-ol (3k, major isomer) and **(3*Z*, 5*E*)-1-(3-chlorophenyl)-6-phenylhexa-3,5-dien-1-ol (3k, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 108.2 mg, 0.5 mmol) and 3-chlorobenzaldehyde (**2e**, 170 μL, 1.5 mmol), afford **3k** (99.3 mg, 66% yield, R_f = 0.40; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 13:1). Yellowish oil.

^{1}H NMR (500 MHz, CDCl$_3$, major isomer) δ 7.37-7.35 (m, 3 H), 7.29 (t, J = 7.5 Hz, 2 H), 7.25-7.19 (m, 4 H), 6.73 (dd, J = 15.5, 10.5 Hz, 1 H), 6.47 (d, J = 15.5 Hz, 1 H), 6.29 (dd, J = 15.5, 10.5 Hz, 1 H), 5.73 (dt, J = 15.5, 7.5 Hz, 1 H), 4.70 (dd, J = 7.5, 5.5 Hz, 1 H), 2.60-2.49 (m, 2 H), 2.22 (brs, 1 H) ppm.

^{1}H NMR (500 MHz, CDCl$_3$, minor isomer) δ 7.40-7.39 (m, 3 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.25-7.19 (m, 4 H), 6.95 (dd, J = 15.5, 10.5 Hz, 1 H), 6.54 (d, J = 15.5 Hz, 1 H), 6.32-6.26 (m, 1 H), 5.48 (dt, J = 10.5, 7.5 Hz, 1 H), 4.73 (dd, J = 7.5, 5.5 Hz, 1 H), 2.78-2.72 (m, 1 H), 2.69-2.63 (m, 1 H), 2.22 (brs, 1 H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 146.04, 137.32, 134.50, 134.47, 131.84, 129.83, 129.58, 128.71, 128.64, 127.77, 127.59, 126.41, 126.10, 124.08, 73.11, 42.96 ppm.

^{13}C NMR (126 MHz, CDCl$_3$, minor isomer) δ 133.82, 132.32, 131.72, 129.38, 129.01, 128.37, 127.84, 126.77, 126.61, 126.15, 124.13, 123.77, 73.30, 37.93 ppm.

IR (neat, cm^{-1}): 3366, 3065, 3022, 2924, 2901, 2853, 2365, 2336, 1944, 1873, 1798, 1641, 1597, 1574, 1476, 1433, 1300, 1198, 1076, 1047, 989, 887, 785, 692.

High-resolution MS, ($C_{18}H_{17}ClO$) *calculated* 284.0968, *found* 284.0968.

3l
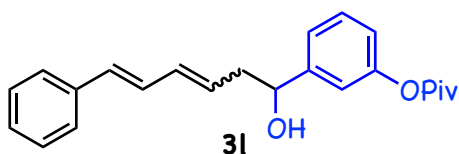
(3_E_, 5_E_)-1-(3-pivaloyloxyphenyl)-6-phenylhexa-3,5-dien-1-ol (3l, major isomer) and **(3_Z_, 5_E_)-1-(3-pivaloyloxyphenyl)-6-phenylhexa-3,5-dien-1-ol (3l, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.6 mg, 0.5 mmol) and 3-(pivaloyloxy)aldehyde (**2f**, 309.4 mg, 1.5 mmol), afford **3l** (121.5 mg, 69% yield, R_f = 0.30; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3_E_, 5_E_: 3_Z_, 5_E_ = 16:1). Yellowish oil.

^{1}H NMR (400 MHz, CDCl$_3$, major isomer) δ 7.36-7.26 (m, 5 H), 7.20-7.15 (m, 2 H), 7.07 (s, 1 H), 6.96-6.94 (m, 1 H), 6.72 (dd, J = 15.6, 10.0 Hz, 1 H), 6.45 (d, J = 15.6 Hz, 1 H), 6.27 (dd, J = 15.6, 10.0 Hz, 1 H), 5.74 (dt, J = 15.6, 7.2 Hz, 1 H), 4.70 (t, J = 7.2 Hz, 1 H), 2.60-2.30 (m, 3 H), 1.34 (s, 9 H) ppm.

^{1}H NMR (400 MHz, CDCl$_3$, minor isomer) δ 7.40-7.26 (m, 5 H), 7.20-7.15 (m, 2 H), 7.07 (s, 1 H), 6.99-6.94 (m, 2 H), 6.52 (d, J = 15.6 Hz, 1 H), 6.30-6.24 (m, 1 H), 5.49 (dt, J = 10.8, 7.6 Hz, 1 H), 4.72 (t, J = 7.6 Hz, 1 H), 2.80-2.63 (m, 2 H), 2.53 (brs, 1 H), 1.34 (s, 9 H) ppm.

^{13}C NMR (101 MHz, CDCl$_3$, major isomer) δ 177.24, 151.28, 145.88, 137.42, 134.05, 131.48, 130.16, 129.37, 128.84, 128.64, 127.43, 126.35, 123.15, 120.59, 119.01, 73.27, 42.81, 39.13, 27.20 ppm.

^{13}C NMR (101 MHz, CDCl$_3$, minor isomer) δ 177.24, 137.40, 133.47, 131.80, 128.99, 128.68, 128.55, 128.31, 127.66, 127.38, 126.56, 124.00, 123.22, 120.66, 73.41, 42.81, 37.77, 27.20 ppm.

IR (neat, cm^{-1}): 3470, 3059, 3024, 2976, 2935, 2907, 2874, 2359, 2341, 1749, 1589, 1479, 1447, 1396, 1366, 1279, 1234, 1148, 1115, 989, 746, 692.

High-resolution MS, (C$_{23}$H$_{26}$O$_3$) *calculated* 350.1882, *found* 350.1882.

3m
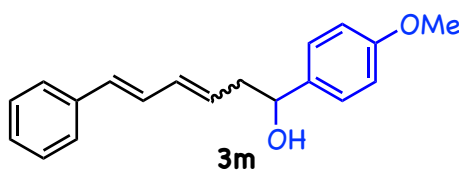
(3_E_, 5_E_)-1-(4-methoxyphenyl)-6-phenylhexa-3,5-dien-1-ol (3m, major isomer) and **(3_Z_,

5*E*)-1-(4-methoxyphenyl)-6-phenylhexa-3,5-dien-1-ol (3m, minor isomer). Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 102.3 mg, 0.5 mmol) and 4-anisaldehyde (**2g**, 185 μL, 1.5 mmol), afford **3m** (116.4 mg, 84% yield, R_f = 0.23; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 11:1). White solid (m.p. 112.2-112.6 °C).

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.36 (d, J = 7.5 Hz, 2 H), 7.32-7.28 (m, 4 H), 7.20 (t, J = 7.5 Hz, 1 H), 6.90-6.87 (m, 2 H), 6.74 (dd, J = 15.5, 10.5 Hz, 1 H), 6.47 (d, J = 15.5 Hz, 1 H), 6.30 (dd, J = 15.5, 10.5 Hz, 1 H), 5.76 (dt, J = 15.5, 7.5 Hz, 1 H), 4.70 (t, J = 7.5 Hz, 1 H), 3.80 (s, 3 H), 2.62-2.54 (m, 2 H), 2.03 (brs, 1 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 7.38 (d, J = 7.5 Hz, 2 H), 7.32-7.28 (m, 4 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.00 (dd, J = 15.5, 10.5 Hz, 1 H), 6.90-6.87 (m, 2 H), 6.54 (d, J = 15.5 Hz, 1 H), 6.30-6.26 (m, 1 H), 5.51 (dt, J = 10.5, 7.5 Hz, 1 H), 4.73 (t, J = 7.5 Hz, 1 H), 3.78 (s, 3 H), 2.84-2.77 (m, 1 H), 2.70-2.64 (m, 1 H), 2.03 (brs, 1 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 159.14, 137.44, 136.16, 133.86, 131.37, 130.59, 128.92, 128.68, 127.46, 127.18, 126.35, 113.92, 73.49, 55.37, 42.88 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 159.20, 133.34, 131.62, 127.77, 127.68, 127.22, 126.55, 124.08, 113.92, 73.64, 55.37, 37.86 ppm.

IR (KBr, cm⁻¹): 3389, 3024, 2924, 2991, 2835, 2359, 2330, 1888, 1612, 1510, 1447, 1246, 1177, 1034, 984, 829, 741, 691.

High-resolution MS, (C₁₉H₂₀O₂) *calculated* 280.1463, *found* 280.1462.
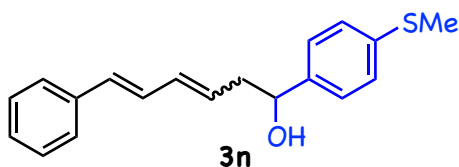
(3*E*, 5*E*)-1-(4-methylthiophenyl)-6-phenylhexa-3,5-dien-1-ol (3n, major isomer) and **(3*Z*, 5*E*)-1-(4-methylthiophenyl)-6-phenylhexa-3,5-dien-1-ol (3n, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 107.3 mg, 0.5 mmol) and 4-(methylthio)benzaldehyde (**2h**, 195 μL, 1.5 mmol), afford **3n** (133.1 mg, 86% yield, R_f = 0.30; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 12:1). White solid (m.p. 126.3-126.9 °C).

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.37 (d, *J* = 7.5 Hz, 2 H), 7.33-7.19 (m, 7 H), 6.74 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.48 (d, *J* = 15.5 Hz, 1 H), 6.31 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.76 (dt, *J* = 15.5, 7.5 Hz, 1 H), 4.73 (t, *J* = 7.5 Hz, 1 H), 2.61-2.53 (m, 2 H), 2.48 (s, 3 H), 2.04 (brs, 1 H) ppm.
**¹H NMR** (500 MHz, CDCl₃, minor isomer) δ 7.39 (d, *J* = 7.5 Hz, 2 H), 7.33-7.19 (m, 7 H), 6.99 (dd, *J* = 15.5, 11.0 Hz, 1 H), 6.55 (d, *J* = 15.5 Hz, 1 H), 6.33-6.28 (m, 1 H), 5.51 (dt, *J* = 11.0, 7.5 Hz, 1 H), 4.75 (t, *J* = 7.5 Hz, 1 H), 2.82-2.77 (m, 1 H), 2.71-2.65 (m, 1 H), 2.46 (s, 3 H), 2.04 (brs, 1 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 140.92, 137.77, 137.42, 134.21, 131.63, 130.15, 128.81, 128.72, 127.55, 126.84, 126.52, 126.40, 73.47, 42.93, 16.07 ppm.
¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 140.92, 133.60, 132.00, 128.65, 127.77, 127.35, 126.90, 126.59, 126.55, 123.98, 73.64, 37.90, 16.07 ppm.

IR (KBr, cm⁻¹): 3377, 3018, 2924, 2918, 2907, 2895, 1900, 1661, 1491, 1447, 1435, 1402, 1329, 1267, 1092, 1045, 982, 887, 812, 747, 692.

High-resolution MS, (C₁₉H₂₀OS) *calculated* 296.1235, *found* 296.1235.

3o
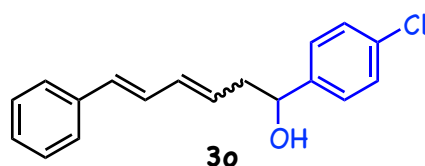
(3*E*, 5*E*)-1-(4-chlorophenyl)-6-phenylhexa-3,5-dien-1-ol (3o, major isomer) and **(3*Z*, 5*E*)-1-(4-chlorophenyl)-6-phenylhexa-3,5-dien-1-ol (3o, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 104.2 mg, 0.5 mmol) and 4-chlorobenzaldehyde (**2i**, 210.8 mg, 1.5 mmol), afford **3o** (104.8 mg, 73% yield, *R_f* = 0.37; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 9:1). White solid (m.p. 103.7-104.2 °C).

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.37 (d, *J* = 7.5 Hz, 2 H), 7.33-7.28 (m, 6 H), 7.23-7.20 (m, 1 H), 6.74 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.48 (d, *J* = 15.5 Hz, 1 H), 6.30 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.74 (dt, *J* = 15.5, 7.5 Hz, 1 H), 4.74 (t, *J* = 7.5 Hz, 1 H), 2.60-2.51 (m, 2 H), 2.14 (brs, 1 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 7.39 (d, *J* = 7.5 Hz, 2 H), 7.33-7.28 (m, 6 H), 7.23-7.20 (m, 1 H), 6.97 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.56 (d, *J* = 15.5 Hz, 1 H), 6.33-6.27 (m, 1 H), 5.48 (dt, *J* = 10.5, 7.5 Hz, 1 H), 4.76 (t, *J* = 7.5 Hz, 1 H), 2.80-2.74 (m, 1 H), 2.69-2.65 (m, 1 H), 2.14 (brs, 1 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 142.42, 137.34, 134.47, 133.34, 131.84, 129.68, 128.73, 128.71, 128.65, 127.61, 127.33, 126.41, 73.12, 43.04 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 135.45, 133.84, 133.42, 132.26, 127.84, 127.37, 126.92, 126.60, 123.80, 73.30, 38.00 ppm.

IR (KBr, cm⁻¹): 3373, 3024, 2926, 2905, 2365, 1908, 1591, 1489, 1406, 1323, 1092, 1047, 1013, 982, 887, 818, 745, 691.

High-resolution MS, (C₁₈H₁₇ClO) *calculated* 284.0968, *found* 284.0969.
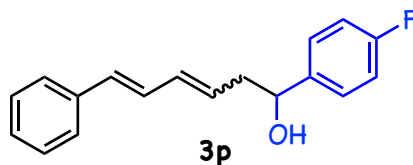
(3*E*, 5*E*)-1-(4-fluorophenyl)-6-phenylhexa-3,5-dien-1-ol (3p, major isomer) and **(3*Z*, 5*E*)-1-(4-fluorophenyl)-6-phenylhexa-3,5-dien-1-ol (3p, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.7 mg, 0.5 mmol) and 4-chlorobenzaldehyde (**2j**, 160 μL, 1.5 mmol), afford **3p** (95.9 mg, 71% yield, *R_f* = 0.33; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 9:1). White solid (m.p. 99.8-100.5 °C).

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.40-7.29 (m, 6 H), 7.21 (t, *J* = 7.5 Hz, 1 H), 7.06-7.02 (m, 2 H), 6.74 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.49 (d, *J* = 15.5 Hz, 1 H), 6.30 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.75 (dt, *J* = 15.5, 7.5 Hz, 1 H), 4.75 (t, *J* = 7.5 Hz, 1 H), 2.62-2.52 (m, 2 H), 2.06 (brs, 1 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 7.40-7.29 (m, 6 H), 7.23-7.20 (m, 1 H), 7.06-7.02 (m, 2 H), 6.99 (dd, *J* = 15.5, 11.0 Hz, 1 H), 6.56 (d, *J* = 15.5 Hz, 1 H), 6.33-6.28 (m, 1 H), 5.50 (dt, *J* = 11.0, 7.5 Hz, 1 H), 4.77 (t, *J* = 7.5 Hz, 1 H), 2.82-2.76 (m, 1 H), 2.70-2.64 (m, 1 H), 2.06 (brs, 1 H) ppm.

13C NMR (126 MHz, CDCl₃, major isomer) δ 162.34 (d, J = 246.5 Hz), 139.70 (d, J = 2.8 Hz), 137.38, 134.38, 131.78, 129.90, 128.74, 127.60, 127.59 (d, J = 7.6 Hz), 126.42, 115.41 (d, J = 21.9 Hz), 73.21, 43.13 ppm.

13C NMR (126 MHz, CDCl₃, minor isomer) δ 162.37 (d, J = 246.5 Hz), 140.09 (d, J = 2.7 Hz), 133.77, 132.15, 127.84, 127.67, 127.14, 126.61, 123.87, 115.41 (d, J = 21.9 Hz), 73.39, 38.09 ppm.

19F NMR (471 MHz, CDCl₃, major isomer) δ -115.04 ppm.
19F NMR (471 MHz, CDCl₃, minor isomer) δ -114.94 ppm.

IR (KBr, cm⁻¹): 3389, 3069, 3018, 2932, 2918, 2901, 2897, 1954, 1894, 1607, 1508, 1447, 1414, 1225, 1157, 1047, 982, 887, 831, 743, 691.

High-resolution MS, (C₁₈H₁₇FO) *calculated* 268.1263, *found* 268.1262.
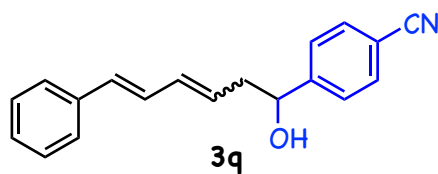
(3*E*, 5*E*)-1-(4-cyanophenyl)-6-phenylhexa-3,5-dien-1-ol (3q, major isomer) and **(3*Z*, 5*E*)-1-(4-cyanophenyl)-6-phenylhexa-3,5-dien-1-ol (3q, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 106.1 mg, 0.5 mmol) and 4-formylbenzonitrile (**2k**, 196.7 mg, 1.5 mmol), afford **3q** (75.9 mg, 54% yield, R_f = 0.15; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 10:1). White solid (m.p. 117.2-118.0 °C).

1H NMR (500 MHz, CDCl₃, major isomer) δ 7.63 (d, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.5 Hz, 2 H), 7.37 (d, J = 7.5 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.22 (t, J = 7.5 Hz, 1 H), 6.73 (dd, J = 15.5, 10.5 Hz, 1 H), 6.49 (d, J = 15.5 Hz, 1 H), 6.30 (dd, J = 15.5, 10.5 Hz, 1 H), 5.73 (dt, J = 15.5, 7.5 Hz, 1 H), 4.83-4.81 (m, 1 H), 2.63-2.49 (m, 2 H), 2.33 (brs, 1 H) ppm.

1H NMR (500 MHz, CDCl₃, minor isomer) δ 7.63 (d, J = 7.5 Hz, 2 H), 7.50 (d, J = 7.5 Hz, 2 H), 7.38 (d, J = 7.5 Hz, 2 H), 7.32 (t, J = 7.5 Hz, 2 H), 7.22 (t, J = 7.5 Hz, 1 H), 6.94 (dd, J = 15.5, 10.5 Hz, 1 H), 6.57 (d, J = 15.5 Hz, 1 H), 6.36-6.30 (m, 1 H), 5.47 (dt, J = 10.5, 7.5 Hz, 1 H), 4.86-4.83

(m, 1 H), 2.79-2.66 (m, 2 H), 2.33 (brs, 1 H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 149.27, 137.18, 134.95, 132.36, 132.19, 128.81, 128.73, 128.37, 127.71, 126.59, 126.42, 118.95, 111.28, 72.92, 43.01 ppm.

^{13}C NMR (126 MHz, CDCl$_3$, minor isomer) δ 149.27, 137.40, 134.18, 132.77, 128.97, 127.95, 126.71, 126.64, 126.08, 123.48, 111.34, 73.11, 37.96 ppm.

IR (KBr, cm^{-1}): 3474, 3088, 3065, 3024, 2953, 2918, 2895, 2876, 2230, 1607, 1595, 1491, 1310, 1285, 1080, 1059, 995, 901, 853, 845, 693.

High-resolution MS, (C$_{19}$H$_{17}$NO) *calculated* 275.1310, *found* 275.1310.
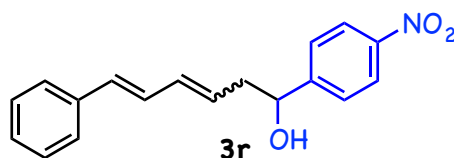
(3*E*, 5*E*)-1-(4-nitrophenyl)-6-phenylhexa-3,5-dien-1-ol (3r, major isomer) and **(3*Z*, 5*E*)-1-(4-nitrophenyl)-6-phenylhexa-3,5-dien-1-ol (3r, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 104.5 mg, 0.5 mmol) and 4-nitrobenzaldehyde (**2l**, 226.6 mg, 1.5 mmol), afford **3r** (55.9 mg, 37% yield, R_f = 0.20; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 9:1). Yellowish solid (m.p. 113.6-114.5 °C).

^{1}H NMR (500 MHz, CDCl$_3$, major isomer) δ 8.21 (d, *J* = 7.5 Hz, 2 H), 7.54 (d, *J* = 7.5 Hz, 2 H), 7.37 (d, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 6.74 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.50 (d, *J* = 15.5 Hz, 1 H), 6.31 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.74 (dt, *J* = 15.5, 7.5 Hz, 1 H), 4.90-4.87 (m, 1 H), 2.66-2.52 (m, 2 H), 2.28 (brs, 1 H) ppm.

^{1}H NMR (500 MHz, CDCl$_3$, minor isomer) δ 8.21 (d, *J* = 7.5 Hz, 2 H), 7.57 (d, *J* = 7.5 Hz, 2 H), 7.37 (d, *J* = 7.5 Hz, 2 H), 7.31 (t, *J* = 7.5 Hz, 2 H), 7.22 (t, *J* = 7.5 Hz, 1 H), 6.93 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.57 (d, *J* = 15.5 Hz, 1 H), 6.38-6.32 (m, 1 H), 5.49 (dt, *J* = 10.5, 7.5 Hz, 1 H), 4.93-4.89 (m, 1 H), 2.81-2.69 (m, 2 H), 2.29 (brs, 1 H) ppm.

^{13}C NMR (126 MHz, CDCl$_3$, major isomer) δ 151.22, 147.43, 137.17, 135.17, 132.35, 128.76, 128.58, 128.31, 127.77, 126.68, 126.46, 123.81, 72.76, 43.12 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 151.22, 147.43, 134.35, 133.01, 128.99, 128.40, 128.00, 126.73, 126.61, 125.83, 123.40, 72.97, 38.08 ppm.

IR (KBr, cm⁻¹): 3352, 3076, 3030, 2953, 2935, 2907, 2881, 2876, 2359, 1609, 1597, 1524, 1489, 1447, 1344, 1312, 1107, 1107, 1051, 986, 854, 750, 694.

High-resolution MS, (C₁₈H₁₇NO₃) *calculated* 295.1208, *found* 295.1206.
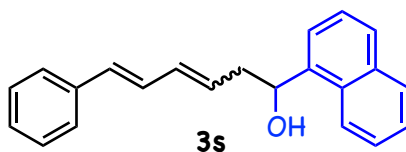
(3*E*, 5*E*)-1-(1-naphthyl)-6-phenylhexa-3,5-dien-1-ol (3s, major isomer) and **(3*Z*, 5*E*)-1-(1-naphthyl)-6-phenylhexa-3,5-dien-1-ol (3s, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.9 mg, 0.5 mmol) and 1-naphthaldehyde (**2m**, 205 μL, 1.5 mmol), afford **3s** (131.9 mg, 87% yield, R_f = 0.37; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3*E*, 5*E*: 3*Z*, 5*E* = 7:1). Colorless oil.

¹H NMR (500 MHz, CDCl₃, major isomer) δ 8.10 (d, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.55-7.48 (m, 3 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.31 (t, *J* = 8.0 Hz, 2 H), 7.21 (t, *J* = 8.0 Hz, 1 H), 6.78 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.51 (d, *J* = 15.5 Hz, 1 H), 6.38 (dd, *J* = 15.5, 10.5 Hz, 1 H), 5.91 (dt, *J* = 15.5, 7.5 Hz, 1 H), 5.58-5.56 (m, 1 H), 2.88-2.83 (m, 1 H), 2.74-2.68 (m, 1 H), 2.16 (brs, 1 H) ppm.

¹H NMR (500 MHz, CDCl₃, minor isomer) δ 8.15 (d, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.56-7.48 (m, 3 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.31 (t, *J* = 8.0 Hz, 2 H), 7.21 (t, *J* = 8.0 Hz, 1 H), 6.95 (dd, *J* = 15.5, 10.5 Hz, 1 H), 6.54 (d, *J* = 15.5 Hz, 1 H), 6.38-6.31 (m, 1 H), 5.67 (dt, *J* = 10.5, 8.0 Hz, 1 H), 5.60-5.56 (m, 1 H), 3.01-2.89 (m, 2 H), 2.18 (brs, 1 H) ppm.

¹³C NMR (126 MHz, CDCl₃, major isomer) δ 139.55, 137.47, 134.07, 133.96, 131.64, 130.71, 130.39, 129.13, 128.88, 128.73, 128.19, 127.55, 126.42, 126.24, 125.70, 125.61, 123.11, 122.99, 70.63, 42.10 ppm.

¹³C NMR (126 MHz, CDCl₃, minor isomer) δ 139.49, 137.42, 133.48, 131.99, 129.20, 129.05, 128.37, 128.27, 127.87, 127.71, 126.57, 126.28, 124.05, 123.17, 71.04, 37.06 ppm.

IR (neat, cm^{-1}): 3408, 3059, 3017, 2930, 2399, 2341, 1597, 1510, 1495, 1448, 1215, 1053, 991, 800, 756, 692, 667.

High-resolution MS, (C$_{22}$H$_{20}$O) *calculated* 300.1514, *found* 300.1512.

3t
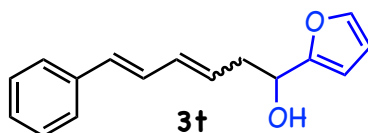
(3E, 5E)-1-(2-furyl)-6-phenylhexa-3,5-dien-1-ol (3t, major isomer) and **(3Z, 5E)-1-(2-furyl)-6-phenylhexa-3,5-dien-1-ol (3t, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 107.6 mg, 0.5 mmol) and furfural (**2n**, 125 μL, 1.5 mmol), afford **3t** (41.4 mg, 33% yield, R_f = 0.50; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3E, 5E: 3Z, 5E = >20:1). Yellow oil.

¹H NMR (400 MHz, CDCl$_3$, major isomer) δ 7.39-7.36 (m, 3 H), 7.29 (t, J = 7.6 Hz, 2 H), 7.22-7.18 (m, 1 H), 6.74 (dd, J = 15.6, 10.8 Hz, 1 H), 6.48 (d, J = 15.6 Hz, 1 H), 6.36-6.26 (m, 3 H), 5.78 (dt, J = 15.6, 7.6 Hz, 1 H), 4.77 (t, J = 7.6 Hz, 1 H), 2.77-2.66 (m, 2 H), 2.15 (brs, 1 H) ppm.
**¹H NMR** (400 MHz, CDCl$_3$, minor isomer) δ 7.43-7.36 (m, 3 H), 7.29 (t, J = 7.6 Hz, 2 H), 7.22-7.18 (m, 1 H), 7.06 (dd, J = 15.6, 10.8 Hz, 1 H), 6.56 (d, J = 15.6 Hz, 1 H), 6.36-6.26 (m, 3 H), 5.51 (dt, J = 10.8, 7.6 Hz, 1 H), 4.81-4.77 (m, 1 H), 2.89-2.85 (m, 2 H), 2.15 (brs, 1 H) ppm.

¹³C NMR (101 MHz, CDCl$_3$, major isomer) δ 156.15, 142.16, 137.43, 134.23, 131.64, 129.52, 128.83, 128.71, 127.53, 126.40, 110.32, 106.32, 67.41, 39.30 ppm.
¹³C NMR (101 MHz, CDCl$_3$, minor isomer) δ 156.06, 142.21, 133.65, 131.99, 128.36, 127.77, 126.74, 126.61, 123.95, 110.32, 106.44, 67.55, 34.42 ppm.

IR (neat, cm^{-1}): 3369, 3024, 2953, 2926, 2876, 2855, 2365, 2336, 1948, 1871, 1595, 1495, 1447, 1294, 1265, 1223, 1148, 1013, 989, 743, 692.

High-resolution MS, (C$_{16}$H$_{16}$O$_2$) *calculated* 240.1150, *found* 240.1150.
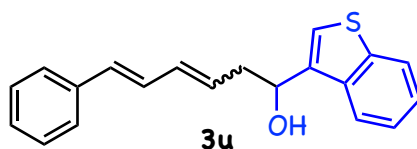
(3E, 5E)-1-(benzo[b]thiophen-3-yl)-6-phenylhexa-3,5-dien-1-ol (3u, major isomer) and **(3Z, 5E)-1-(benzo[b]thiophen-3-yl)-6-phenylhexa-3,5-dien-1-ol (3u, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 104.8 mg, 0.5 mmol) and benzo[b]thiophene-3-carboxaldehyde (**2o**, 243.3 mg, 1.5 mmol), afford **3u** (122.9 mg, 79% yield, R_f = 0.40; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (3E, 5E: 3Z, 5E = 12:1). Yellow oil.

¹H NMR (500 MHz, CDCl₃, major isomer) δ 7.86-7.83 (m, 2 H), 7.39-7.17 (m, 8 H), 6.73 (dd, J = 15.6, 10.4 Hz, 1 H), 6.46 (d, J = 15.6 Hz, 1 H), 6.32 (dd, J = 15.6, 10.4 Hz, 1 H), 5.82 (dt, J = 15.6, 7.2 Hz, 1 H), 5.12-5.09 (m, 1 H), 2.82-2.66 (m, 2 H), 2.31 (brs, 1 H) ppm.
**¹H NMR** (500 MHz, CDCl₃, minor isomer) δ 7.91-7.83 (m, 2 H), 7.39-7.17 (m, 8 H), 6.90 (dd, J = 15.6, 10.8 Hz, 1 H), 6.51 (d, J = 15.6 Hz, 1 H), 6.35-6.29 (m, 1 H), 5.57 (dt, J = 10.8, 7.6 Hz, 1 H), 5.15-5.09 (m, 1 H), 2.97-2.85 (m, 2 H), 2.31 (brs, 1 H) ppm.

¹³C NMR (101 MHz, CDCl₃, major isomer) δ 141.08, 138.94, 137.39, 137.28, 134.18, 131.66, 130.12, 128.78, 128.71, 127.54, 126.39, 124.56, 124.19, 123.09, 122.43, 122.32, 69.40, 40.99 ppm.
¹³C NMR (101 MHz, CDCl₃, minor isomer) δ 141.10, 138.79, 137.34, 137.31, 133.56, 132.09, 127.71, 126.55, 124.23, 123.90, 123.17, 122.67, 69.69, 35.93 ppm.

IR (neat, cm⁻¹): 3383, 3059, 3022, 2959, 2924, 2876, 2856, 2399, 2365, 1944, 1871, 1595, 1524, 1495, 1427, 1256, 1217, 1059, 1026, 989, 735, 692, 667.

High-resolution MS, (C₂₀H₁₈OS) *calculated* 306.1078, *found* 306.1077.
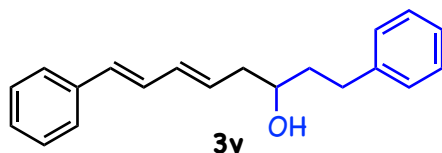
(5E, 7E)-1,8-diphenylocta-5,7-dien-3-ol (3v). Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.1 mg, 0.5 mmol) and benzenepropanal (**2p**, 200 μL, 1.5 mmol), afford **3v** (45.8 mg, 33% yield, R_f = 0.33; hexane/EtOAc = 4/1 v/v). Colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.39-7.37 (m, 2 H), 7.32-7.27 (m, 4 H), 7.23-7.17 (m, 4 H), 6.76 (dd, J = 15.5, 10.5 Hz, 1 H), 6.49 (d, J = 15.5 Hz, 1 H), 6.30 (dd, J = 15.5, 10.5 Hz, 1 H), 5.81 (dt, J = 15.5, 7.5 Hz, 1 H), 3.74-3.69 (m, 1 H), 2.85-2.80 (m, 1 H), 2.73-2.67 (m, 1 H), 2.43-2.38 (m, 1 H), 2.32-2.26 (m, 1 H), 1.87-1.76 (m, 2 H), 1.60 (brs, 1 H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ 142.14, 137.46, 134.10, 131.48, 130.56, 128.86, 128.74, 128.60, 128.57, 127.55, 126.40, 126.01, 77.16, 70.60, 41.28, 38.69, 32.22 ppm.

IR (neat, cm⁻¹): 3423, 3088, 3065, 3024, 2930, 2858, 2359, 2341, 1944, 1867, 1603, 1495, 1452, 1333, 1261, 1217, 1136, 1047, 1030, 989, 700, 667.

High-resolution MS, (C₂₀H₂₂O) *calculated* 278.1671, *found* 278.1671.

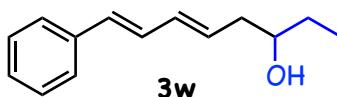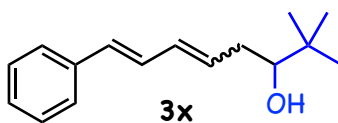**(5*E*, 7*E*)-8-phenylocta-5,7-dien-3-ol (3w)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.1 mg, 0.5 mmol) and propanal (**2q**, 110 μL, 1.5 mmol), afford **3w** (75.7 mg, 75% yield, R_f = 0.33; hexane/EtOAc = 4/1 v/v). Colorless oil.

¹H NMR (500 MHz, CDCl₃) δ 7.38 (d, J = 7.5 Hz, 2 H), 7.30 (t, J = 7.5 Hz, 2 H), 7.21 (t, J = 7.5 Hz, 1 H), 6.77 (dd, J = 15.5, 10.5 Hz, 1 H), 6.48 (d, J = 15.5 Hz, 1 H), 6.30 (dd, J = 15.5, 10.5 Hz, 1 H), 5.83 (dt, J = 15.5, 7.5 Hz, 1 H), 3.64-3.59 (m, 1 H), 2.41-2.36 (m, 1 H), 2.28-2.21 (m, 1 H), 1.65 (brs, 1 H), 1.58-1.46 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 137.51, 133.82, 131.27, 130.98, 128.96, 128.72, 127.48, 126.37, 72.70, 40.60, 29.80, 10.09 ppm.

IR (neat, cm⁻¹): 3435, 3059, 3018, 2966, 2934, 2878, 2399, 1950, 1595, 1495, 1462, 1217, 1113, 1072, 989, 758, 692, 667.

High-resolution MS, (C₁₄H₁₈O) *calculated* 202.1358, *found* 202.1358.

(5*E*, 7*E*)-2,2-dimethyl-8-phenylocta-5,7-dien-3-ol (3x, major isomer) and **(5*Z*, 7*E*)-2,2-dimethyl-8-phenylocta-5,7-dien-3-ol (3x, minor isomer)**. Following the general procedure B using 2-benzyl-3-hydroxypent-4-enoic acid (**1a**, 103.7 mg, 0.5 mmol) and 2,2-dimethyl-propanal (**2r**, 170 μL, 1.5 mmol), afford **3x** (78.1 mg, 67% yield, R_f = 0.60; hexane/EtOAc = 4/1 v/v) as a mixture of stereoisomers (5*E*, 7*E*: 5*Z*, 7*E* = >20:1). Colorless oil.

¹H NMR (400 MHz, CDCl₃, major isomer) δ 7.38 (d, *J* = 7.2 Hz, 2 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 6.77 (dd, *J* = 15.6, 10.8 Hz, 1 H), 6.48 (d, *J* = 15.6 Hz, 1 H), 6.31 (dd, *J* = 15.6, 10.8 Hz, 1 H), 5.86 (dt, *J* = 15.6, 7.2 Hz, 1 H), 3.31-3.29 (m, 1 H), 2.44-2.41 (m, 1 H), 2.13-2.05 (m, 1 H), 1.61 (brs, 1 H), 0.94 (s, 9 H) ppm.

¹H NMR (400 MHz, CDCl₃, minor isomer) δ 7.41 (d, *J* = 7.2 Hz, 2 H), 7.30 (t, *J* = 7.2 Hz, 2 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.04 (dd, *J* = 15.6, 10.8 Hz, 1 H), 6.57 (d, *J* = 15.6 Hz, 1 H), 6.36-6.31 (m, 1 H), 5.62 (dt, *J* = 10.8, 8.0 Hz, 1 H), 3.33-3.29 (m, 1 H), 2.50-2.32 (m, 2 H), 1.61 (brs, 1 H), 0.98 (s, 9 H) ppm.

¹³C NMR (101 MHz, CDCl₃, major isomer) δ 137.56, 133.54, 132.73, 131.13, 129.00, 128.72, 127.46, 126.38, 78.93, 35.71, 34.92, 25.89 ppm.

¹³C NMR (101 MHz, CDCl₃, minor isomer) δ 133.28, 129.05, 128.74, 128.40, 127.70, 126.57, 124.11, 79.44, 35.71, 30.71, 25.93 ppm.

IR (neat, cm⁻¹): 3429, 3024, 2955, 2907, 2868, 2365, 2336, 1944, 1641, 1597, 1495, 1479, 1448, 1364, 1290, 1238, 1177, 1070, 988, 743, 691.

High-resolution MS, (C₁₆H₂₂O) *calculated* 230.1671, *found* 230.1671.
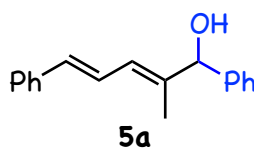
(2*E*, 4*E*)-2-methyl-1,5-diphenylpenta-2,4-dien-1-ol (5a).

¹H NMR (500 MHz, CDCl₃) δ 7.40-7.17 (m, 10 H), 6.99 (dd, J = 15.5, 11.0 Hz, 1 H), 6.58 (d, J = 15.5 Hz, 1 H), 6.44 (d, J = 11.0 Hz, 1 H), 5.14 (s, 1 H), 2.38 (brs, 1 H), 1.69 (s, 3 H) ppm.

¹³C NMR (126 MHz, CDCl₃) δ 142.09, 140.06, 137.66, 132.87, 128.68, 128.44, 127.62, 127.50, 126.52, 126.40, 125.78, 124.79, 78.98, 13.20 ppm.

IR (neat, cm⁻¹): 3441, 3065, 3018, 2982, 2959, 2930, 2858, 2359, 2336, 1597, 1491, 1447, 1373, 1250, 1217, 1105, 1074, 1045, 964, 908, 700, 667.

High-resolution MS, (C₁₈H₁₈O) *calculated* 250.1358, *found* 250.1358.

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Chapter 1

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Other related publications

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