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Doctoral Dissertation

Studies on Formation of Carbon-Carbon or Carbon-Oxygen Bonds by Activation of Alkenes and Alkynes Using Heavier Group 13 Metal Salts

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January 2019

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Preface and Acknowledgements

The work of this thesis has been performed from 2013 to 2019 under the guidance of Prof. Dr. Makoto Yasuda at Department of Applied Chemistry, Graduate School of Engineering, Osaka University. The thesis describes transformation of alkenes or alkynes using heavier group 13 metal salts for formation of carbon-carbon or carbon-oxygen bonds.

First and foremost, I would like to express my sincerest gratitude to Prof. Dr. Makoto Yasuda for their precise guidances, helpful suggestions, and hearty encouragements throughout this work.

I would also like to thank Professors Dr. Ikuya Shibata and Dr. Sensuke Ogoshi for their helpful advice and kind assistance.

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List of Publications

1) Coupling Reaction of Enol Derivatives with Silyl Ketene Acetals Catalyzed by Gallium Trihalides
Y. Nishimoto, Y. Kita, H. Ueda, H. Imaoka, K. Chiba, M. Yasuda, A. Baba
Chem. Eur. J. **2016**, *22*, 11837-11845.

2) Indium Catalyzed Hydrofunctionalization of Styrene Derivatives Bearing a Hydroxy Group with Organosilicon Nucleophiles
Y. Kita, T. Yata, Y. Nishimoto, M. Yasuda
J. Org. Chem. **2018**, *83*, 740-753.

3) Selective Oxymetalation of Terminal Alkynes *via* 6-*Endo* Cyclization: Mechanistic Investigation and Application to the Efficient Synthesis of 4-Substituted Isocoumarins
Y. Kita, T. Yata, Y. Nishimoto, K. Chiba, M. Yasuda
Chem. Sci. **2018**, *9*, 6041-6052.

4) Synthesis of 2,4,6-Triarylpyryliums Bearing a Carbon-Metal Bond and their Application to Bifunctional Photocatalyst
Y. Kita, Y. Nishimoto, M. Yasuda
Manuscript under preparation

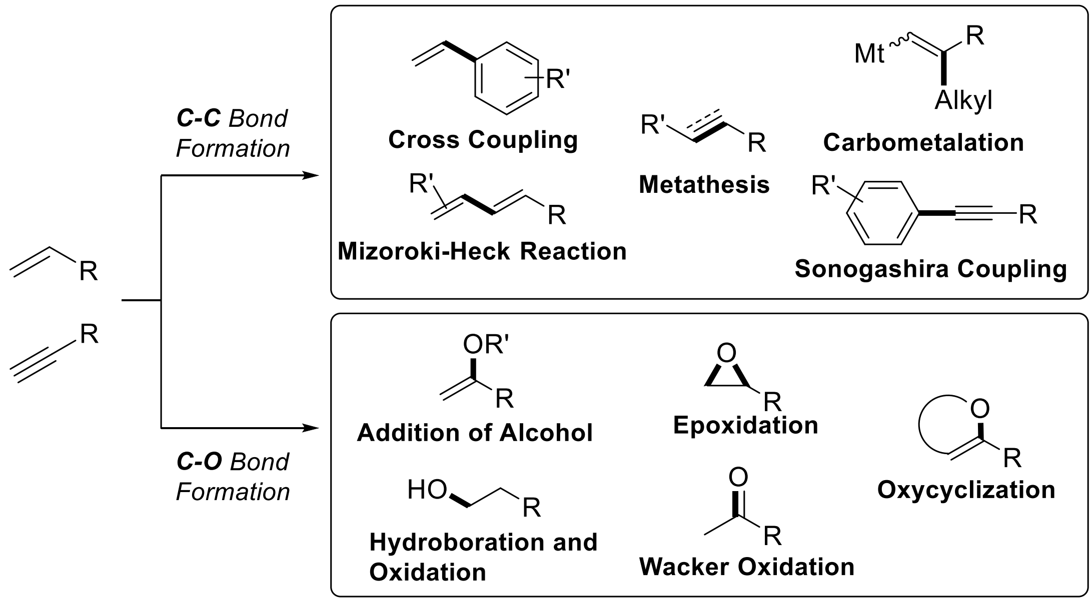
Supplementary List of Publications

1) Kinetic Resolution of α-Hydroxy-Substituted Oxime Ethers by Enantioselective Cu-H-Catalyzed Si-O Coupling
X. Dong, Y. Kita, M. Oestreich
Angew. Chem. Int. Ed. **2018**, *57*, 10728-10731.

Contents

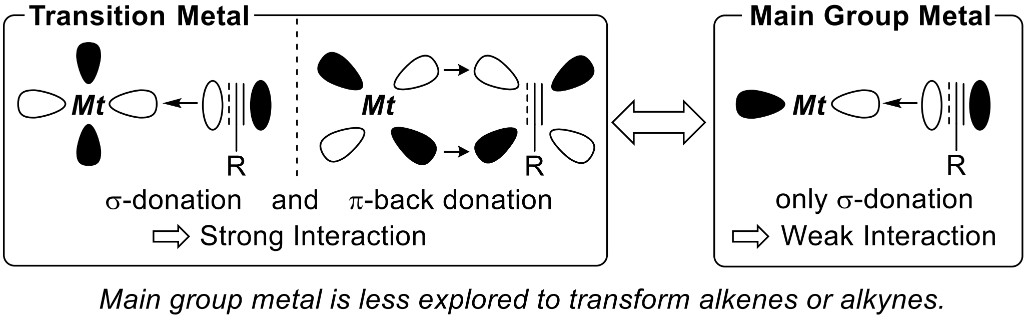
General Introduction

Transformation of alkenes and alkynes is one of the important research topics in organic chemistry because alkenes and alkynes are fundamental materials and their transformation provides a basic and significant strategy to synthesize various organic molecules. Especially, the transformation via formation of carbon-carbon bonds is an essential method to access complex molecular structures (Scheme 1, upper). Chemists have developed a lot of useful reactions to form carbon-carbon bonds such as Mizoroki-Heck reaction, cross-couplings, alkene- or alkyne-metathesis, Sonogashira coupling and carbometalations.[1] The reactions with formation of carbon-oxygen bonds have also been studied (Scheme 1, lower). Addition reactions of alcohols or H_2O to carbon-carbon multiple bonds and oxidation reactions such as epoxidation and Wacker process are known as representative examples.[2] The construction of heterocyclic compounds has recently attracted much attention in fine chemical synthesis.[3] However, development of new reaction systems, which can introduce functional groups into alkenes and alkynes directly with high selectivety, is highly desired even today in terms of efficient utilization of carbon resources.



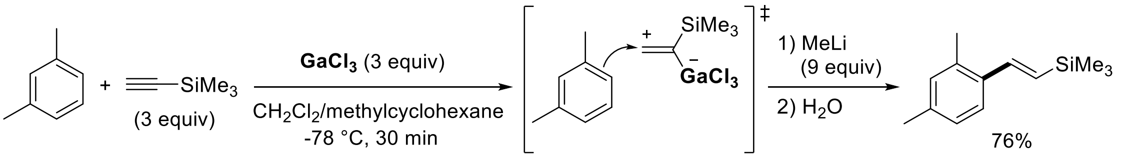
Scheme 1. Transformation of alkenes and alkynes with formation of carbon-carbon or carbon-oxygen bonds.

In the synthesis of fine chemicals, the transformation of carbon-carbon multiple bonds mainly depends on transition metal catalysts. On the other hand, main group metals such as aluminum and boron have been utilized as Lewis acid catalysts for activation of carbonyl compounds.[4] However, transformation of unactivated alkenes and alkynes using main group metals has been less explored in comparison with transition metals because main group metals have no d-orbitals interacting with π and π* orbitals to show weak interaction with carbon-carbon multiple bonds (Scheme 2). If there is a novel concept that main group metals can activate carbon-carbon multiple bonds, new reaction systems can be developed because main group metals and transition metals show quite differenet reactivity.



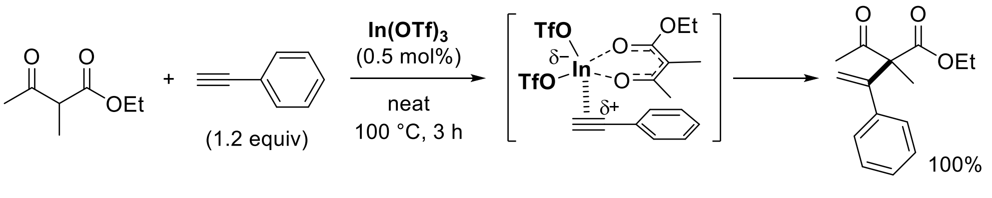
Scheme 2. Different character between transition metal and main group metal in the interaction with alkenes and alkynes.

Heavier group 13 metals such as gallium and indium have been utilized to functionalize carbon-carbon multiple bonds.[5] As a pioneering example for gallium-mediated transformation, Yamaguchi reported Friedel-Crafts alkenylations via activation of trimethylsilylacetyrene using $GaCl_3$ (Eq. 1).[6]



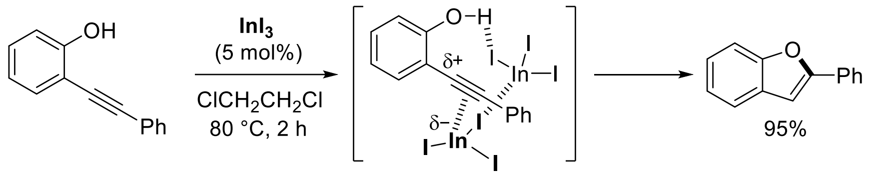
(Eq. 1)[6]

Nakamura achived Conia-ene reaction of 1,3-dicarbonyl compounds with simple alkynes in the presence of $In(OTf)_3$ (Eq. 2).[7] This reaction is one of the representative examples for indium-catalyzed transformation of unactivated alkynes, and the indium moiety of an In-enolate generated *in situ* worked as a Lewis acid to activate the alkynes.



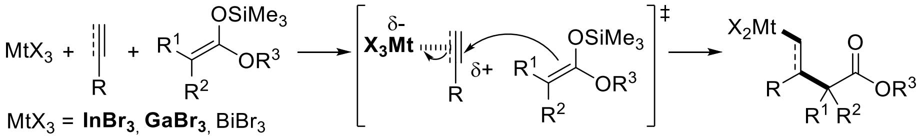
(Eq. 2)[7]

For the formation of carbon-oxygen bonds, Sestelo developed InI_3-catalyzed cyclization of 2-alkynylphenols to synthesize benzofurans (Eq. 3).[8] In this report, theoretical calculation suggested that a dimer of InI_3 efficintly activates the alkyne as well as OH group.



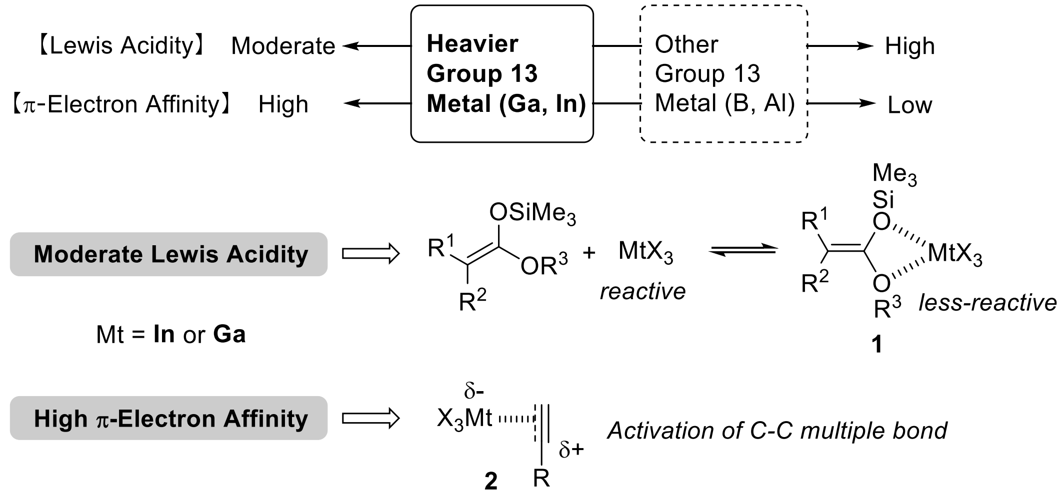
(Eq. 3)[8]

Our group has also reported regio- and stereoselective carbometalation of alkenes or alkynes with silyl ketene acetals using indium or gallium salts (Eq. 4).[9]



(Eq. 4)[9]

These results indicated that gallium and indium show two distinctive properties, moderate Lewis acidity and high π-electron affinity, in contrast to the other group 13 metals (Scheme 3). If a metal salt has high Lewis acidity in the case of the carbometalation, the coordination of a silyl ketene acetal deactivates the Lewis acidic metal salt (**1**). However, heavier group 13 metal salts can dissociate from silyl ketene acetals due to the moderate Lewis acidity, and their high π-electron affinity can lead to activation of simple carbon-carbon multiple bonds (**2**) to accomplish the carbometalation. In other words, gallium and indium can work as a Lewis acid to transform unactivated alkenes and alkynes even in the presence of Lewis basic functional groups such as ether and carbonyl groups.

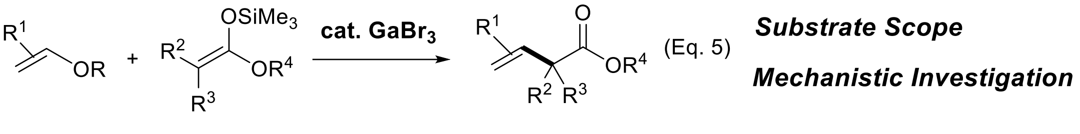


Scheme 3. Characteristic properties of heavier group 13 metal salts.

Based on the strategy of the transformation of carbon-carbon multiple bonds using heavier group 13 metal salts, I developed new synthetic reactions using alkenes and alkynes to form carbon-carbon or carbon-oxygen bonds. This thesis consists of the following four chapters.

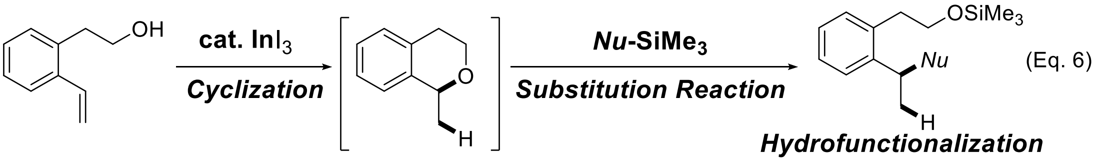
Chapter 1 describes the $GaBr_3$-catalyzed cross-coupling of enol derivatives with silyl ketene acetals (Eq. 5). This reaction is the first example of cross-coupling between enol derivatives and metal enolates. For the improvement of this coupling, expansion of scope of enol derivatives and mechanistic investigation such as determination of reaction intermediate, kinetic studies and theoretical calculations were carried out.

Chapter 1: Coupling Reaction of Enol Derivatives with Silyl Ketene Acetals Catalyzed by Gallium Trihalides



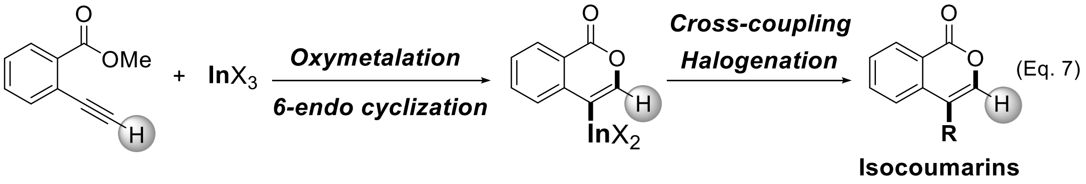
Chapter 2 deals with the InI_3-catalyzed formal hydrofunctionalization of styrene derivatives bearing a hydroxy group with organosilicon nucleophiles (Eq. 6). Various types of functional groups were added to the less-polar alkenes in a single synthetic operation. The intramolecular hydroxy group of styrene derivatives plays an important role to accomplish this hydrofunctionalization.

Chapter 2: Indium Catalyzed Hydrofunctionalization of Styrene Derivatives Bearing a Hydroxy Group with Organosilicon Nucleophiles



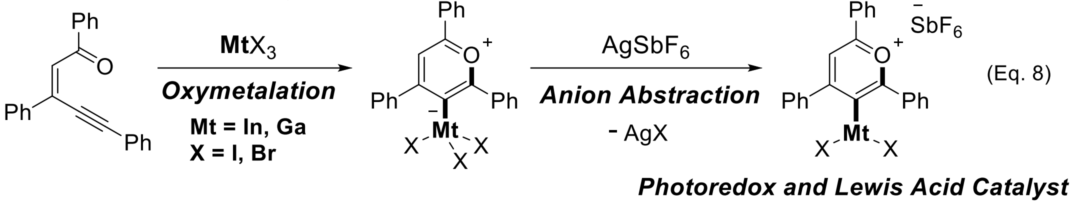
Chapter 3 provides the 6-*endo* selective intramolecular oxyindation of terminal alkynes with an ester moiety to synthesize isocoumarins (Eq. 7). The regioselectivity is striking different with previously reported Lewis acid mediated cyclization of terminal alkynes in which 5-*exo* cyclization occurred due to the Markovnikov rule. Isocoumarins bearing a carbon-metal bond at 4-position were selectively synthesized and the metalated isocoumarins worked as a useful synthetic precursor of isocoumarin derivatives.

Chapter 3: Selective Oxymetalation of Terminal Alkynes via 6-*Endo* Cyclization: Mechanistic Investigation and Application to the Efficient Synthesis of 4-Substituted Isocoumarins



Chapter 4 reports the synthesis of triphenylpyryliums bearing a carbon-metal bond via intramolecular oxymetalation and its application to a photocatalyst possessing a Lewis acid moiety (Eq. 8). This new type of triphenylpyryliums showed a unique reactivity in a photo-induced reaction compared with a well-established triphenylpyrylium photocatalyst.

Chapter 4: Synthesis of 2,4,6-Triarylpyryliums Bearing a Carbon-Metal Bond and their Application to Bifunctional Photocatalyst



(Eq. 8)

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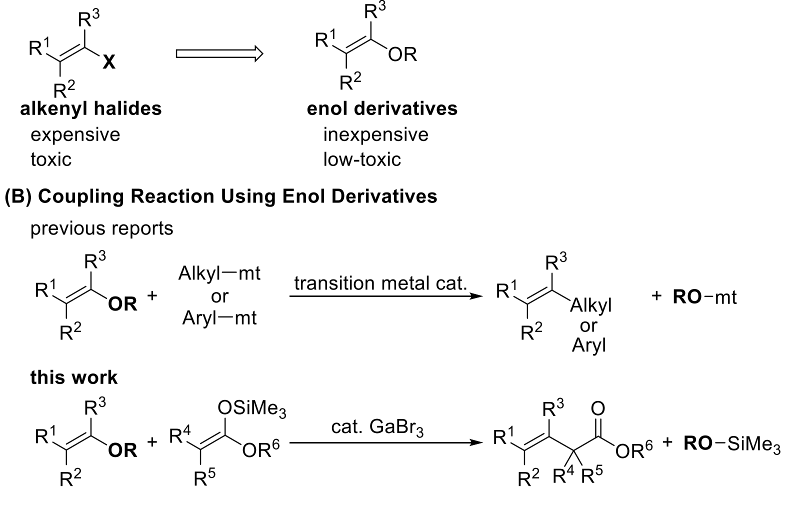
Chapter 1

Coupling Reaction of Enol Derivatives with Silyl Ketene Acetals Catalyzed by Gallium Trihalides

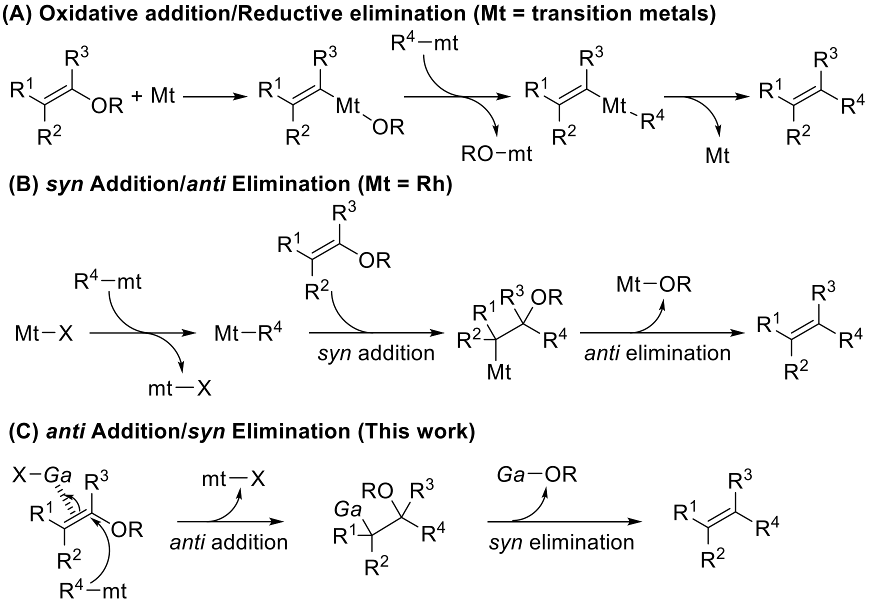
1-1. Introduction

The cross-coupling reaction using alkenyl electrophiles is one of the most important methods for the construction of carbon frameworks such as pharmaceuticals, natural products, and organic materials.[1] Generally, alkenyl halides are used as an electrophilic coupling partner because of their high reactivity, while they have some problems such as relatively high cost and potential toxicity, as well as the formation of metal halide salts as by-products. In this context, enol derivatives such as enol ethers and alkenyl carboxylates have attracted much attention because they are inexpensive, readily available, and environmentally benign (Scheme 1A).[2] However, a coupling reaction using enol derivatives remains a challenging issue because the intrinsic feature of inert C-O bonds disturbs the achievement of desirable coupling reactions. Although several types of transition metal-catalyzed couplings using enol ethers,[3] alkenyl carboxylates,[4] alkenyl carbamates,[5] alkenyl phosphates,[6] and silyl enol ethers[7] have been reported, applicable organometallic partners have been limited to alkyl or aryl metals (Scheme 1B). As far as other types of nucleophiles, such as metal enolates, only two catalytic coupling reactions, the Pd-catalyzed dimerization of silyl vinyl ethers[8] and our reported $InBr_3$-catalyzed coupling of enol ethers with ketene silyl imines,[9] have previously been achieved.[10] To the best of our knowledge, the cross coupling between enol derivatives and metal enolates had never been achieved prior to our previous report of a $GaBr_3$-catalyzed coupling between enol ethers and silyl ketene acetals.[11,12]



Scheme 1. Coupling reaction using enol derivatives as electrophiles.

Herein, we report the full details of the coupling reaction of enol derivatives such as enol ethers and alkenyl carboxylates with silyl ketene acetals catalyzed by $GaBr_3$ (Scheme 1B). This paper (1) elucidates the scope of enol derivatives and silyl ketene acetals, and (2) describes the mechanistic study via kinetic experiments, the observation of a key intermediate, and theoretical calculations. Typical transition metal-catalyzed coupling reactions using enol derivatives proceed via a mechanism that includes oxidative addition/reductive elimination (Scheme 2A).[3,4,5,6,7] Recently, Kambe et al. reported Rh-catalyzed coupling between enol ethers and Grignard reagents via the *syn* addition of an organorhodium/*anti* elimination of a rhodium alkoxide (Scheme 2B).[3i] We revealed that the present coupling reaction of enol derivatives with silyl ketene acetals occurs via a novel reaction mechanism that involves *anti* carbogallation by three components, $GaBr_3$, an enol derivative, and a silyl ketene acetal, followed by *syn* elimination of a gallium alkoxide (Scheme 2C).



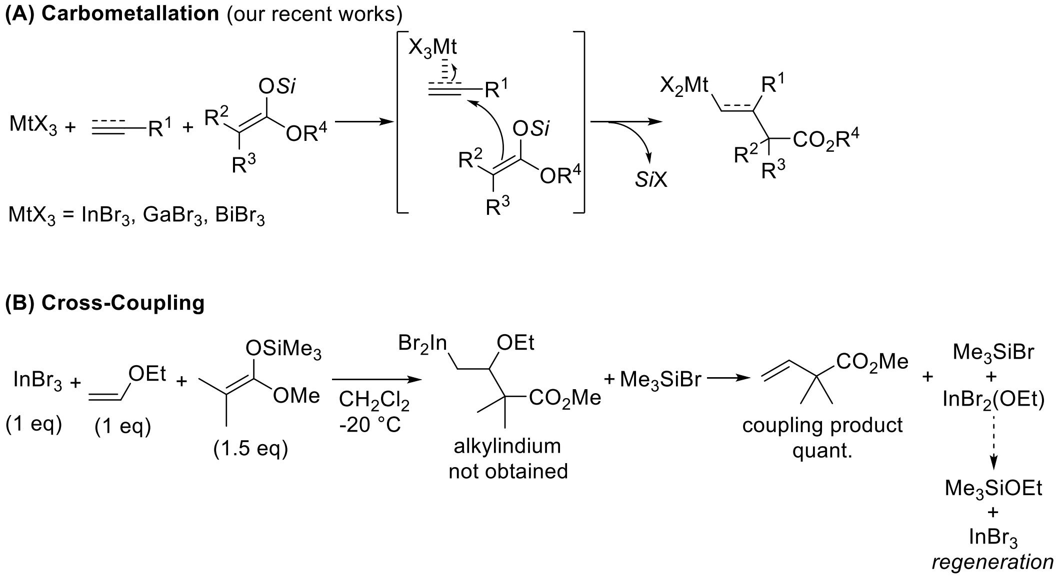
Scheme 2. Comparison of reaction mechanisms of coupling reaction using enol derivatives.

1-2. Results and Discussion

Coupling Reaction of Enol Ethers with Silyl Ketene Acetals

(i) Optimization of Reaction Conditions in the Coupling Reaction between Enol Ether and Silyl Ketene Acetal

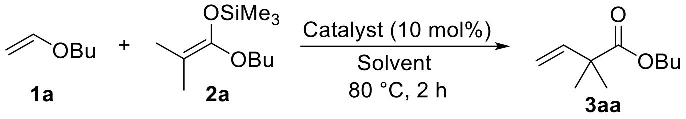
We recently developed carbometalations of alkenes and alkynes using silyl ketene acetals and metal halides such as $InBr_3$[13], $GaBr_3$[14], and $BiBr_3$[15]. The moderate Lewis acidity of these metal halides promoted the effective activation of carbon-carbon multiple bonds without deactivation by the coordination of an oxygen atom of ketene silyl acetates to achieve carbometallation in an *anti*-addition fashion (Scheme 3A). During the course of a study on this carbometallation, when ethyl vinyl ether was employed as an alkene the predictable alkylindium compound was not obtained, but the corresponding coupling product was obtained quantitatively (Scheme 3B). The generation of Me_3SiBr and $InBr_2(OEt)$ via carbogallation and β-elimination from the alkylindium compound, respectively, should be possible based on these results. Therefore, we investigated the catalytic coupling of enol ethers with silyl ketene acetals in expectation of the regeneration of $InBr_3$ by the transmetallation between Me_3SiBr and $InBr_2(OEt)$.



Scheme 3. Unexpected coupling reaction based on our developed carbometalation.

We examined the effect of catalysts on the coupling of butyl vinyl ether **1a** with dimethylketene trimethylsilyl acetal **2a** in dichloroethane at 80 °C (Table 1). At first, this coupling reaction did not occur without a catalyst (entry 1). A survey of $InBr_3$, $GaBr_3$, and $BiBr_3$, that effectively promoted carbometallation,[13,14,15] was carried out. A catalytic amount of $InBr_3$ (10 mol%) smoothly accelerated the desired coupling reaction to afford α-vinyl ester **3aa** in 86% yield (entry 2). The reaction catalyzed by $GaBr_3$ gave an excellent yield, 97% (entry 3). In contrast, $BiBr_3$ showed a low catalytic effect (entry 4). Other indium and gallium salts such as $InCl_3$, InI_3, $In(OTf)_3$, $GaCl_3$, GaI_3, and $Ga(OTf)_3$ effectively accelerated the coupling reaction to give the product **3aa** (entries 5-10), while other bismuth salts were ineffective (entries 11-13). When employing indium and gallium salts at a lower temperature (50 °C), $GaBr_3$ and GaI_3 showed high catalytic ability (entries 14-19). While $ZnCl_2$ showed modest catalytic ability (entry 20), typical strong Lewis acids such as $BF_3{\bullet}OEt_2$, $AlCl_3$, and $TiCl_4$ were ineffective (entries 21-23). $Sc(OTf)_3$ and $Y(OTf)_3$ also produced no desired product (entries 24 and 25). Transition metal salts did not work as catalysts (entries 26 and 27). These results show that the characteristic features of gallium and indium halides are important for the completion of a catalytic reaction system. The effect of solvents was also investigated. As far as non-polar solvents, toluene can be employed though the reaction in hexane gave low yield (entries 28 and 29). Polar solvents such as CH_3CN and THF were unsuitable because they coordinated with $GaBr_3$ to disturb the reaction (entries 30 and 31). Finally, GaI_3 and $GaBr_3$ were the most effective catalysts, and, thus, we decided to use entry 3 as the standard condition.

Table 1. Investigation of effects of catalyst and solvents.[a]



Entry	Catalyst	Solvent	Yield of **3aa** [%][b]
1	none	$ClCH_2CH_2Cl$	0
2	$InBr_3$	$ClCH_2CH_2Cl$	86
3	$GaBr_3$	$ClCH_2CH_2Cl$	97
4	$BiBr_3$	$ClCH_2CH_2Cl$	trace
5	$GaCl_3$	$ClCH_2CH_2Cl$	100
6	GaI_3	$ClCH_2CH_2Cl$	96
7	$Ga(OTf)_3$	$ClCH_2CH_2Cl$	64
8	$InCl_3$	$ClCH_2CH_2Cl$	100
9	InI_3	$ClCH_2CH_2Cl$	94
10	$In(OTf)_3$	$ClCH_2CH_2Cl$	92
11	$BiCl_3$	$ClCH_2CH_2Cl$	trace
12	BiI_3	$ClCH_2CH_2Cl$	trace
13	$Bi(OTf)_3$	$ClCH_2CH_2Cl$	17
14[c]	$GaCl_3$	$ClCH_2CH_2Cl$	52
15[c]	$GaBr_3$	$ClCH_2CH_2Cl$	95
16[c]	GaI_3	$ClCH_2CH_2Cl$	94
17[c]	$InCl_3$	$ClCH_2CH_2Cl$	trace
18[c]	$InBr_3$	$ClCH_2CH_2Cl$	21

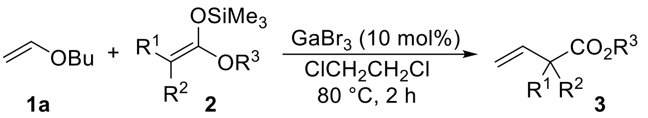
19[c]	InI_3	$ClCH_2CH_2Cl$	59
20	$ZnCl_2$	$ClCH_2CH_2Cl$	59
21	$BF_3 \cdot OEt_2$	$ClCH_2CH_2Cl$	2
22	$AlCl_3$	$ClCH_2CH_2Cl$	trace
23	$TiCl_4$	$ClCH_2CH_2Cl$	trace
24	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	trace
25	$Y(OTf)_3$	$ClCH_2CH_2Cl$	0
26	$CuBr_2$	$ClCH_2CH_2Cl$	trace
27	$PdCl_2$	$ClCH_2CH_2Cl$	trace
28	$GaBr_3$	toluene	71
29	$GaBr_3$	hexane	24
30	$GaBr_3$	CH_3CN	11
31	$GaBr_3$	THF	20

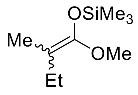
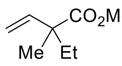
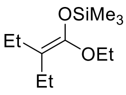
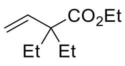
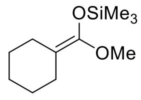
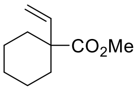
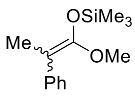
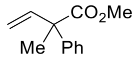
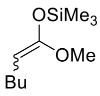
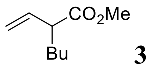
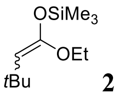
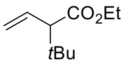
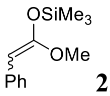
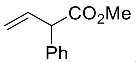
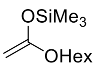
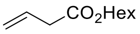
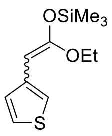
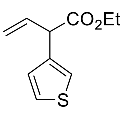
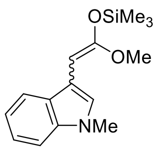
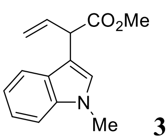
[a] **1a** (1 equiv), **2a** (1.5 equiv), catalyst (0.1 equiv), solvent (0.5 M), 80 °C, 2 h. [b] Yields were determined by GC. [c] 50 °C, 30 min.

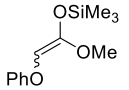
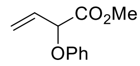
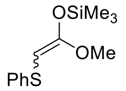
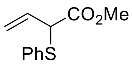
(ii) Scope of Ketene Silyl Acetals and Enol Ethers

The scope of ketene silyl acetals **2** for the $GaBr_3$-catalyzed coupling was investigated, and the results are summarized in Table 2. Dialkylketene silyl acetals **2b**, **2c**, and **2d** were more bulky than **2a**, and afforded the corresponding α-vinyl esters in high yields (entries 1-3). Alkyl arylketene silyl acetal **2e** was also a suitable nucleophile (entry 4). As far as a monosubstituted ketene silyl acetal, reactions using various types of alkylketene and arylketene silyl acetals gave the desired products in high yields (entries 5-7). The reaction with unsubstituted ketene silyl acetal **2i** resulted in a low yield because **2i** would decompose under these conditions (entry 8). Heteroaryl-substituted ketene silyl acetals **2j** and **2k** worked as effective nucleophiles (entries 9 and 10). *O*- and *S*-substituted ketene silyl acetals **2l** and **2m** were applicable to give moderate yields of the corresponding functionalized α-vinyl esters **3al** and **3am**, respectively (entries 11 and 12).

Table 2. Scope of silyl ketene acetal **2** in coupling reaction of butyl vinyl ether **1a**.[a]



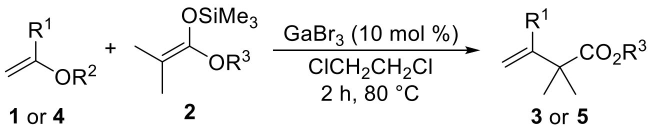
Entry	Silyl Ketene Acetal **2**	Product **3**	Yield [%][b]
1	 **2b**	 **3ab**	92
2	 **2c**	 **3ac**	93
3	 **2d**	 **3ad**	90
4	 **2e**	 **3ae**	81
5	 **2f**	 **3af**	82
6	 **2g**	 **3ag**	43
7	 **2h**	 **3ah**	83
8[c]	 **2i**	 **3ai**	12
9	 **2j**	 **3aj**	80
10	 **2k**	 **3ak**	84

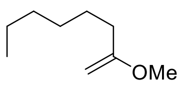
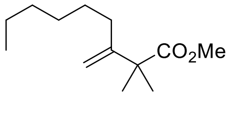
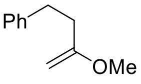
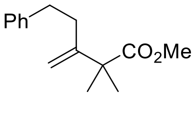
11	 **2l**	 **3al**	44
12	 **2m**	 **3am**	59

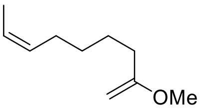
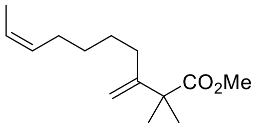
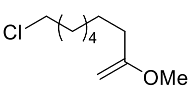
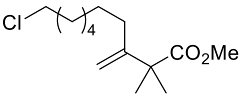
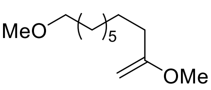
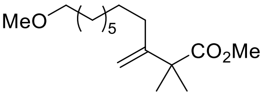
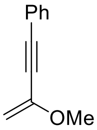
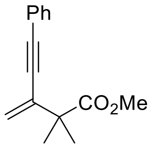
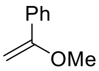
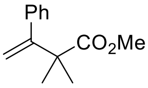
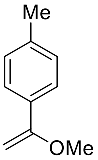
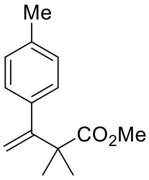
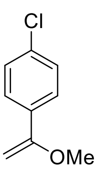
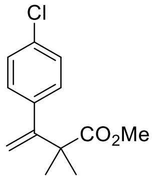
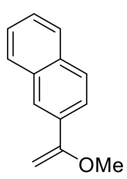
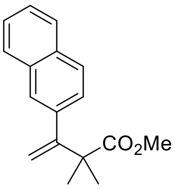
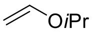
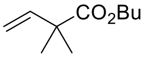
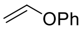
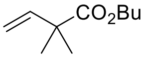
[a] **1a** (1 equiv), **2** (1.5 equiv), $GaBr_3$ (0.1 equiv), $ClCH_2CH_2Cl$, 80 °C, 2 h. [b] Isolated yields. [c] **2** (3 equiv), $GaBr_3$ (0.2 equiv).

Next, we examined the scope of enol ethers, as shown in Table 3. A variety of α-substituted enol ethers **4** were found to be suitable substrates. The reaction of alkyl-substituted enol ethers **4a** and **4b** smoothly occurred to give the desired products **5an** and **5bn** in 77 and 69% yields, respectively (entries 1 and 2). Functional groups such as internal alkene, chloro, and alkoxy moieties tolerated these reaction conditions, and a loading of 30 mol% of $GaCl_3$ rather than $GaBr_3$ effectively accelerated the reactions of substrates **4c**, **4d**, and **4e** to give the corresponding products **5cn**, **5dn**, and **5en**, respectively (entries 3-5).[16] Methoxy enyne **4f** also reacted with ketene silyl acetal to smoothly produce the ester **5fn** with an enyne moiety in 73% yield (entry 6). Aryl-substituted enol ethers **4g**, **4h**, **4i**, and **4j** were applicable to the coupling reaction, although the yields were moderate (entries 7-10). The isopropyl vinyl ether **1b** as well as the butyl vinyl ether **1a** were applicable to this reaction system, though the yield was moderate (entry 11). In contrast, the phenyl vinyl ether **1c** gave a high yield in spite of the steric hindrance of **1c** that was similar to that of isopropyl vinyl ether **1b** (entry 12).[17] Therefore, the leaving ability of an alkoxy group influenced the reaction rate.

Table 3. Scope of enol ethers in coupling reaction with silyl ketene acetal **2**.[a]



Entry	Enol Ether **1** or **4**	Product **3** or **5**	Yield (%)[b]
1[c]	 **4a**	 **5an**	77
2[c]	 **4b**	 **5bn**	69

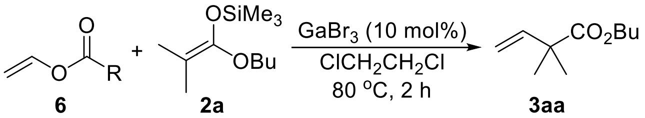
3[d]	 **4c**	 **5cn**	30
4[d]	 **4d**	 **5dn**	72
5[d]	 **4e**	 **5en**	56
6	 **4f**	 **5fn**	73
7	 **4g**	 **5gn**	43
8	 **4h**	 **5hn**	43
9	 **4i**	 **5in**	61
10	 **4j**	 **5jn**	59
11[e]	 **1b**	 **3aa**	50[f]
12[e]	 **1c**	 **3aa**	98[f]

[a] **1** or **4** (1 equiv), **2n** (1.5 equiv), $GaBr_3$ (0.1 equiv), $ClCH_2CH_2Cl$ (0.5 M), 2 h, 80 ºC. [b] Isolated yields. [c] Reaction time 12 h. [d] $GaCl_3$ (30 mol%), **2n** (3 equiv). [e] **2a** (1.5 equiv). [f] Yields were determined by GC.

Coupling of Vinyl Carboxylates with Silyl Ketene Acetals

Vinyl carboxylates as well as enol ethers are very valuable as alkenylation reagents because they are more stable and easier to handle than enol ethers.[4] We investigated the coupling reaction of various vinyl carboxylates **6** with silyl ketene acetal **2a** (Table 4). The reaction of vinyl acetate **6a** with silyl ketene acetal **2a** at 80 °C in the presence of $GaBr_3$ catalyst gave the coupling product **3aa** in 29% yield (entry 1). Vinyl 2-ethylhexanoate **6b**, vinyl pivalate **6c**, and vinyl benzoate **6d**, which possess the steric hindrance of a carboxylate moiety, afforded high yields (entries 2-4). The low yield shown in entry 1 can likely be ascribed to Claisen condensation between vinyl acetate **6a** and silyl ketene acetal **2a**.[18]

Table 4. $GaBr_3$-Catalyzed coupling reaction of vinyl carboxylate **6** with silyl ketene acetal **2a**.[a]

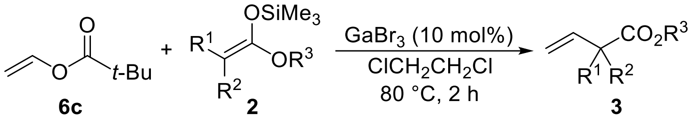


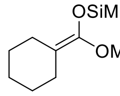
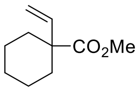
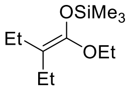
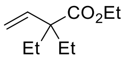
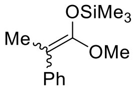
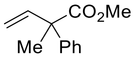
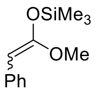
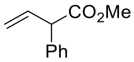
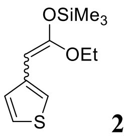
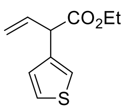
Entry	R		Yield of **3aa** [%][b]
1	Me	**6a**	29
2	CH(Et)Bu	**6b**	84
3	*t*Bu	**6c**	80
4	Ph	**6d**	74

[a] **6** (1 equiv), **2a** (1.5 equiv), $GaBr_3$ (0.1 equiv), $ClCH_2CH_2Cl$ (0.5 M), 80 °C, 2 h. [b] Yields were determined by ^1H NMR.

The scope of silyl ketene acetals **2** was surveyed in the reaction of vinyl pivalate **6c** (Table 5). Dialkylketene silyl acetals **2d** and **2c** were applicable to the coupling reaction of vinyl pivalate **6c** while bulky diethylketene silyl acetal **2c** gave only 22% yield (entries 1 and 2). The reaction using phenyl-substituted ketene silyl acetals **2e** and **2h** afforded the corresponding products in moderated yields (entries 3 and 4). Thiophenyl-substituted ketene silyl acetal **2j** also underwent cross coupling to give a high yield (entry 5). On the whole, the yields of the reaction using vinyl carboxylate **6** were slightly lower than those of the reaction using vinyl ether **1**. Therefore, vinyl carboxylate **6** had lower reactivity than vinyl ether **1** in the present coupling reaction, although the yields were satisfactory.

Table 5. Scope of silyl ketene acetal **2** in reaction of vinyl pivalate **6c**.[a]



Entry	Silyl Ketene Acetal **2**	Product **3**	Yield (%)[b]
1	 **2d**	 **3ad**	79
2	 **2c**	 **3ac**	22
3	 **2e**	 **3ae**	51
4	 **2h**	 **3ha**	63
5	 **2j**	 **3ja**	83

[a] **6c** (1 equiv), **2** (1.5 equiv), $GaBr_3$ (0.1 equiv), $ClCH_2CH_2Cl$ (0.5 M), 80 °C, 2 h. [b] Yields were determined by ^1H NMR.

Monitoring of Coupling Reaction between Vinyl Ether and Silyl Ketene Acetal

To reveal the reaction mechanism, we monitored the coupling reaction of vinyl ether **1** with silyl ketene acetal **2** via NMR spectroscopy. When conducting the coupling reaction among vinyl ether **1d**, the silyl ketene acetal **2n**, and $GaBr_3$ at room temperature, the alkylgallium intermediate **7**, coupling product **3dn**, and Me_3SiBr were observed via ^1H NMR after 5 min (Figure 1).[19] The methoxy signal of intermediate **7** appeared at 4.03 ppm (0.37 ppm downfield shift in comparison with that of coupling product **3dn**). This result indicated the intramolecular coordination of a carbonyl group to gallium to form a six-membered ring.[20] Vinyl ether **1d** was consumed after 25 min, and then the intermediate **7** was transformed into the coupling product **3dn** after 70 min. To avoid an overlapping of the signals in the spectrum, the reaction of phenyl vinyl ether **1c** with deuterated silyl ketene acetal **2o** was conducted (Scheme 4). Alkylgallium intermediate **8** was successfully observed without the corresponding coupling product under low-temperature conditions.[21] This result suggested that the elimination from the alkylgallium intermediate **8** to give the coupling product was slower than the carbogallation. Coupling constant values, ^{2}J (H^{1a}-H^{1e}) = 14 Hz, ^{3}J (H^{1a}-H^{2}) = 3 Hz, and ^{3}J (H^{1e}-H^{2}) = 4 Hz, of alkylgallium **8** clearly show that the PhO group occupies the axial position in the chair-like six-membered ring due to anomeric effect.[22,23] In contrast to vinyl ether **1**, the intermediate from vinyl carboxylate **6c** was not observed even at low temperature and only starting materials and the coupling product were confirmed.

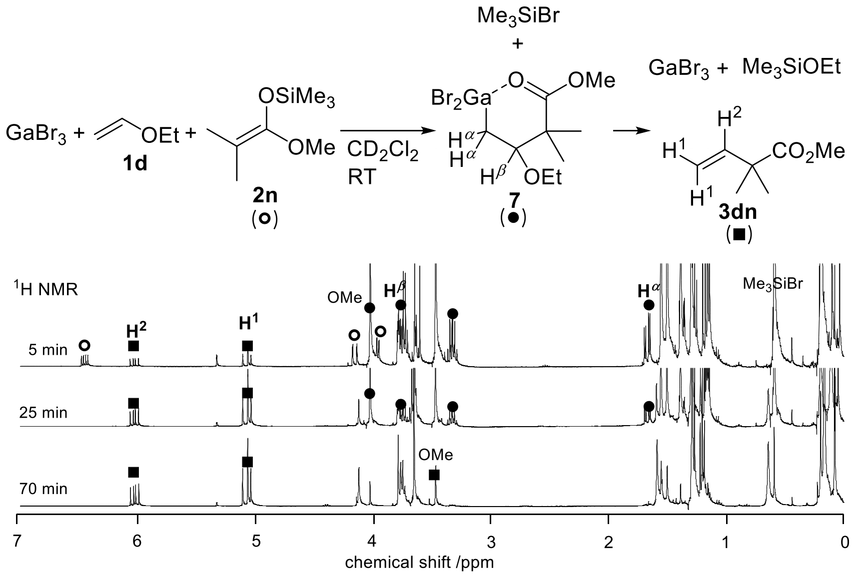
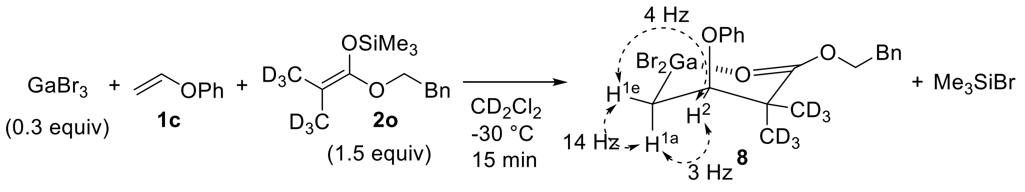


Figure 1. Monitoring of the coupling reaction of vinyl ether **1d** with silyl ketene acetal **2n** in the presence of $GaBr_3$ by ^{1}H NMR. $GaBr_3$ (0.5 equiv), **1d** (1 equiv), **2n** (1.5 equiv), CD_2Cl_2, room temperature.



Scheme 4. Observation of alkylgallium intermediate **8** in the reaction of vinyl ether **1c** with deuterated silyl ketene acetal **2o** by ^{1}H NMR.

Mechanistic Studies on Coupling Reaction of Enol Derivatives with Silyl Ketene Acetal

Kinetic studies were carried out to gain insight into the turnover-limiting step of the $GaBr_3$-catalyzed coupling reaction of vinyl ether **1** with silyl ketene acetal **2**. We investigated the dependence of the initial rate of the $GaBr_3$-catalyzed coupling reaction of vinyl ether **1a** with silyl ketene acetal **2a** in dichloroethane at 30 °C on the varied concentrations of each reagent (Figure 2). The plots of the initial rates vs. the concentrations of $GaBr_3$, vinyl ether **1a**, and ketene silyl acetal **2a** are shown in Figure 2.

The kinetic analysis shows that this coupling reaction was of the zeroth order for vinyl ether **1a** and silyl ketene acetal **2a**, and was of the first order for $GaBr_3$ (rate = $k_{obs}[GaBr_3]$). Next, we performed kinetic studies for the $GaBr_3$-catalyzed coupling between vinyl pivalate **6c** and silyl ketene acetal **2a**, and the results are shown in Figure 3. In contrast to vinyl ether **1a**, a coupling reaction using vinyl pivalate **6c** was of the first order for vinyl pivalate **6c** and the $GaBr_3$ catalyst, and was of the zeroth order for silyl ketene acetal (rate = $k_{obs}[GaBr_3]$[**6c**]). Therefore, the leaving group had a significant effect on the turnover-limiting step.

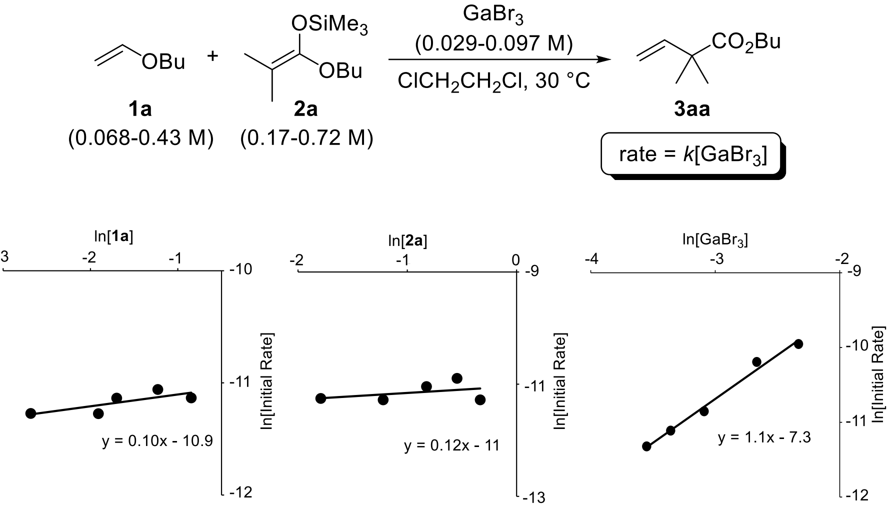


Figure 2. Initial rate kinetics of $GaBr_3$-catalyzed coupling reaction of butyl vinyl ether **1a** with silyl ketene acetal **2a**.

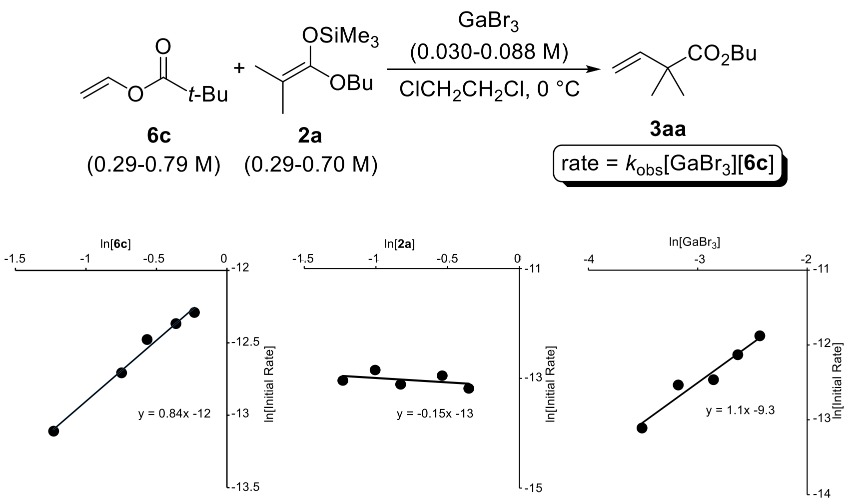
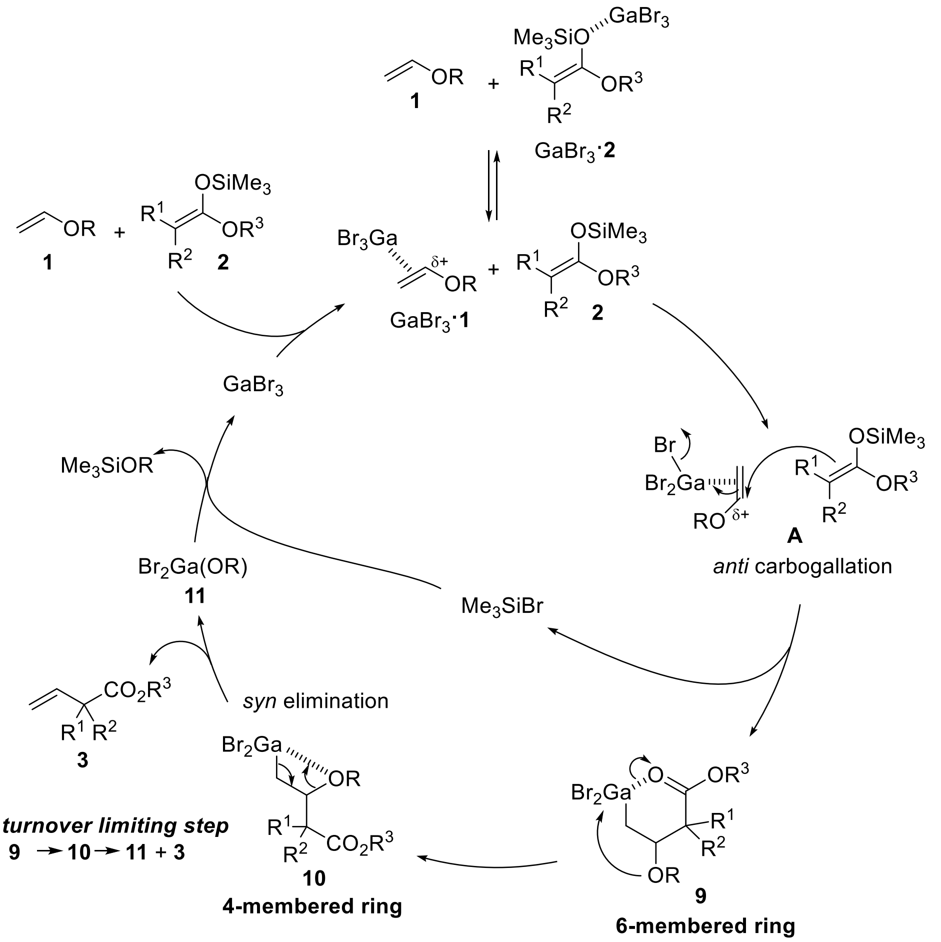


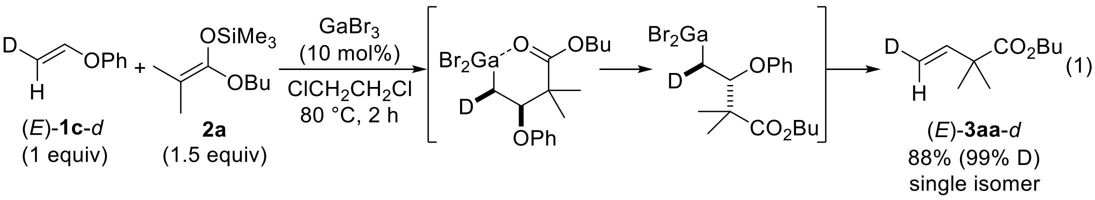
Figure 3. Initial rate kinetics of $GaBr_3$-catalyzed coupling reaction of vinyl pivalate **6c** with ketene silyl acetal **2a**.

A plausible mechanism for the coupling reaction using vinyl ether **1** based on the kinetic studies and a confirmation of the alkylgallium intermediate is illustrated in Scheme 5.[24] $GaBr_3$ is coordinated by not only vinyl ether **1** but also silyl ketene acetal **2** so that the equilibrium between the $GaBr_3$-vinyl ether complex ($GaBr_3 \cdot$**1**) and the $GaBr_3$-ketene silyl acetal complex ($GaBr_3 \cdot$**2**) should be considered. The interaction between $GaBr_3$ and the olefin moiety of vinyl ether **1** increases the positive charge at the *α*-carbon of oxygen. The positive charge is stabilized by the OR group. The nucleophilic attack of silyl ketene acetal **2** regioselectively occurs in an *anti*-addition fashion (**A**) to provide *β*-oxyalkylgallium intermediate **9** and Me_3SiBr. The gallium atom is coordinated by the intramolecular carbonyl oxygen to form a six-membered ring. The OR group coordinates to gallium to kick out the ester moiety, and then *syn*-elimination (**10**) between $GaBr_2$ and the OR group proceeds to give the coupling product **3**.[25] Finally, the transmetalation of $Br_2Ga(OR)$ **11** with Me_3SiBr regenerates the $GaBr_3$ catalyst. Recently, we reported that carbogallation, carboindation, and carbobismuthination of alkenes/alkynes using silyl ketene acetals proceeded in an *anti*-addition manner.[13,14,15] In the *D*-labeled experiment, the *E*-isomer of deuterated phenyl vinyl ether **1c**-*d* reacted with **2a** to exclusively furnish *E*-isomer product **3aa**-*d* with the retention of its stereochemical configuration (Eq. 1). This result suggests that the coupling reaction using vinyl ether **1** occurs stereospecifically. Therefore, the proposed *anti*-addition/*syn*-elimination is supported by our reported carbometalations and the *D*-labeled experiment. The elimination process (**9** → **10** → **3** and **11**) is a turnover-limiting step because of the dependence of the reaction rate on only the concentration of $GaBr_3$ (rate = $k_{obs}[GaBr_3]$) (Figure 2), which was also shown by observation of the alkylgallium intermediate **9** (Figure 1 and Scheme 4).[26]

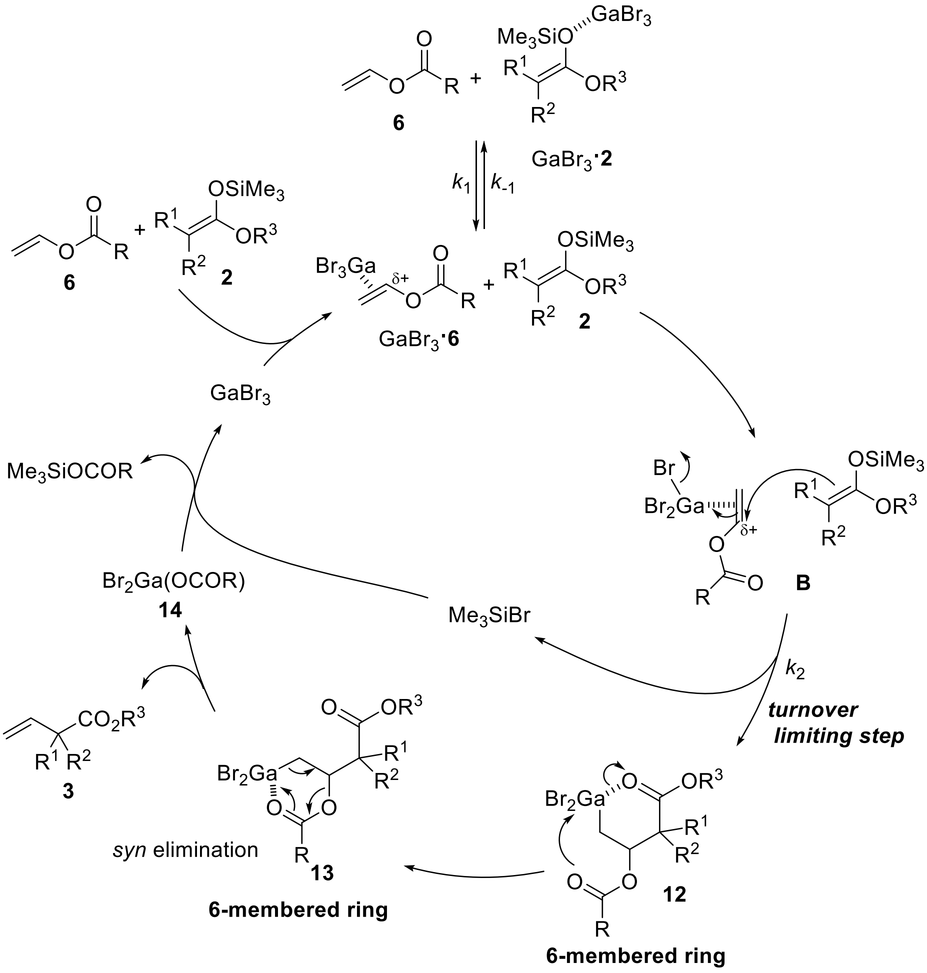
The coupling reaction of vinyl carboxylate **6** would also proceed via the *anti*-carbogallation/*syn*-elimination mechanism illustrated in Scheme 6. The mechanism of vinyl carboxylate **6** significantly differs from that of vinyl ether **1** in that the *syn*-elimination occurs via the six-membered ring intermediate **14** including the coordination to gallium of the carbonyl oxygen of the leaving group. The turnover-limiting step is either the coordination of vinyl carboxylate **6** to $GaBr_3$ or the carbogallation because the rate equation is presented by $k_{obs}[GaBr_3]$[**6**] (Figure 3) and alkylgallium intermediates **12** and **13** could not be observed in monitoring the coupling reaction via NMR spectroscopy. Bulky silyl ketene acetals such as diethyl-, methylphenyl-, and phenylsubstituted ones (**2c**, **2e**, and **2h**) had lower reactivities than dimethylsubstituted one **2a** (entry 3 in Table 4, and entries 2, 3, and 4 in Table 5), suggesting that silyl ketene acetal **2** participates in the turnover-limiting step. Therefore, we assumed that silyl ketene acetal **2** has the inhibition effect via the coordination to $GaBr_3$ ($GaBr_3$•**6** + **2** → **6** + $GaBr_3$•**2**), and that carbogallation among $GaBr_3$, vinyl carboxylate **6**, and silyl ketene acetal **2** is the turnover limiting step. Actually, the experimental rate equation, rate = $k_{obs}[GaBr_3]$[**6**] is consistent with the theoretical rate equation, rate = $k_1k_2k_{-1}^{-1}[GaBr_3]$[**6**].[27] In contrast to vinyl ether **1**, the conformational change from the six-membered ring of intermediate **12** to the six-membered ring of intermediate **13** and β-elimination via a six-membered cyclic transition state would easily occur. On the other hand, the diminished stabilization effect of a positive charge by the carboxylate group slowed the carbogallation step. Therefore, the turnover-limiting step in the coupling reaction of vinyl carboxylate **6** was different from that of vinyl ether **1**.



Scheme 5. Plausible mechanism for coupling of vinyl ether **1** with silyl ketene acetal **2**.



(1)



Scheme 6. Plausible mechanism for coupling of vinyl carboxylate **6** with silyl ketene acetal **2**.

Investigation of Elimination Process in Coupling Reaction of Vinyl Ether 1

The conformational change (**9** → **10**) in the turnover-limiting step of the coupling reaction of vinyl ether **1** (Scheme 5) seemed unlikely to occur because the stable six-membered ring structure via the coordination of the carbonyl group to gallium transforms into a strained four-membered ring structure. Therefore, we investigated our proposed elimination process (**9** → **10** → **3** + **11**) via theoretical calculation to verify the possibility of this conformational change and to consider the influence of conformational change and *syn*-elimination (**10** → **3** + **11**) on the turnover-limiting step. Figure 4 shows the potential energy profile of the elimination process from alkylgallium intermediate **9a** which is afforded by the reaction of butyl vinyl ether **1a** with silyl ketene acetal **2n**. In the conformational change from the stable six-membered ring structure of **9a** to the strained four-membered ring structure of **10a**, the dissociation of the carbonyl group and the association of the alkoxy group occur in concert (**TS9a**). As expected, the four-membered ring structure of **10a** is less stable than the six-membered ring structure of **9a**. The activation energy of the path from **9a** is 14.3 kcal/mol, which supports the possibility of this conformational change. The elimination pathway from the four-membered ring structure of **10a** to **17a** via transition state **TS10a** is exothermic and requires activation energies of 13.6 kcal/mol. The important bond lengths (Ga-C^1, Ga-O, C^1-C^2, and C^2-O) of intermediate **10a** and the transition state of **TS10a** are shown in Figure 5. The C^2-O bond is elongated from 1.48 Å to 2.08 Å, and the degree of its length change is larger than that of the other bonds. The Ga-O and C^1-C^2 bonds are shortened. On the other hand, the Ga-C^1 bond distance is only minutely changed. Therefore, the cleavage of the C^2-O bond by the assistance of the gallium is precedent in the elimination step. The overall potential energy surface of the elimination process showed that both the conformational change and the elimination step require a large energy barrier in order to influence the reaction rate. These theoretical results suggested that the moderate Lewis acidity of gallium is important for the conformational change from the stable six-membered ring structure of **9a** to the strained four-membered ring structure of **10a**, and for the *syn*-elimination with the cleavage of the carbon-oxygen bond. If the Lewis acidity was strong, such a flexible conformational change would not occur, and if the Lewis acidity was weak, the carbon-oxygen bond would not be cleaved.

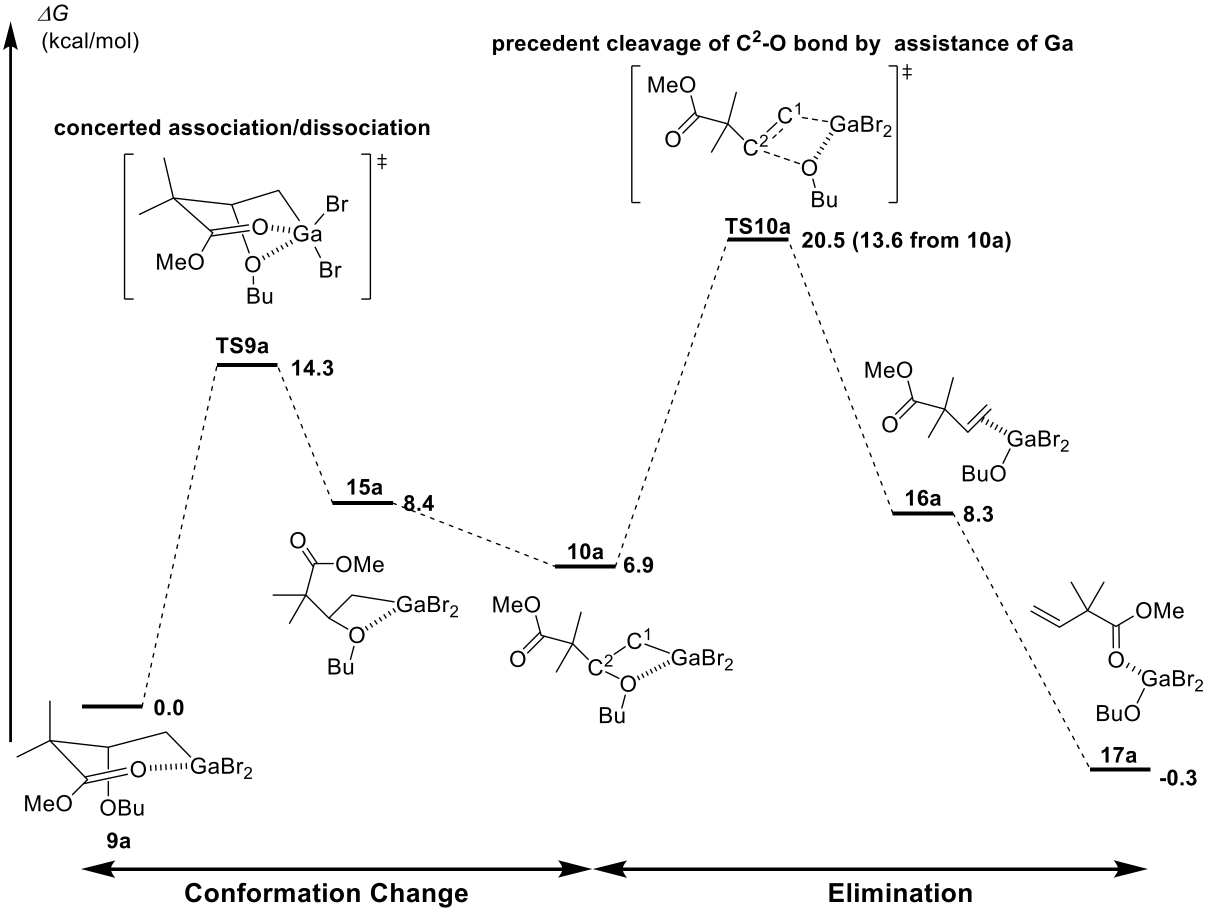


Figure 4. Potential energy profile of the elimination step from **9a** to **17a** in the reaction of vinyl ether **1a** with silyl ketene acetal **2n**.

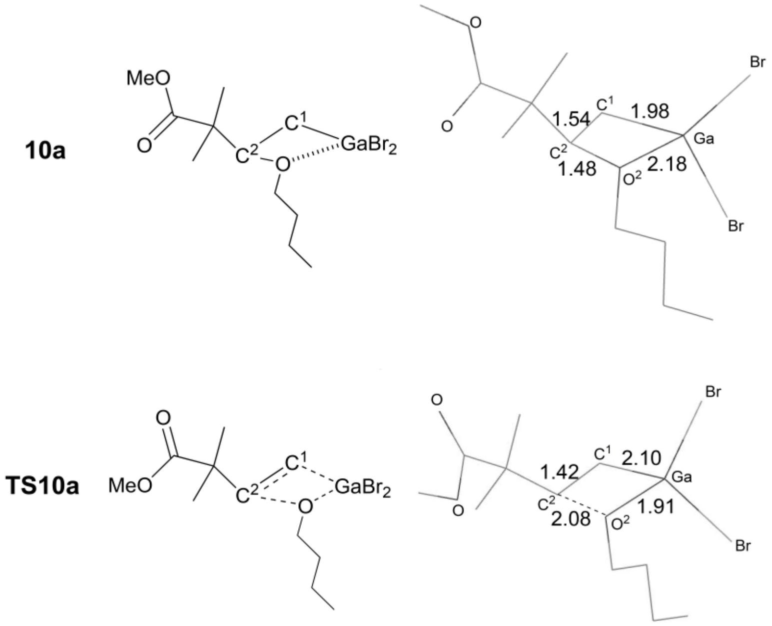
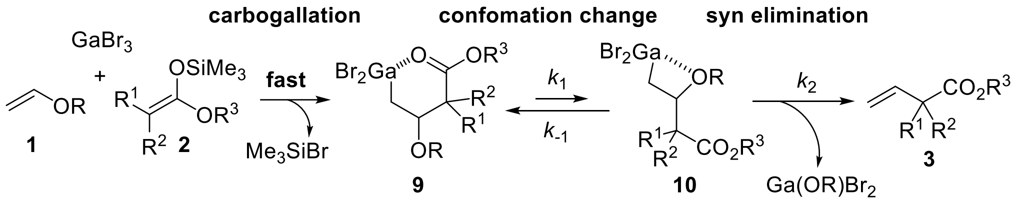


Figure 5. Optimized structures and some bond lengths in intermediate **10a** and transition state **TS10a** (distances in Å).

Next, we considered the rate equation of the coupling reaction between vinyl ether **1** and silyl ketene acetal **2** on the basis of mechanistic studies. Theoretical calculation analysis revealed that the conformational change from a four-membered ring to a six-membered ring (**10** → **9**) proceeds via a much smaller energy barrier than that required for the elimination of GaBr$_2$(OR) so that the elimination process involves an equilibrium between **9** and **10** that lies toward **9** (Eq. 2). Therefore, assuming a steady state for **10** allows the theoretical rate equation of the production of **3** to be expressed as rate = $k_1k_2k_{-1}^{-1}$[GaBr$_3$], which is consistent with the experimental rate equation (Eq. 3).[27] And, the constant term $k_1k_2k_{-1}^{-1}$ suggested that both conformational change and *syn*-elimination steps determine the reaction rate. Using equation 3, we obtained excellent fits with $k_{\text{obs (303 K)}} = 4.2 \times 10^{-4}$ s^{-1} for the production of **3** in the catalytic run using different amounts of GaBr$_3$, as shown in Figure 3. An Arrhenius plot using k_{obs}s at some temperatures experimentally gave an activation energy of 15.6 kcal/mol.[28] This activation energy approximated the computed activation energy (Figure 6), which suggested that the elimination process revealed by theoretical calculation is probable.



(2)

$$\frac{d[\mathbf{3}]}{dt} = \frac{k_1 k_2}{k_{-1}}[\mathrm{GaBr_3}] = k_{\mathrm{obs}}[\mathrm{GaBr_3}] \qquad (3)$$

1-3. Conclusion

We have established a novel coupling reaction of enol derivatives with silyl ketene acetals catalyzed by $GaBr_3$ catalyst. Various types of enol ethers such as vinyl ether **1** and α-substituted enol ether **4** were applicable to this reaction system. Functionalized enol ethers possessing chloro, olefin, and ether moieties afforded the corresponding products smoothly. We successfully demonstrated the wide scope of suitable ketene silyl acetals **2** via the use of those bearing phenoxy, thiophenyl, indolyl, and thiophenyl groups. Vinyl carboxylate **6** as well as vinyl ether **1** were also found to be feasible alkenylating reagents. In this paper, we revealed the details of the reaction mechanism based on the observation of intermediates, kinetic studies, and computational analysis. As for the reaction of vinyl ether **1**, we observed the alkylgallium intermediate of a reaction of vinyl ether **1** with silyl ketene acetal **2** via ^{1}H-NMR spectroscopy, which strongly supported the carbogallation/elimination mechanism. Kinetic studies have shown that the coupling reaction of vinyl ether **1** is on the order of zero for enol ether **1** and silyl ketene acetal **2**, and is of the first order for $GaBr_3$ (rate = $k_{\mathrm{obs}}[\mathrm{GaBr_3}]$) and that the turnover-limiting step is the elimination process. On the other hand, the rate equation of the reaction of vinyl carboxylate **6** can also be represented as rate = $k_{\mathrm{obs}}[\mathrm{GaBr_3}][\mathbf{6}]$, and the turnover-limiting step involved carbogallation. We investigated the details of the β-elimination process in a coupling reaction using vinyl ether **1** via computational analysis in order to show that the moderate Lewis acidity of $GaBr_3$ contributes to the flexible conformational change of the alkylgallium intermediate from a stable six-membered ring to a strained four-membered ring and *syn*-elimination with the C-O bond cleavage.

1-4. Experimental Section

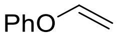
General

New compounds were characterized by ^{1}H and ^{13}C NMR, ^{13}C off-resonance techniques, ^{1}H-^{1}HCOSY, NOE, NOESY, HMQC, HMBC, IR, MS, HRMS, and elemental analysis. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained with TMS as internal standard. IR spectra were recorded as thin films or as solids in KBr pellets. Column chromatography was performed on silica gel (MERK C60 or Fuji Silysia FL100DX). Bulb-to-bulb distillation (Kugelrohr) was accomplished at the oven temperature and pressure indicated. Yields were determined by ^{1}H NMR using internal standards (1,1,2,2-tetrachloroethane or 1,1,1,2-tetrachloroethane). We applied the HF/DFT hybrid method originally proposed by Becke,9 referenced as B3LYP three parameter hybrid functional. All calculations were performed with Gaussian09 rev.C.01 and 6-31+G (d,p) for H, C, O, Br, DGDZVP for Ga were used for basis sets. All molecular geometries were fully optimized and energies were calculated including zero point energy correction by the normal mode analysis for each structure.

Materials

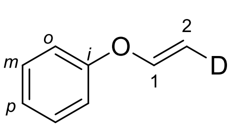
Dehydrated CH_2Cl_2 and dehydrated $ClCH_2CH_2Cl$ were purchased and used as obtained. Enol ethers **1a**, **1b**, **1d**, and **4k** are commercially available. All enol carboxylates are commercially available. Silyl ketene acetal **2n** is commercially available. Synthetic methods and spectral data of enol ethers **1c**, **1c-*d***, **4a**, **4b**, **4f**, **4g**, **4h**, **4i**, **4j**, and silyl ketene actals **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i**, **2j**, **2k**, **2l**, **2o**, and **2p** were reported in our previous communication, and these compounds were re-described. Silyl ketene acetal **2a**, **2m**, and enol ethers **4c**, **4d**, **4e** are new compounds, and synthetic methods and spectral data of these compounds are shown below. All metal salt catalysts are commercially available.

(1c) (vinyloxy)benzene[29]



To a solution of (2-bromoethoxy)benzene (64 mmol, 12.9 g) in DMSO (50 mL) was added the solution of potassium *tert*-butoxide (54 mmol, 6.1 g) in DMSO (30 mL) at 15 ºC. After the reaction mixture was stirred at room temperature for overnight, 1 M HCl (30 mL) was added dropwise at 0 ºC. The mixture was extracted with diethyl ether (10 x 3 mL) and washed with sat. $NaHCO_3$ aq. The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by distillation under reduced pressure to give the product (4.6 g, 59%).

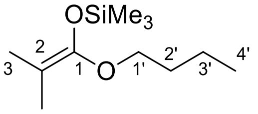
(1c-*d*) (*E*)-2-deuterio-1-phenoxyethylene[30]



To a solution of lithium aluminum hydride (44.5 mmol, 1.7 g) in 60 mL of diglyme, phenoxy-deuterioacetylene (39 mmol, 4.6 g) was added dropwise at 0 °C. After the reaction mixture was stirred for 2 h at 0 °C, water was added dropwise. The mixture was extracted with diethyl ether (10 x 3 mL) and washed with sat. $NaHCO_3$ aq. The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by distillation under reduced pressure to give the product (1.58

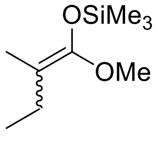
g, 33%). bp: 107 °C/52 mmHg; IR: (neat) 1628 (OC=C) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.36 (dd, *J* = 8.8, 7.2 Hz, 2H, *m*), 7.11 (t, *J* = 7.2 Hz, 1H, *p*), 7.04 (d, *J* = 8.8 Hz, 2H, *o*), 6.68 (d, *J* = 13.8 Hz, 1H, 1-H), 4.79 (d, *J* = 13.8 Hz, 3H, 2-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 156.8 (s, *i*), 148.1 (d, C-1), 129.6 (d, *m*), 123.1 (d, *p*), 117.0 (d, *o*), 94.8 (t, J_{CD} = 24.7 Hz, C-2); MS: (EI, 70 eV) *m/z* 121 (M^+, 100), 92 (69); HRMS: (EI, 70 eV) Calculated (C_8H_7DO) 121.0638 (M^+) Found: 121.0635.

(2a) 1-Butoxy-2-methyl-1-trimethylsiloxy-1-propene



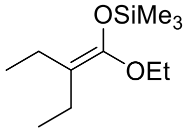
To a solution of diisopropylamine (13.0 g, 129 mmol) in THF (100 mL) was added n-BuLi (80 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at 0 ºC. Then, butyl isobutyrate (17.5 g, 121 mmol) and trimethylsilylchloride (18 mL, 141 mmol) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 30 min at -78 ºC, the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured into cold sat. $NaHCO_3$ aq. and hexane, and the resulted mixture was extracted with hexane. The organic phase was washed with sat. $NaHCO_3$ aq., dried ($MgSO_4$) and concentrated. The obtained crude oil was purified by distillation under the reduced pressure to give the desired product (24.6 g, 94%). bp: 42-47 °C/0.082 mmHg; ^{1}H NMR: (400 MHz, $CDCl_3$) 3.68 (t, *J* = 6.4 Hz, 2H, 1'-H_2), 1.61-1.53 (m, 2H, 2'-H_2), 1.57 (s, 3H), 1.51 (s, 3H), 1.44-1.34 (m, 2H, 3'-H_2), 0.92 (t, *J* = 7.2 Hz, 4'-H_3), 0.19 (s, 9H, $SiMe_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) 148.3 (s, C-1), 91.4 (s, C-2), 68.7 (t, C-1'), 31.6 (t, C-2'), 19.3 (t, C-3'), 16.9 (q), 16.3 (q), 13.9 (q, C-4'), 0.03 (q, $SiMe_3$); MS: (EI, 70 eV) *m/z* 216 (M+, 24), 144 (30), 129 (43), 75 (35), 73 (59), 70 (100); HRMS: (EI, 70 eV) Calculated ($C_{11}H_{24}O_2Si$) 216.1546 (M^+) Found: 216.1549.

(2b) 1-Methoxy-1-trimethylsiloxy-2-methyl-1-butene[31]



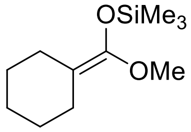
To a solution of diisopropylamine (13.2 g, 120 mmol) in THF (100 mL) was added n-BuLi (75 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, a solution of methyl 2-methylbutanoate (11.3 g, 100 mmol) in THF (20 mL) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2 h at -78 ºC, trimethylsilylchloride (13.0 g, 120 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The obtained crude oil was purified by distillation (bp. 72-76 ºC, 25 mmHg) to give the desired product (8.6 g, 46%).

(2c) 2-Ethyl-1-ethoxy-1-trimethylsiloxy-1-butene[32]



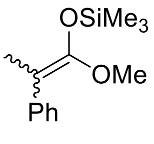
To a solution of diisopropylamine (13.2 g, 120 mmol) in THF (100 mL) was added n-BuLi (75 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, a solution of ethyl 2-ethylbutanoate (14.2 g, 100 mmol) in THF (20 mL) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2h at -78 ºC, trimethylsilylchloride (13.0 g, 120 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The obtained crude oil was purified by distillation (bp. 88-94 ºC, 20 mmHg) to give the desired product (12.4 g, 62%).

(2d) {Cyclohexylidene(methoxy)methoxy}trimethylsilane[33]



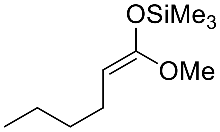
To a solution of diisopropylamine (11.5 g, 110 mmol) in THF (80 mL) was added n-BuLi (63 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, a solution of methyl cyclohexanecarboxyrate (11.4 g, 80 mmol) in THF (30 mL) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2h at -78 ºC, trimethylsilylchloride (10.8 g, 100 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The obtained crude oil was purified by distillation (bp. 100-102 ºC, 20 mmHg) to give the desired product (14.3 g, 83%).

(2e) 1-Methoxy-1-trimethylsiloxy-2-phenylpropene[33]



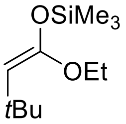
To a solution of diisopropylamine (9.4 g, 93 mmol) in THF (50 mL) was added n-BuLi (59 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, a solution of methyl 2-phenylpropanoate (12.7 g, 78 mmol) in THF (30 mL) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2 h at -78 ºC, trimethylsilylchloride (10.8 g, 100 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The obtained crude oil was purified by distillation (bp. 74 ºC, 1.9 mmHg) to give the desired product (13.2 g, 72%).

(2f) (1-Methoxyhex-1-enyloxy)trimethylsilane[40]



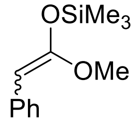
To a solution of diisopropylamine (15.2 g, 150 mmol) in THF (95 mL) was added n-BuLi (86 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, a solution of methyl hexanoate (14.0 g, 100 mmol) in THF (30 mL) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2 h at -78 ºC, trimethylsilylchloride (16.1 g, 150 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The obtained crude oil was purified by distillation (bp. 65-70 ºC, 5 mmHg) to give the desired product (16.4 g, 75%).

(2g) (*E*)-((1-Ethoxy-3,3-dimethylbut-1-en-1-yl)oxy)trimethylsilane[34]



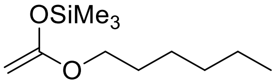
To a solution of diisopropylamine (9.0 g, 90 mmol) in THF (150 mL) was added n-BuLi (56 mL, 90 mmol, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, ethyl 3,3-dimethylbutanoate (10.8 g, 80 mmol) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 1 h at -78 ºC, trimethylsilylchloride (13.5 g, 120 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The obtained crude oil was purified by distillation (1.1 mmHg) to give the desired product (13.4 g, 82%).

(2h) Phenylketene methyl trimethylsilyl acetal[35]



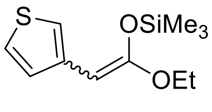
To a solution of diisopropylamine (85 mmol, 8.6 g) in THF (60 mL) was added *n*-BuLi (53 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, a solution of methyl phenylacetate (85 mmol, 12.8 g) in THF (20 mL) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2 h at -78 ºC, chlorotrimethylsilane (213 mmol, 23.1 g) was added to the reaction mixture, and the reaction mixture was stirred for overnight at room temperature. The solvent was evaporated, and pentane (100 mL) was added to the residual mixture. Pentane was evaporated from the filtrate. The obtained crude oil was purified by distillation (bp. 70 ºC, 0.24 mmHg) to give the desired product (15.7 g, 91%).

(2i) ((1-(Hexyloxy)vinyl)oxy)trimethylsilane[36]



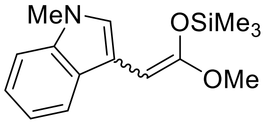
To a solution of diisopropylamine (120 mmol, 12.5 g) in THF (60 mL) was added *n*-BuLi (70 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at 0 ºC. Then, a solution of hexyl acetate (100 mmol, 14.4 g), trimethylsilyl chloride (120 mmol, 12.3 g) in THF (20 mL) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 20 min at -78 ºC, the reaction mixture was stirred for 2 h at room temperature. The solvent was evaporated, and pentane (100 mL) was added to the residual mixture. Pentane was evaporated from the filtrate. The obtained crude oil was purified by distillation to give the desired product (8.9 g).

(2j) ((1-Ethoxy-2-(thiophen-3-yl)vinyl)oxy)trimethylsilane (***E*/*Z*** =50:50)



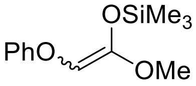
To a solution of diisopropylamine (70 mmol, 7.1 g) in THF (80 mL) was added *n*-BuLi (45 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, ethyl 2-(thiophen-3-yl)acetate (60 mmol, 10.3 g) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2 h at -78 ºC, chlorotrimethylsilane (80 mmol, 8.7 g) was added to the reaction mixture, and the reaction mixture was stirred for overnight at room temperature. The solvent was evaporated, and pentane (100 mL) was added to the residual mixture. Pentane was evaporated from the filtrate. The obtained crude oil was purified by distillation (bp. 70 ºC, 0.2 mmHg) to give the desired product (10.0 g, 69%) including a small amount of the starting ester and some by-product. b.p. 93 ºC/1.6 mmHg; ^{1}H NMR: (400 MHz, $\mathrm{CDCl_3}$) 6.71-6.65 (m, 2H), 6.60-6.57 (m, 2H), 6.47-6.43 (m, 2H), 4.77 (s, 1H, 2-H), 4.68 (s, 1H, 2-H), 3.75 (q, J = 6.8 Hz, 2H, $\mathrm{OC}H_2\mathrm{CH_3}$), 3.57 (q, J = 6.8 Hz, 2H, $\mathrm{OC}H_2\mathrm{CH_3}$), 1.07 (t, J = 6.8 Hz, 3H, $\mathrm{OCH_2C}H_3$), 1.03 (t, J = 6.8 Hz, $\mathrm{OCH_2C}H_3$), 0.03 (s, 9H, $\mathrm{SiMe_3}$), 0.00 (s, 9H, $\mathrm{SiMe_3}$); ^{13}C NMR: (100 MHz, $\mathrm{CDCl_3}$) 156.1 (s, C-1), 153.3 (s, C-1), 140.7 (s, C-3), 140. 0 (s, C-3), 126.11 (d), 126.06 (d), 121.1 (d), 121.0 (d), 120.5 (d), 120.3 (d), 82.4 (d, C-2), 75.3 (d, C-2), 63.7 (t, $\mathrm{O}C\mathrm{H_2CH_3}$), 62.9 (t, $\mathrm{O}C\mathrm{H_2CH_3}$), 14.9 (q, $\mathrm{OCH_2}C\mathrm{H_3}$), 14.3 (t, $\mathrm{OCH_2}C\mathrm{H_3}$), 0.5 (q, $\mathrm{SiMe_3}$), -0.3 (q, $\mathrm{SiMe_3}$); MS: (EI, 70 eV) m/z one isomer 242 (M^+, 30), 124 (100), 73 (51), another isomer 242 (M^+, 31), 124 (100), 73 (49); HRMS: (CI, 200 eV) Calculated ($\mathrm{C_{11}H_{18}O_2SSi}$) 242.0797 (M + 1) Found: one isomer 242.0807, another isomer 242.0805.

(2k) ((1-Methoxy-2-(thiophen-3-yl)vinyl)oxy)trimethylsilane[37]



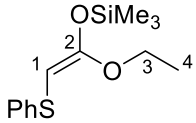
To a solution of diisopropylamine (15 mmol, 1.6 g) in THF (20 mL) was added *n*-BuLi (10 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, methyl 2-(1-methyl-1*H*-indol-3-yl)acetate (12 mmol, 2.5 g) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2 h at -78 ºC, chlorotrimethylsilane (20 mmol, 2.2 g) was added to the reaction mixture, and the reaction mixture was stirred for overnight at room temperature. The solvent was evaporated, and pentane (100 mL) was added to the residual mixture. Pentane was evaporated from the filtrate. The obtained crude oil was purified by distillation (bp. 165-180 ºC, 0.23 mmHg) to give the desired product (3.0 g, 86%) including a small amount of the starting ester and some by-product.

(2l) ((1-Methoxy-2-phenoxyvinyl)oxy)trimethylsilane[38]



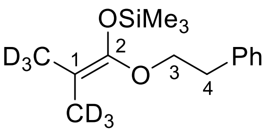
To a solution of diisopropylamine (60 mmol, 6.1 g) in THF (80 mL) was added *n*-BuLi (38 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, methyl 2-phenoxyacetate (50 mmol, 8.1 g) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2 h at -78 ºC, chlorotrimethylsilane (75 mmol, 8.2 g) was added to the reaction mixture, and the reaction mixture was stirred for overnight at room temperature. The solvent was evaporated, and pentane (100 mL) was added to the residual mixture. Pentane was evaporated from the filtrate. The obtained crude oil was purified by distillation (bp. 70 ºC, 0.2 mmHg) to give the desired product (5.7 g, 48%) including a small amount of the starting ester and some by-product.

(2m) ((1-ethoxy-2-(phenylthio)vinyl)oxy)trimethylsilane



To a solution of ${}^{i}Pr_2NH$ (3.57 g, 35.3 mmol) in THF (60 mL) was added n-BuLi (1.6 M in hexane, 22.5 mL, 36 mmol) at 0 °C. After stirring at 0 °C for 5 min, ethyl 2-(phenylthio)acetate (5.80 g, 29.6 mmol) was dropwised to the reaction mixture at -78 °C . The mixture was stirred at -78 °C for 1 h and then Me_3SiCl (5.16 g, 47.5 mmol) was dropwised to the mixture at -78 °C. The solution was stirred at -78 °C for 2 h and then warmed to room temperature. The solvent of the reaction mixture was evaporated and diluted with dry hexane (30 mL). The hexane layer was removed and concentrated by rotary evaporator. The residue was purified by distillation under reduced pressure to give the crude product (5.29g (73 wt%), 49%) including α-silyl ester and starting material, thioester. IR: (neat) 1612 (C=C) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.34-7.02 (m, 5H, Ar), 4.27 (s, 1H, 1-H), 3.95 (q, *J* = 7.3 Hz, 2H, 3-H_2), 1.36 (t, *J* = 7.3 Hz, 3H, 4-H_3), 0.206 (s, 9H, $SiMe_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) 162.9 (s, C-2), 140.4 (s, *i*), 128.4 (d), 125.3 (d), 124.2 (d, *p*), 64.4 (d, C-1), 64.0 (t, C-3), 14.4 (q, C-4), 0.279 (q, $SiMe_3$); MS: (CI, 200 eV) *m/z* 269 (M + 1, 100), 223 (M - OEt, 59), 195 (M - $SiMe_3$, 41); HRMS: (CI, 200 eV) Calculated ($C_{13}H_{21}O_2SSi$) 269.1032 (M + 1) Found: 269.1026.

(2o) Trimethyl((2-(methyl-d_3)-1-phenethoxyprop-1-en-1-yl-3,3,3-d_3)oxy)silane



To a solution of ethyl cyanoacetate (11.3 g, 100 mmol) and K_2CO_3 (55 g, 400 mmol) in anhydrous acetone (150 mL) was added CD_3I (34.2 g, 240 mmol). After the reaction mixture was refluxed for 4 h, the reaction was quenched by water. The aqueous layer was extracted with ether, and the combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated. This crude product, ethyl 2-cyano-2-(methyl-d_3)propanoate-3,3,3-d_3 was not purified further and was carried on directly to the next step.

To a solution of KOH (6.8 g, 120 mmol) in EtOH (250 mL) and H_2O (25 mL) was added ethyl 2-cyano-2-(methyl-d_3)propanoate-3,3,3-d_3. After the reaction mixture was refluxed for 3 h, the reaction was quenched by water. The aqueous layer was acidified by 1 N HCl aq., and was extracted with ether. the combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated to yield 9.0 g, 80 mmol of the crude product. This crude product was not purified further and was carried on directly to the next step.

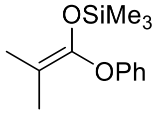
To 12 N HCl aq. (90 mL) was added 2-cyano-2-(methyl-d_3)propanoic-3,3,3-d_3 acid (4.7 g), and then the reaction mixture was heated 120 ºC for 2 h. After the mixture was cooled at 0 ºC, conc. H_2SO_4 (45 mL) was added slowly. The reaction heated at 160 ºC for 20 h. The reaction was poured into cold water (0 ºC), and the aqueous layer was extracted with ether. The combined organic layer was dried over Na_2SO_4 and concentrated to give the crude product, 2-(methyl-d_3)propanoic-3,3,3-d_3 acid. The same reaction using 2.3 g of 2-cyano-2-(methyl-d_3)propanoic-3,3,3-d_3 acid was carried out. The combined crude product (5.6 g) was not purified further and was carried on directly to the next step.

To a solution of 2-(methyl-d_3)propanoic-3,3,3-d_3 acid (5.6 g) and K_2CO_3 (15.3 g, 110 mmol) in DMF (150 mL) was added 2-bromoethylbenzene (16.6 g, 90 mmol). The reaction mixture was stirred at room temperature for 38 h. The mixture was poured into water, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine, dried over MgSO4, concentrated, and purified by column chromatography to give the product, phenethyl 2-(methyl-d_3)propanoate-3,3,3-d_3 (8.1 g, 41 mmol). Total yield from ethyl cyanoacetate was 41%.

^{1}H NMR (400 Mz, $CDCl_3$) 7.33-7.21 (m, 5H), 4.28 (t, J = 6.5 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H), 2.49 (s, 1H), ^{13}C NMR (100 Mz, $CDCl_3$) 176.9, 137.8, 128.8, 128.3, 126.4, 64.6, 35.0, 33.4, 17.9, HRMS: (EI, 70 eV) Calculated ($C_{12}H_{11}D_6O_2$) 199.1605 (M^+) Found: 199.1605.

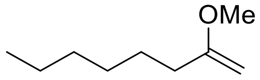
To a solution of $^{i}Pr_2NH$ (1.35 g, 13.3 mmol) in THF (10 mL) was added n-BuLi (1.6 M in hexane, 7.5 mL, 12.0 mmol) at 0 °C. After stirring at 0 °C for 5 min, phenethyl 2-(methyl-d_3)propanoate-3,3,3-d_3 (2.07 g, 10.4 mmol) was dropwised to the reaction mixture at -78 °C . The mixture was stirred at -78 °C for 55 min and then Me_3SiCl (1.18 g, 10.9 mmol) was dropwised to the mixture at -78 °C. The solution was stirred at -78 °C for 35 min and then warmed to rt. The solvent of the reaction mixture was evaporated and diluted with diethyl ether (20 mL). This solution was washed by saturated $NaHCO_3$ aq. (30 mL x 3) and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by distillation under reduced pressure to give the product (1.69 g, 60%). bp: 120 °C /0.15 mmHg; IR: (neat) 1697 (C=C) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.26-7.13 (m, 5H, Ar), 3.89 (t, J = 7.2, 2H, 3-H_2), 2.88 (t, J = 7.2 Hz, 2H, 4-H_2), 0.15 (s, 9H, $SiMe_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) 148.0 (s, C-2), 138.4 (s, *i*), 128.9 (d), 128.3 (d), 126.1 (d, *p*), 91.3 (s, C-1), 69.3 (t, C-3), 35.9 (t, C-4), 16.0 (septet, $J^{1}_{C\text{-}D}$ = 18.0 Hz, 1-CD_3), 15.4 (septet, $J^{1}_{C\text{-}D}$ = 19.7 Hz, 1-CD_3), -0.05 (q, $SiMe_3$) MS: (CI, 200 eV) *m/z* 271 (M + 1, 60), 105 (100); HRMS: (CI, 200 eV) Calculated ($C_{15}H_{19}D_6O_2Si$) 271.2000 (M + 1) Found: 271.1998; Analysis: $C_{15}D_6H_{18}O_2Si$ (270.19) Calculated: C, 66.61; D, 4.47; H, 6.71, Found: C, 66.69; D, 4.62; H, 6.94.

(2p) Trimethyl{(2-methyl-1-phenoxyprop-1-en-1-yl)oxy}silane[39]



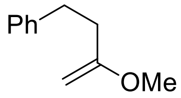
To a solution of diisopropylamine (133 mmol, 13.4 g) in THF (140 mL) was added *n*-BuLi (122 mmol, 76 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, a solution of isobutyric acid phenyl ester (111 mmol, 18.3 g), chlorotrimethylsilane (140 mmol, 15.9 g) and THF (50 mL) was slowly added to the LDA solution at -78 ºC. The reaction mixture was stirred for 1 h at -78 ºC, and for further 8 h at room temperature. The solvent was evaporated, and hexane (100 mL) was added to the residual mixture. Hexane was evaporated from the filtrate. The obtained crude oil was purified by distillation (bp. 70 ºC, 0.2 mmHg) to give the desired product (25.5 g, 97%).

(4a) 2-Methoxyoct-1-ene[40]



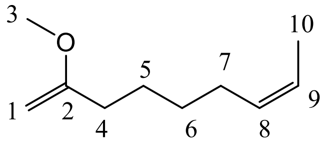
To a solution of 2,2-dimethoxyoctane (6.7 mmol, 1.17 g) in CH_2Cl_2 (40 mL) was added triisobutylaluminum (17 mL, 1 M in toluene) at room temperature. The reaction mixture was stirred at room temperature for 6 h. The reaction was quenched with an excess of 20% aq. trisodium citrate (3 h stirring). The mixture was extracted with diethyl ether (10 x 3 mL) and washed with sat. $NaHCO_3$ aq.. The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.80 g, 84%).

(4b) (3-Methoxybut-3-en-1-yl)benzene[41]



According to the synthetic method for **1d**, this compound was synthesized from (3,3-dimethoxybutyl)benzene (30 mmol). The yield was 77%.

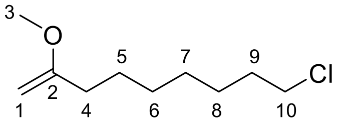
(4c) (*Z*)-2-methoxynona-1,7-diene



To a 100 mL three necked flask filled with THF (20 mL) was added n-BuLi (1.6 M in hexane, 32.5 mL, 50.0 mmol) at 0 °C. The mixture was cooled at -90 °C and then 2-methoxypropene (14.6 g, 202 mmol) was dropwised over 5 min. The solution of ^{t}BuOK (5.69 g, 50.7 mmol) in THF (35 mL) was dropwised into the reaction mixture over 10 min and the mixture was stirred at -75 °C for 30 min. The mixture was stirred at -50 °C for 30 min and then (*Z*)-6-bromohex-2-ene (8.49 g, 52.0 mmol) was dropwised over 5 min. After stirring at -50 °C for 10 min, the reaction mixture was warmed to 0 °C and quenched by water (75 mL). The solution was extracted by diethyl ether (50 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and concentrated under 100 Torr, 50 °C to give the product (6.62 g, 86%).

IR: (neat) 1655 (C=C) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 5.48-5.34 (m, 2H, 8-H and 9-H), 3.85 (s, 2H, 1-H_2), 3.52 (s, 3H, 3-H_3), 2.10 (t, J = 7.3 Hz, 2H, 4-H_2), 2.04 (dt, J = 7.2, 7.3 Hz, 2H, 7-H_2), 1.60 (d, J = 6.3 Hz, 3H, 10-H_3), 1.54-1.46 (m, 2H, 5-H_2), 1.40-1.30 (m, 2H, 6-H_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 164.3 (s, C-2), 130.6 (d), 123.8 (d), 80.1 (t, C-1), 54.7 (q, C-3), 34.8 (t, C-4), 29.0 (t, C-6), 27.0 (C-5, t), 26.6 (C-7, t), 12.7 (q, C-10); MS: (CI, 200 eV) m/z 155 (M + 1, 100); HRMS: (CI, 200 eV) Calculated ($C_{10}H_{19}O$) 155.1436 (M + 1) Found: 155.1438

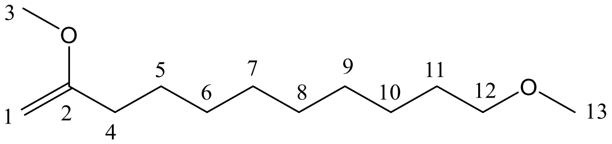
(4d) 9-chloro-2-methoxynon-1-ene



To a 100 mL three necked flask filled with THF (20 mL) was added n-BuLi (1.6 M in hexane, 32.5 mL, 50.0 mmol) at 0 °C. The mixture was cooled at -90 °C and then 2-methoxypropene (15.1 g, 209 mmol) was dropwised over 5 min. The solution of ^{t}BuOK (5.65 g, 50.3 mmol) in THF (35 mL) was dropwised into the reaction mixture over 10 min and the mixture was stirred at -75 °C for 30 min. The mixture was stirred at -50 °C for 30 min and then 1-bromo-6-chlorohexane (10.4 g, 52.2 mmol) was dropwised over 5 min. After stirring at -50 °C for 25 min, the reaction mixture was warmed into 0 °C and the solvent of the mixture was evaporated. The residue was washed by dry hexane (50 mL x 2) and the hexane layer was concentrated. The residue was purified by distillation under reduced pressure to give the product (2.42 g, purify: 80 wt%, 25% yield).

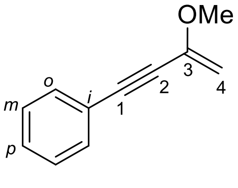
bp: 45 °C /0.09 mmHg; IR: (neat) 1655 (C=C) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$)
3.84 (s, 2H, 1-H_2), 3.56-3.50 (2H, 10-H_2), 3.52 (s, 3H, 1-H_3), 2.08 (t, J = 7.25 Hz, 2H, 4-H_2), 1.83-1.72 (m, 2H, 9-H_2), 1.54-1.38 (m, 4H, 5-H_2 and 8-H_2), 1.38-1.24 (m, 4H, 6-H_2 and 7-H_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 164.3 (s, C-2), 80.0 (t, C-1), 54.6 (q, C-3), 45.1 (t, C-10), 34.8 (t, C-4), 32.6 (t, C-9), 28.9 (t), 28.6 (t), 27.2 (t), 26.7 (t); MS: (EI, 90 eV) m/z 192 (M^+ + 2, 6) 190 (M^+, 17), 155 (M^+ - Cl, 19), 85 (100), 72 (27), 55 (63); HRMS: (EI, 90 eV) Calculated ($C_{10}H_{19}ClO$) 190.1124 (M^+) Found: 190.1123

(4e) 2,11-dimethoxyundec-1-ene



To a 100 mL three necked flask filled with THF (12 mL) was added n-BuLi (1.6 M in hexane, 19 mL, 30 mmol) at 0 °C. The mixture was cooled at -90 °C and then 2-methoxypropene (6.06 g, 84 mmol) was dropwised over 5 min. The solution of ^{t}BuOK (3.37 g, 30.0 mmol) in THF (20 mL) was dropwised into the reaction mixture over 10 min and the mixture was stirred at -75 °C for 30 min. The mixture was stirred at -50 °C for 30 min and then 1-bromo-8-methoxyoctane (4.44 g, 19.9 mmol) was dropwised over 5 min. After stirring at -50 °C for 25 min, the reaction mixture was warmed into 0 °C and the solvent of the mixture was evaporated. The residue was washed by dry hexane (20 mL x 2) and the hexane layer was concentrated. The residue was purified by distillation under reduced pressure to give the product (1.21 g, 61%). bp: 60 °C /0.14 mmHg; IR: (neat) 1655 (C=C) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 3.84 (s, 2H, 1-H$_2$), 3.52 (s, 3H, 3-H$_3$), 3.36 (t, J = 6.8 Hz, 2H, 12-H$_2$), 3.33 (s, 3H, 13-H$_3$), 2.07 (t, J = 7.7 Hz, 2H, 4-H$_2$), 1.60-1.53 (m, 2H, 11-H$_2$), 1.51-1.43 (m, 2H, 5-H$_2$), 1.37-1.20 (m, 10H, 6-H$_2$, 7-H$_2$, 8-H$_2$, 9-H$_2$ and 10-H$_2$); ^{13}C NMR: (100 MHz, CDCl$_3$) 164.4 (s, C-2), 79.9 (t, C-1), 72.9 (t, C-12), 58.5 (q, C-13), 54.6 (q, C-3), 34.9 (t, C-4), 29.6 (t, C-11), 29.5 (t), 29.4 (t), 29.3 (t), 29.1 (t), 27.3 (t, C-5), 26.1 (t); MS: (EI, 90 eV) m/z 214 (M$^+$, 9), 85 (97), 72 (100); HRMS: (EI, 90 eV) Calculated (C$_{13}$H$_{26}$O$_2$) 214.1933 (M$^+$) Found: 214.1933.

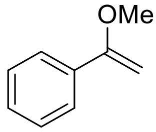
(4f) 3-Methoxy-1-phenyl-3-buten-1-yne



According to the synthetic method for **1f**, benzoic acid (2.5 mmol, 0.31 g), followed by trimethylsilyl chloride (75 mmol, 9.5 mL) was added to 3,3-dimethoxy-1-phenyl-1-butyne (25 mmol, 4.7 g) in pyridine (25 mL). The mixture had been stirred at 70 °C for 3 h, and then, was cooled to 0 °C. Aqueous NaOH (15 %, 60 mL) was added slowly, and the aqueous layer was extracted with ether. Then, the wash with an equal volume of dilute aqueous NaOH removed pyridine. The organic layer was washed with brine and dried (MgSO$_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 100:0, column length 11 cm) and distillation under reduced pressure. (2.7 g, 68%). bp: 120 °C/1.2 mmHg; IR: (neat) 1604 (OC=C) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.52-7.47 (m, 2H, *o*), 7.36-7.30 (m, 3H, *m* and *p*), 4.68 (d, J = 2.4 Hz, 1H, 4-*H*H), 4.58 (d, J =

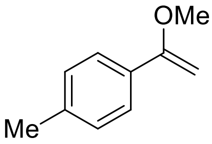
2.4 Hz, 1H, 4-H*H*), 3.65 (s, 3H, OMe); ^{13}C NMR: (100 MHz, $CDCl_3$) 145.2 (s, C-3), 131.7 (d, *o*), 128.7 (d, *p*), 128.3 (d, *m*), 122.0 (s, *i*), 93.0 (t, C-4), 87.4 (s, C-1), 84.6 (s, C-2), 55.4 (q, OMe); MS: (EI, 70 eV) *m/z* 158 (M^+, 83), 128 (M^+ - OMe, 100), 127 (30), 115 (35); HRMS: (EI, 70 eV) Calculated ($C_{11}H_{10}O$) 158.0732 (M^+) Found: 158.0734.

(4g) (1-Methoxyvinyl)benzene[42]



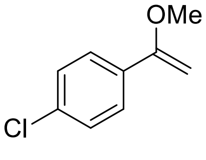
Benzoic acid (3.0 mmol, 0.37 g), followed by trimethylsilyl chloride (90 mmol, 9.7 g) was added to the dimethyl acetal of acetophenone (30 mmol, 4.8 g) in pyridine (30 mL). The mixture had been stirred at 70 °C for 3 h, and then, was cooled to 0 °C. Aqueous NaOH (15%, 60 mL) was added slowly, and the aqueous layer was extracted with ether. Then, the wash with an equal volume of dilute aqueous NaOH removed pyridine. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 100:0, column length 11 cm) (2.5 g, 64%).

(4h) 1-(1-Methoxyvinyl)-4-methylbenzene[43]



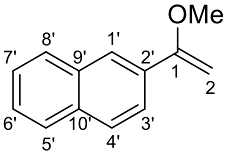
According to the synthetic method for **1f**, benzoic acid (5 mmol, 0.61 g), followed by trimethylsilyl chloride (150 mmol, 15.9 g) was added to the dimethyl acetal of *p*-methyacetophenone (50 mmol, 8.1 g) in pyridine (25 mL). The mixture had been stirred at 70 °C for 3 h, and then, was cooled to 0 °C. Aqueous NaOH (15%, 60 mL) was added slowly, and the aqueous layer was extracted with ether. Then, the wash with an equal volume of dilute aqueous NaOH removed pyridine. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 100:0, column length 11 cm) to give the pure product (3.0 g, 41%).

(4i) 1-Chloro-4-(1-methoxyvinyl)benzene[43]



According to the synthetic method for **1f**, benzoic acid (3.5 mmol, 0.45 g), followed by trimethylsilyl chloride (105 mmol, 11.3 g) was added to the dimethyl acetal of *p*-chloroacetophenone (35 mmol, 7.0 g) in pyridine (30 mL). The mixture had been stirred at 70 °C for 3 h, and then, was cooled to 0 °C. Aqueous NaOH (15%, 60 mL) was added slowly, and the aqueous layer was extracted with ether. Then, the wash with an equal volume of dilute aqueous NaOH removed pyridine. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 100:0, column length 11 cm) (6.7 g, 71%).

(4j) 2-(1-Methoxyethenyl)naphthalene



According to the synthetic method for **1f**, benzoic acid (5.4 mmol, 0.66 g), followed by TMSCl (150 mmol, 16.2 g) was added to the dimethyl acetal of 2-acetonaphthalene (44 mmol, 9.5 g) in pyridine (25 mL). The mixture had been stirred at 70 °C for 3 h, and then, was cooled to 0 °C. Aqueous NaOH (15%, 60 mL) was added slowly, and the aqueous layer was extracted with ether. Then, the wash with an equal volume of dilute aqueous NaOH removed pyridine. The organic layer was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 100:0, column length 11 cm) (4.9 g, 60%). IR: (neat) 1643 (OC=C) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 8.20 (d, *J* = 1.2 Hz, 1H, 1'-H), 7.94-7.81 (m, 2H, 5'-H and 8'-H), 7.84 (d, *J* = 8.8 Hz, 1H, 4'-H), 7.76 (dd, *J* = 8.8, 1.2 Hz, 1H, 3'-H), 7.55-7.47 (m, 2H, 6'-H and 7'-H), 4.86 (d, *J* = 2.8 Hz, 1H, 2-*H*H), 4.37 (d, *J* = 2.8 Hz, 1H, 2-H*H*), 3.85 (s, 3H, OMe); ^{13}C NMR: (100 MHz, $CDCl_3$) 160.6 (s, C-1), 133.5 (s), 133.3 (s), 133.1 (s), 128.5 (d, C-8'), 127.6 (d), 127.5 (d), 126.1 (d), 124.3 (d, C-1'), 123.4 (d, C-3'), 82.4 (t, C-2), 55.3 (q, OMe); MS: (EI, 70 eV) *m/z* 184 (M^+, 100), 183 (71), 154 (33), 153 (51), 152 (28), 141 (63); HRMS: (EI, 70 eV) Calculated ($C_{13}H_{12}O$) 184.0888 (M^+) Found: 184.0885.

Typical Procedure for coupling reaction of enol ether with ketene silyl acetal (Table 1, entry 2)

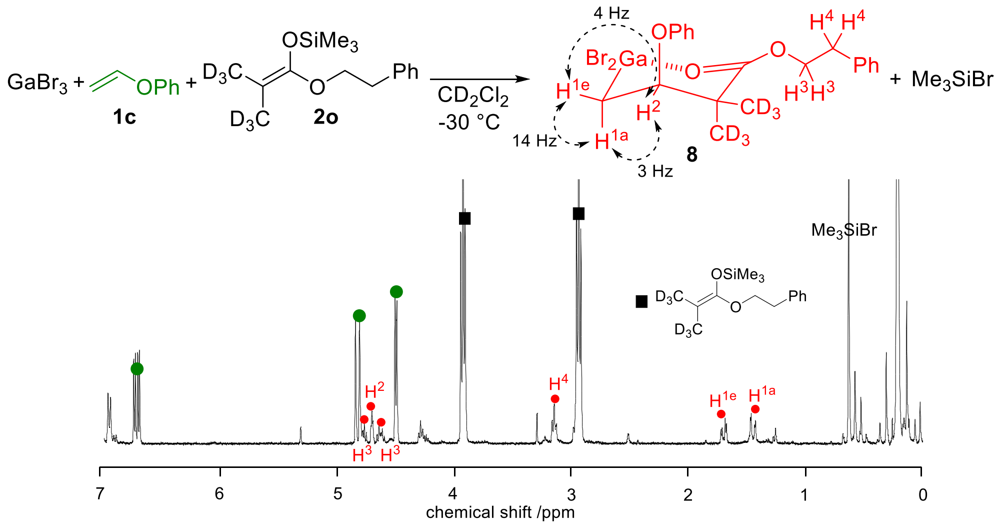
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 6 mL) and ethylmethylketene methyl trimethylsilyl acetal (4.5 mmol, 0.849 g) was added butyl vinyl ether (3.0 mmol, 0.300 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HCl aq. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.391 g, 92%).

Experimental Procedure in the observation of alkylgallium intermediate 7 (Figure 1)

To a solution of dimethylketene trimethylsilyl acetal **2n** (1.5 mmol), $GaBr_3$ (0.5 mmol), and CD_2Cl_2 (1.5 mmol) was added a solution of ethyl vinyl ether **1d** (1 mmol) and CD_2Cl_2 (1 mmol) at -30 ºC. After the reaction mixture was stirred for a few minute, a portion of the reaction mixture was added to NMR tube. And then, the coupling reaction was monitored by 1H NMR at room temperature.

Experimental Procedure in the observation of alkylgallium intermediate 8 (Scheme 4)

A solution of $GaBr_3$ (0.3 mmol), deuterated ketene silyl acetal **2o** (2 mmol) and CD_2Cl_2 (1 mL) was prepared (solution A). Solution A (0.4 mL) was added to NMR tube, and then the tube was cooled to -78 ºC. A solution of vinyl ether **1c** (1 mmol) and CD_2Cl_2 (1 mL) was prepared (solution B). To cooled NMR tube of solution A was added 0.4 mL of solution B. This sample was monitored by 1H NMR at -30 ºC.



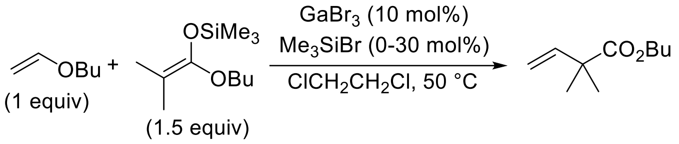
Experimental Procedure in the initial rate kinetics of the coupling reaction of butyl vinyl ether 1a with ketene silyl acetal 2a (Figure 2)

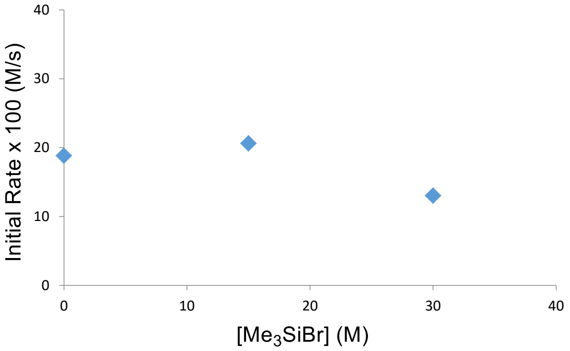
To a solution of $GaBr_3$ (x mmol) and $ClCH_2CH_2Cl$ (1 mL) was added 1 M $ClCH_2CH_2Cl$ solution of silyl ketene acetal **2a** (y mmol, y mL) and dodecane as an internal standard, and then, the resulting solution was stirred at 30 ºC. 1 M $ClCH_2CH_2Cl$ solution of butyl vinyl ether **1a** (z mmol, z mL) was added to the resulting solution. After stirring for indicated period, small amount of reaction mixture was sampled via syringe and poured into ethyl acetate to quench the reaction. The yield was observed by GC.

The effect of injection of Me_3SiBr on the coupling reaction

To a solution of $GaBr_3$ (0.1 mmol) and $ClCH_2CH_2Cl$ (4 mL) was added silyl ketene acetal **2a** (1.5 mmol) and dodecane as an internal standard, and then, the resulting solution was stirred at 50 ºC. Me_3SiBr followed by butyl vinyl ether 1a (1 mmol) was added to the resulting solution. After stirring for indicated period, small amount of reaction mixture was sampled via syringe and poured into ethyl acetate to quench the reaction. The yield was observed by GC.

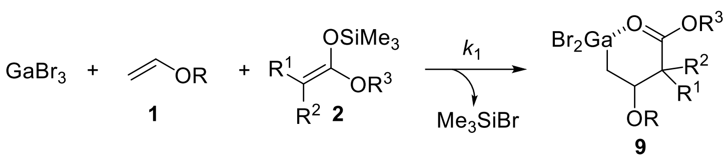
[TMSBr]/ M	[TMSBr]/ mol%	initial rate
0	0	0.000188
0.04083	15	0.000206
0.0822	30	0.000130

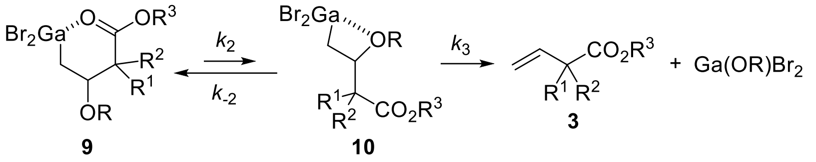




Derivation of rate equation of reaction between vinyl pivalate 6c and silyl ketene acetal 2

Calculations revealed the details of the elimination process (Eq. 2). We derived the rate equation from the results of kinetic studies and calculations. The facts that the carboindation is fast (Eq. 1) and that the elimination process is the turnover-limiting step (Eq. 2), established the inequality, k_2, $k_3 < k_1$ (Eq. 3). Therefore, the concentration of $[GaBr_3]$ is nearly zero under catalytic conditions, $[GaBr_3] << $ [**1**], [**2**] (Eq. 4), and the total amount of gallium species is expressed by equation 5. Assuming a steady-state situation for **7** (Eq. 2 and 6) allows its concentration to be expressed according to equation 7. Substitution of equation 5 into equation 7 furnishes equation 8 relating [**7**] to $[GaBr_3]_0$. Therefore, the reaction rate depends on only the concentration of loaded $GaBr_3$, $[GaBr_3]_0$ (Eq. 9). Considering the relationship, k_2, $k_3 << k_{-2}$, led to by calculations for the elimination process (Eq. 10), the rate equation is represented by equation 11. The first order rate-dependence on the concentrations of loaded $GaBr_3$ is consistent with kinetic studies.


(1)


(2)

$$k_2,\ k_3 << k_1 \tag{3}$$

$$[\mathrm{GaBr_3}] < [\mathbf{1}],\ [\mathbf{2}] \tag{4}$$

$$[\mathrm{GaBr_3}] = [\mathbf{9}] + [\mathbf{10}] \tag{5}$$

$$\frac{d[\mathbf{10}]}{dt} = k_2[\mathbf{9}] - k_{-2}[\mathbf{9}] - k_3[\mathbf{10}] = 0 \tag{6}$$

$$[\mathbf{9}] = \frac{k_{-2} + k_3}{k_2}[\mathbf{10}] \tag{7}$$

$$[\mathbf{10}] = \frac{k_2}{k_2 + k_{-2} + k_3}[\mathrm{GaBr_3}] \tag{8}$$

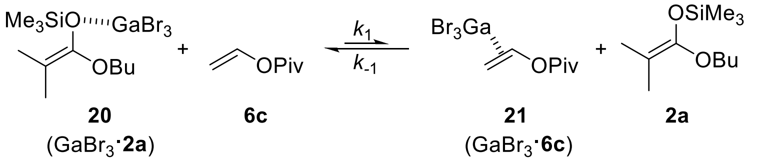
$$rate = \frac{d[\mathbf{3}]}{dt} = k_3[\mathbf{10}] = \frac{k_2 k_3}{k_2 + k_{-2} + k_3}[\mathrm{GaBr_3}] \tag{9}$$

$$k_2,\ k_3 << k_{-2} \tag{10}$$

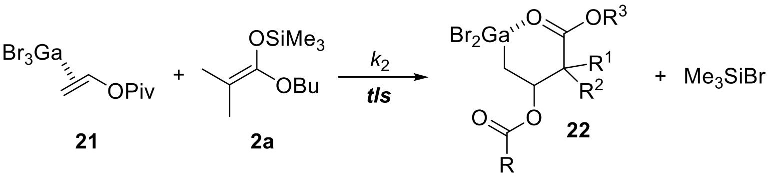
$$rate = \frac{k_2 k_3}{k_{-2}}[\mathrm{GaBr_3}] = k_{\mathrm{obs}}[\mathrm{GaBr_3}] \tag{11}$$

Derivation of rate equation of reaction between vinyl pivalate 6c and silyl ketene acetal 2

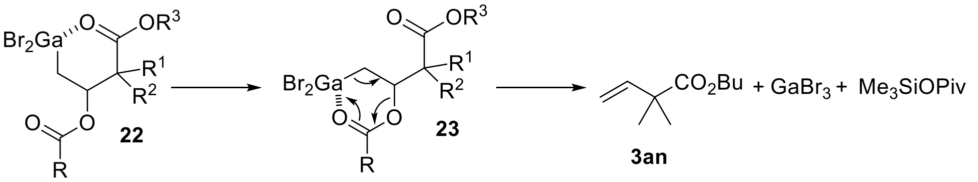
We considered that silyl ketene acetal **2** has the inhibition effect via the coordination to $\mathrm{GaBr_3}$ (Eq. 14) and carbogallation among $\mathrm{GaBr_3}$, **6c**, and **2a** is the turnover limiting step (Eq. 15). Assuming the equilibrium among $\mathrm{GaBr_3}$, **2a**, and **6c** (Eq. 17) leads to the rate equation, Eq. 18, involving the concentrations of **6c** and **20**. The relation among amount of loaded $\mathrm{GaBr_3}$, **20**, and **21** is expressed by Eq. 19. Using Eqs 17 and 19, equation 20 for the concentration of **20** is led. Substitution of equation 20 into rate low (equation 18) furnishes equation 21. The equilibrium among $\mathrm{GaBr_3}$, **2a**, and **6c** (Eq. 14) lies to the left ($K_1 < 1$), which is supported by theoretical calculation (Figure A), so that the approximation 22 is possible. Finally, the rate low depending on $[\mathrm{GaBr_3}]_0$ and [**6c**] is obtained.



(14)



(15)



(16)

$$k_1[\mathbf{6c}][\mathbf{20}] = k_{-1}[\mathbf{21}][\mathbf{2a}] \tag{17}$$

$$\frac{d[\mathbf{22}]}{dt} = k_2[\mathbf{21}][\mathbf{2a}] = K_1k_2[\mathbf{6c}][\mathbf{20}] \quad \left(K_1 = \frac{k_1}{k_{-1}}\right) \tag{18}$$

$$[\mathrm{GaBr_3}] = [\mathbf{20}] + [\mathbf{21}] \tag{19}$$

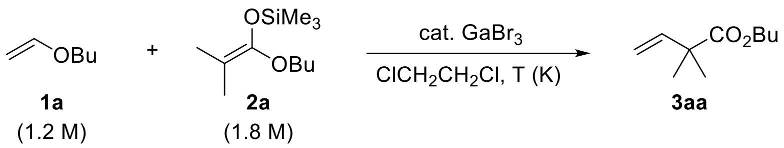
$$[\mathbf{20}] = \frac{[\mathrm{GaBr_3}][\mathbf{2a}]}{[\mathbf{2a}] + K_1[\mathbf{6c}]} \tag{20}$$

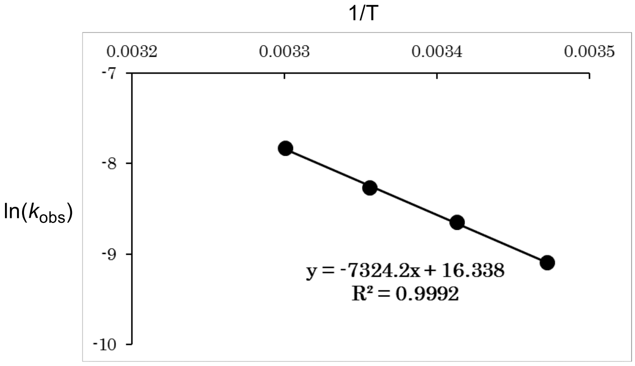
$$\frac{d[\mathbf{22}]}{dt} = \frac{K_1k_2[\mathrm{GaBr_3}][\mathbf{6c}][\mathbf{2a}]}{[\mathbf{2a}] + K_1[\mathbf{6c}]} \tag{21}$$

$$[\mathbf{2a}] + K_1[\mathbf{6c}] \approx [\mathbf{2a}] \quad (K_1 << 1) \tag{22}$$

$$\frac{d[\mathbf{22}]}{dt} = K_1k_2[\mathrm{GaBr_3}][\mathbf{6c}] = k_{\mathrm{obs}}[\mathrm{GaBr_3}][\mathbf{6c}] \tag{23}$$

Arrhenius plot using k_{obs}s of the coupling reaction of vinyl ether 1a with ketene silyl acetal 2a catalyzed $\mathrm{GaBr_3}$



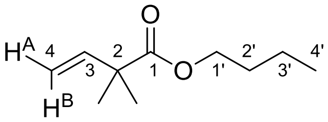


apparent E_{act} =7324.2 x 8.3145/4.183/1000 = 14.6 kcal/mol

Product Data

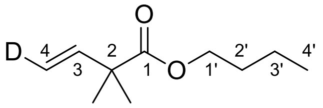
Spectral data of the products **3ab**, **3ac**, **3ad**, **3ae**, **3af**, **3ah**, **3ai**, **5an**, **5gn**, **5hn**, and **5in** were in an excellent agreement with reported data. Spectral data for the products **3aa**, **(*E*)-3aa-*d*,** **3aj**, **3ak**, **5fn**, and **5jn** were described in our previous paper, and were reshown below. Spectral data for the products, **3am**, **5cn**, **5dn**, **5en**, **5kn**, and Phenethyl 2,2-bis(methyl-d$_3$)but-3-enoate which are new compounds, were also shown below.

(3aa) Butyl 2,2-dimethyl-3-butenoate



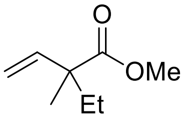
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 6 mL) and dimethylketene butyl trimethylsilyl acetal (4.5 mmol, 0.976 g) was added butyl vinyl ether (3.0 mmol, 0.304 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.457 g, 93%). IR: (neat) 1732 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 6.00 (dd, *J* = 17.6, 10.8 Hz, 1H, 3-H), 5.06 (dd, *J* = 17.6, 1.2 Hz, 1H, 4-H^B), 5.03 (dd, *J* = 10.8, 1.2 Hz, 1H, 4-H^A), 4.04 (t, *J* = 6.6 Hz, 2H, 1'-H_2), 1.63-1.54 (m, 2H, 2'-H_2), 1.41-1.31 (m, 2H, 3'-H_2), 1.27 (s, 6H, 2-Me_2), 0.90 (t, *J* = 7.4 Hz, 3H, 4'-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 176.3 (s, C-1), 142.6 (d, C-3), 112.6 (t, C-4), 64.5 (t, C-1'), 44.8 (s, C-2), 30.6 (t, C-2'), 24.5 (q, 2-Me_2), 19.7 (t, C-3'), 13.6 (q, C-4'); MS: (EI, 70 eV) *m/z* 170 (M^+, 0.72), 69 (M^+ - $CO_2C_4H_9$, 100), 57 (48), 41 (35); HRMS: (EI, 70 eV) Calculated ($C_{10}H_{18}O_2$) 170.1307 (M^+) Found: 170.1299; Analysis: $C_{10}H_{18}O_2$ (170.25) Calcd: C, 70.55; H, 10.66 Found: C, 70.67; H, 10.65.

{(*E*)-3aa-*d*} Butyl (*E*)-4-deuterio-2,2-dimethyl-3-butenoate



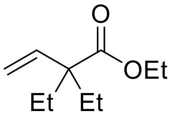
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 2 mL) and dimethylketene butyl trimethylsilyl acetal (1.5 mmol, 0.325 g) was added *trans*-1-deuterio-2-phenoxy ethene (1.0 mmol, 0.116 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) to give the product (0.127 g, 77%). IR: (neat) 1732 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 6.03 (dt, J_{HH} = 17.6 Hz, J_{HD} = 1.4 Hz, 1H, 3-H), 5.07 (d, J = 17.6 Hz, 1H, 4-H), 4.07 (t, J = 6.6 Hz, 2H, 1'-H_2), 1.65-1.56 (m, 2H, 2'-H_2), 1.43-1.34 (m, 2H, 3'-H_2), 1.30 (s, 6H, 2-Me_2), 0.93 (t, J = 7.4 Hz, 3H, 4'-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 176.4 (C-1), 142.6 (C-3), 112.4 (J_{CD} = 24.7 Hz, C-4), 64.6 (C-1'), 44.9 (C-2), 30.6 (C-2'), 24.6 (2-Me_2), 19.1 (C-3'), 13.7 (C-4'); MS: (EI, 70 eV) *m/z* 171 (M^+, 1.62), 70 (M^+ - $CO_2C_4H_9$, 100), 57 (54), 41 (32); HRMS: (EI, 70 eV) Calculated ($C_{10}H_{17}DO_2$) 171.1370 (M^+) Found: 171.1368.

(3ab) Methyl 2-ethyl-2-methyl-3-butenoate[44]



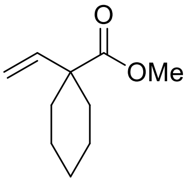
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 6 mL) and ethylmethylketene methyl trimethylsilyl acetal (4.5 mmol, 0.849 g) was added butyl vinyl ether (3.0 mmol, 0.300 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.391 g, 92%). This compound is known, and NMR spectra are shown below.

(3ac) Ethyl 2,2-diethyl -3-butenoate[45]



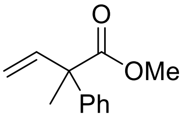
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 6 mL) and diethylketene ethyl trimethylsilyl acetal (4.5 mmol, 0.957 g) was added butyl vinyl ether (3.0 mmol, 0.307 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.391 g, 92%). This compound is known, and NMR spectra are shown below.

(3ad) Methyl 1-vinylcyclohexanecarboxylate[46]



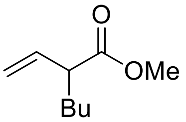
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 6 mL) and ketene methyl trimethylsilyl acetal (4.5 mmol, 0.964 g) was added butyl vinyl ether (3.0 mmol, 0.305 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.461 g, 90%). This compound is known, and NMR spectra are shown below.

(3ae) methyl 2-methyl-2-phenylbut-3-enoate[47]



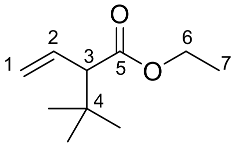
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 2 mL) and ketene methyl trimethylsilyl acetal (1.5 mmol, 0.380 g) was added butyl vinyl ether (1.0 mmol, 0.101 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.156 g, 81%).

(3af) Methyl 2-vinylhexanoate[48]



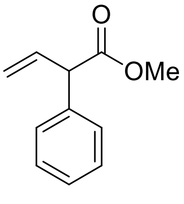
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 6 mL) and butylketene methyl trimethylsilyl acetal (4.5 mmol, 0.900 g) was added butyl vinyl ether (3.0 mmol, 0.302 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.379 g, 82%).

(3ag) ethyl 2-(tert-butyl)but-3-enoate



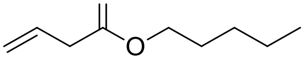
To a solution of $GaBr_3$ (0.0324 g, 0.105 mmol) and *tert*-butylketene ethyl trimethylsilyl acetal (0.321 g, 1.48 mmol) in dichloroethane (2 mL) was added butyl vinyl ether (0.123 g, 1.23 mmol). The mixture was stirred at 80 °C for 2 h and then quenched by diethyl ether (2 mL) and sat.Na_2CO_3 solution (2 mL). The mixture was extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm, diameter 26 mm, Spherical silica gel) to give the product (0.090 g, 43%). IR: (neat) 1734 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 5.94 (dt, J = 16.9, 10.1 Hz, 1H, 2-H), 5.16 (dd, J = 10.1, 1.9 Hz, 1H, 1-H^A), 5.08 (dd, J = 16.9, 1.9 Hz, 1H, 1-H^B), 4.15 (dq, J = 10.6, 7.0 Hz, 1H, 6-H^A), 4.12 (dq, J = 10.6, 7.0 Hz, 1H, 6-H^B), 2.77 (d, J = 10.1 Hz, 1H, 3-H), 1.26 (t, J = 7.0 Hz, 3H, 7-H_3), 0.969 (s, 9H, 4-Me_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 173.1 (s, C-5), 134.2 (d, C-2), 118.3 (t, C-1), 61.0 (d, C-3), 60.0 (t, C-6), 33.6 (s, C-4), 27.6 (q, 4-Me), 14.2 (q, C-7); MS: (CI, 200 eV) *m/z* 171 (M + 1, 100); HRMS: (CI, 200 eV) Calculated ($C_{10}H_{19}O_2$) 171.1385 (M + 1) Found: 171.1383.

(3ah) Methyl 2-phenylbut-3-enoate[49]



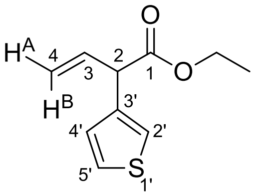
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 2 mL) and phenylketene methyl trimethylsilyl acetal (1.5 mmol, 0.338 g) was added butyl vinyl ether (1.0 mmol, 0.102 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.148 g, 83%).

(3ai) Pentyl but-3-enoate[50]



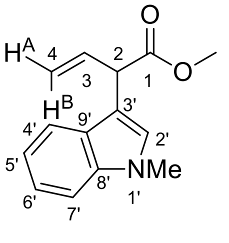
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 6 mL) and phenylketene methyl trimethylsilyl acetal (9.0 mmol, 1.96 g) was added butyl vinyl ether (3.0 mmol, 0.305 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.0621 g, 12%).

(3aj) Ethyl 2-(3-thiophenyl)-3-butenoate



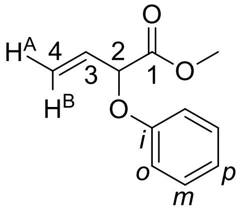
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 2 mL) and 1-ethoxy-2-(3-thiophenyl)-1-(trimethylsiloxy)ethene (1.5 mmol, 0.364 g) was added butyl vinyl ether (1.0 mmol, 0.104 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.151 g, 80%). IR: (neat) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.25-7.22 (m, 1H, 5'-H), 6.99-6.94 (m, 2H, 2'-H and 4'-H), 6.19 (ddd, J = 17.6, 10.0, 8.8 Hz, 1H, 3-H), 5.25 (d, J = 10.0 Hz, 1H, 4-H^A), 5.24 (d, J = 17.6, 1H, 4-H^B), 4.57 (d, J = 8.8 Hz, 1H, 2-H), 4.21 (q, J = 7.2 Hz, 2H, CH_2CH_3), 1.28 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.2 (s, C-1), 140.0 (s, C-3'), 135.1 (d, C-3), 126.7 (d), 125.3 (d), 124.9 (d, C-5'), 117.8 (t, C-4), 61.3 (t, CH_2CH_3), 51.0 (d, C-2), 14.0 (q, CH_2CH_3); MS: (EI, 70 eV) *m/z* 196 (M$^+$, 26), 123 (M$^+$ - $CO_2CH_2CH_3$, 100); HRMS: (EI, 70 eV) Calculated ($C_{10}H_{12}O_2S$) 196.0558 (M$^+$) Found: 196.0562.

(3ak) Methyl 2-(*N*-methylindol-3-yl)-3-butenoate



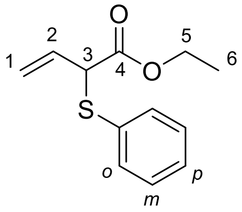
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 2 mL) and *N*-methyl-3-indolylketene methyl trimethylsilyl acetal (1.5 mmol, 0.407 g) was added butyl vinyl ether (1.0 mmol, 0.098 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.189 g, 84%). IR: (neat) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.71 (d, *J* = 8.2 Hz, 1H, 4'-H), 7.35 (t, *J* = 8.2 Hz, 1H, 7'-H), 7.30 (d, *J* = 8.2 Hz, 1H, 6'-H), 7.20 (t, *J* = 8.2 Hz, 1H, 5'-H), 7.10 (s, 1H, 2'-H), 6.28 (ddd, *J* = 17.2, 10.0, 7.8 Hz, 1H, 3-H), 5.23 (dt, *J* = 17.2, 1.2 Hz, 1H, 4-H^B), 5.21 (dt, *J* = 10.0, 1.2 Hz, 1H, 4-H^A), 4.61 (dd, *J* = 7.8, 1.2 Hz, 1H, 2-H), 3.77 (s, 3H), 3.72 (s, 3H); ^{13}C NMR: (100 MHz, CDCl$_3$) 173.2 (s, C-1), 136.9 (s, C-8'), 135.3 (d, C-3), 126.9 (d, C-2'), 126.5 (s, C-9'), 121.7 (d, C-6), 119.13 (d), 119.10 (d), 116.8 (t, C-4), 110.8 (s, C-3'), 109.3 (d, C-7'), 52.0 (q, OMe), 47.1 (d, C-2), 32.6 (q, NMe); MS: (EI, 70 eV) *m/z* 229 (M$^+$, 35), 170 (M$^+$ - CO$_2$Me, 100); HRMS: (EI, 70 eV) Calculated (C$_{14}$H$_{15}$NO$_2$) 229.1103 (M$^+$) Found: 229.1103.

(3al) Methyl 2-phenoxy-3-butenoate



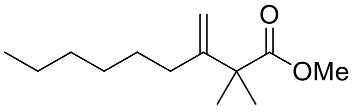
To a solution of GaBr$_3$ (0.05 M in dichloroethane, 2 mL) and phenoxyketene methyl trimethylsilyl acetal (1.5 mmol, 0.349 g) was added butyl vinyl ether (1.0 mmol, 0.102 g). The mixture was stirred at 80 °C for 2 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried (MgSO$_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.085 g, 44%). IR: (neat) 1759 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.29 (t, *J* = 7.6 Hz, 2H, *m*), 7.00 (t, *J* = 7.6 Hz, 1H, *p*), 6.94 (d, *J* = 7.6 Hz, 2H, *o*), 6.07 (ddd, *J* = 16.8, 10.8, 5.6 Hz, 1H, 3-H), 5.62 (dt, *J* = 16.8, 1.4 Hz, 1H, 4-H^B), 5.42 (dt, *J* = 10.8, 1.4 Hz, 1H, 4-H^A), 5.18 (dd, *J* = 5.6, 1.4 Hz, 1H, 2-H), 3.77 (s, 3H, OMe); ^{13}C NMR: (100 MHz, CDCl$_3$) 170.0 (s, C-1), 157.1 (s, *i*), 131.5 (d, C-3), 129.4 (d, *m*), 121.7 (d, *p*), 119.2 (t, C-4), 115.2 (d, *o*), 77.3 (d, C-2), 52.4 (q, OMe); MS: (EI, 70 eV) *m/z* 192 (M$^+$, 33), 160 (31), 133 (M$^+$ - CO$_2$Me, 100), 105 (38), 99 (41), 77 (30); HRMS: (EI, 70 eV) Calculated (C$_{11}$H$_{12}$O$_3$) 192.0786 (M$^+$) Found: 197.0787.

(3am) ethyl 2-(phenylthio)but-3-enoate



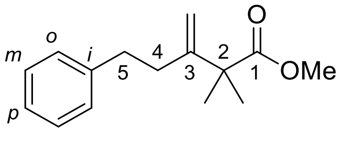
To a solution of GaI_3 (0.1032 g, 0.229 mmol) and phenylthioketene ethyl trimethylsilyl acetal (0.8823 g, 2.40 mmol) in dichloroethane (2 mL) was added butyl vinyl ether (0.1974 g, 1.97 mmol). The mixture was stirred at 80 °C for 4 h and then quenched by diethyl ether (2 mL) and sat.$NaHCO_3$ solution (2 mL). The mixture was extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm, diameter 26 mm, Spherical silica gel) to give the product (0.258 g, 59%). IR: (neat) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.48-7.23 (m, 5H, Ar), 5.96 (ddd, *J* = 17.4, 10.5, 9.2 Hz, 1H, 2-H), 5.192 (d, *J* = 17.4 Hz, 1H, 1-H^A), 5.190 (d, *J* = 10.5 Hz, 1H, 1-H^B), 4.28 (d, *J* = 9.2 Hz, 1H, 3-H), 4.13 (q, *J* = 7.2 Hz, 2H, 5-H$_2$), 1.20 (t, *J* = 7.2 Hz, 3H, 6-H$_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.0 (s, C-4), 133.6 (d), 132.6 (s, *i*), 132.1 (d, C-2), 128.9 (d), 128.2 (d, *p*), 119.0 (t, C-1), 61.5 (t, C-5), 54.5 (d, C-3), 13.9 (q, C-6); MS: (CI, 200 eV) *m/z* 223 (M +1, 100), 177 (M - OEt, 11), 149 (M - CO_2Et, 10); HRMS: (EI, 70 eV) Calculated ($C_{12}H_{14}O_2S$) 222.0715 (M$^+$) Found: 222.0716.

(5an) Methyl 2,2-dimethyl-3-methylenenonanoate[13a]



To a solution of $GaBr_3$ (0.05 M in dichloroethane, 2 mL) and dimethylketene methyl trimethylsilyl acetal (1.5 mmol, 0.270 g) was added 2-methoxyoct-1-ene (1.0 mmol, 0.137 g). The mixture was stirred at 80 °C for 12 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.145 g, 71%).

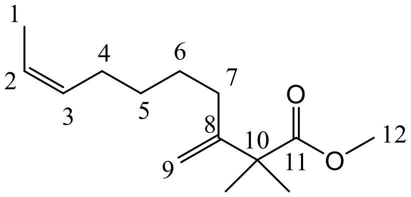
(5bn) Methyl 2,2-dimethyl-3-methylidene-5-phenylpentanoate



To a solution of $GaBr_3$ (0.05 M in dichloroethane, 2 mL) and dimethylketene methyl trimethylsilyl acetal (1.5 mmol, 0.270 g) was added 2-methoxy-4-phenyl-1-butene (0.9 mmol, 0.152 g). The mixture was stirred at 80 °C for 12 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.114 g, 69%). IR: (neat) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.33-7.27 (m, 2H, *m*), 7.24-7.17 (m, 3H, *o* and *p*), 5.09 (s, 1H, 3-C*H*H), 5.03 (s, 1H, 3-CH*H*), 3.67 (s, 3H, OMe), 2.79 (t, *J* =

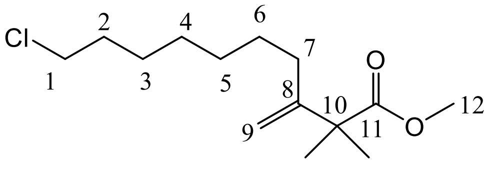
8.6 Hz, 2H, 5-H_2), 2.28 (t, *J* = 8.6 Hz, 2H, 4-H_2), 1.36 (s, 6H, 2-Me_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.0 (s, C-1), 151.4 (s, C-3), 142.0 (s, *i*), 128.32 (d), 128.30 (d), 125.9 (d, *p*), 109.0 (t, 3-CH_2), 52.0 (q, OMe), 48.2 (s, C-2), 34.9 (t, C-5), 34.0 (t, C-4), 24.8 (q, 2-Me_2); MS: (CI, 200 eV) *m*/*z* 233 (M^+ + 1, 100), 173 (25), 131 (27); HRMS: (CI, 200 eV) Calculated ($C_{15}H_{21}O_2$) 233.1542 (M + 1) Found: 233.1540.

(5cn) methyl (Z)-2,2-dimethyl-3-methylenedec-8-enoate



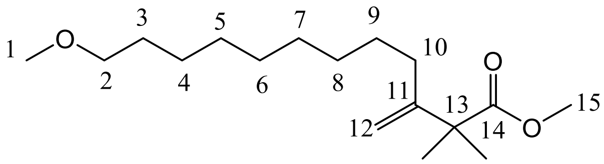
To a solution of $GaCl_3$ (0.0535 g, 0.304 mmol) and dimethylketene methyl trimethylsilyl acetal (0.511 g, 2.93 mmol) in dichloroethane (2 mL) was added (*Z*)-7-bromohept-2-ene (0.204 g, 1.07 mmol). The mixture was stirred at 80 °C for 2 h and then quenched by diethyl ether (2 mL) and sat.$NaHCO_3$ solution (2 mL). The mixture was extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm, diameter 26 mm, Spherical silica gel) to give the product (0.07 g, 30%). IR: (neat) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 5.48-5.32 (m, 2H, 2-H and 3-H), 4.98 (s, 1H, 9-H^A), 4.89 (s, 1H, 9-H^B), 3.65 (s, 3H, 12-H_3), 2.03 (dt, *J* = 7.2, 7.3 Hz, 2H, 4-H_2), 1.95 (t, *J* = 7.7 Hz, 2H, 7-H_2), 1.59 (d, *J* = 6.3 Hz, 3H, 1-H_3), 1.51-1.41 (m, 2H, 6-H_2), 1.41-133 (m, 2H, 5-H_2), 1.31 (s, 6H, 10-Me_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.2 (s, C-11), 152.0 (s, C-8), 130.5 (d, C-2), 123.8 (d, C-3), 108.4 (t, C-9), 51.9 (q, C-12), 48.1 (s, C-10), 32.4 (t, C-7), 29.3 (t, C-5), 28.0 (t, C-6), 26.7 (t, C-4), 24.8 (q, 10-Me), 12.7 (q, C-1); HRMS: (EI, 90 eV) Calculated ($C_{14}H_{24}O_2$) 224.1776 (M^+) Found: 224.1774.

(5dn) methyl 10-chloro-2,2-dimethyl-3-methylenedecanoate



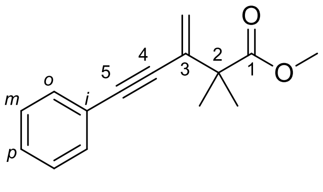
To a solution of $GaCl_3$ (0.0535 g, 0.304 mmol) and dimethyllketene methyl trimethylsilyl acetal (0.511 g, 2.93 mmol) in dichloroethane (2 mL) was added 9-chloro-2-methoxynon-1-ene (0.262 g, 1.10 mmol). The mixture was stirred at 80 °C for 2 h and then quenched by diethyl ether (2 mL) and sat. Na_2CO_3 solution (2 mL). The mixture was extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm, diameter 26 mm, Spherical silica gel) to give the product (0.20 g, 72%). IR: (neat) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 5.00 (s, 1H, 9-H^{A}), 4.90 (s, 1H, 9-H^{B}), 3.66 (s, 3H, 12-H_3), 3.52 (t, J = 6.4 Hz, 2H, 1-H_2), 1.93 (t, J = 7.7 Hz, 2H, 7-H_2), 1.76 (tt, J = 7.3, 7.2 Hz, 2H, 2-H_2), 1.52-1.39 (m, 4H, 3-H_2 and 6-H_2), 1.37-1.27 (m, 10H, 4-H_2, 5-H_2 and 9-Me_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.2 (s, C-11), 152.0 (s, C-8), 108.4 (t, C-9), 51.9 (q, C-12), 48.2 (s, C-10), 45.1 (t, C-1), 32.6 (t, C-2), 32.0 (t, C-7), 29.3 (t), 28.8 (t), 28.3 (t), 26.8 (t, C-3), 24.8 (q, 10-Me_2); HRMS: (EI, 90 eV) Calculated ($C_{14}H_{25}ClO_2$) 260.1543 (M^+) Found: 260.1537

(5en) methyl 12-methoxy-2,2-dimethyl-3-methylenedodecanoate



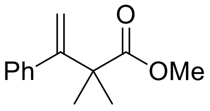
To a solution of $GaCl_3$ (0.0525 g, 0.298 mmol) and dimethyllketene methyl trimethylsilyl acetal (0.519 g, 2.98 mmol) in dichloroethane (2 mL) was added 2,10-dimethoxydec-1-ene (0.166 g, 0.774 mmol). The mixture was stirred at 80 °C for 2 h and then quenched by diethyl ether (2 mL) and sat. Na_2CO_3 solution (2 mL). The mixture was extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm, diameter 26 mm, Spherical silica gel) to give the product (0.123 g, 56%). IR: (neat) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 4.91 (s, 1H, 12-H^{A}), 4.82 (s, 1H, 12-H^{B}), 3.66 (s, 3H, 15-H_3), 3.36 (t, J = 6.2 Hz, 2H, 2-H_2), 3.33 (s, 3H, 1-H_3), 1.94 (t, J = 7.7 Hz, 2H, 10-H_2), 1.59-1.53 (m, 2H, 3-H_2), 1.48-1.41 (m, 2H, 9-H_2), 1.32 (s, 6H, 13-Me_2), 1.39-1.18 (m, 10H, 4-H_2, 5-H_2, 6-H_2, 7-H_2 and 8-H_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.2 (s, C-14), 152.1 (s, C-11), 108.3 (t, C-12), 72.9 (t, C-2), 58.4 (q, C-1), 51.9 (q, C-15), 48.1 (s, C-13), 32.1 (t, C-10), 29.6 (t, C-3), 29.5 (t), 29.44 (t), 29.41 (t), 28.4 (t, C-9), 26.1 (t), 24.8 (q, 13-Me); HRMS: (EI, 90 eV) Calculated ($C_{17}H_{32}O_3$) 284.2351 (M^+) Found: 284.2354.

(5fn) Methyl 2,2-dimethyl-3-methylidene-5-phenylpentynoate



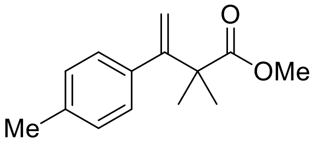
To a solution of $GaBr_3$ (0.05 M in dichloroethane, 2 mL) and dimethylketene methyl trimethylsilyl acetal (1.5 mmol, 0.262 g) was added 2-methoxy-4-phenyl-1-buten-3-yne (1.0 mmol, 0.154 g). The mixture was stirred at 80 °C for 12 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.162 g, 73%). IR: (neat) 1736 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.47-7.39 (m, 2H, *o*), 7.33-7.26 (m, 3H, *m* and *p*), 5.58 (s, 1H, 3-C*H*H), 5.45 (s, 1H, 3-CH*H*), 3.72 (s, 3H, OMe), 1.47 (s, 6H, 2-Me_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 175.8 (s, C-1), 135.4 (s, C-3), 131.5 (d, *o*), 128.24 (d, *p*), 128.20 (d, *m*), 122.9 (s, *i*), 119.8 (t, 3-CH_2), 90.7 (s, C-5), 87.8 (s, C-4), 52.2 (q, OMe), 47.8 (s, C-2), 24.6 (q, 2-Me_2); MS: (EI, 70 eV) *m/z* 228 (M^+, 75), 213 (65), 200 (20), 169 (49), 168 (M^+ - CO_2Me, 100), 167 (21), 154 (25), 153 (27), 127 (36), 115 (39); HRMS: (EI, 70 eV) Calculated ($C_{15}H_{16}O_2$) 228.1150 (M^+) Found: 228.1154.

(5gn) Methyl 2,2-dimethyl-3-phenylbut-3-enoate[14]



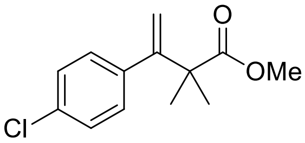
To a solution of $GaBr_3$ (0.1 M in dichloroethane, 2 mL) and dimethylketene methyl trimethylsilyl acetal (3.0 mmol, 0.526 g) was added (1-methoxyvinyl)benzene (1.0 mmol, 0.124 g). The mixture was stirred at 80 °C for 12 h and then was quenched by 1 M HClaq.. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.086 g, 43%).

(5hn) Methyl 2,2-dimethyl-3-(p-tolyl)but-3-enoate[13a]



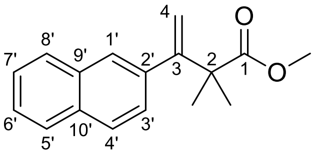
To a solution of $GaBr_3$ (0.1 M in dichloroethane, 2 mL) and dimethylketene methyl trimethylsilyl acetal (3.0 mmol, 0.521 g) was added 1-(1-methoxyvinyl)-4-methylbenzene (1.0 mmol, 0.141 g). The mixture was stirred at 80 °C for 12 h and then was quenched by 1 M HCl aq. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.089 g, 43%).

(5in) Methyl 3-(4-chlorophenyl)-2,2-dimethylbut-3-enoate[13a]



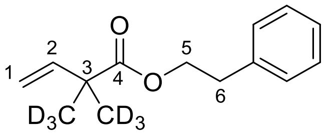
To a solution of $GaBr_3$ (0.1 M in dichloroethane, 2 mL) and dimethylketene methyl trimethylsilyl acetal (3.0 mmol, 0.517 g) was added 1-chloro-4-(1-methoxyvinyl)benzene (1.0 mmol, 0.173 g). The mixture was stirred at 80 °C for 12 h and then was quenched by 1 M HCl aq. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography to give the product (0.148 g, 61%).

(5jn) Methyl 2,2-dimethyl-3-(2-naphthyl)-3-butenoate



To a solution of $GaBr_3$ (0.1 M in dichloroethane, 2 mL) and dimethylketene methyl trimethylsilyl acetal (2.9 mmol, 0.512 g) was added 1-(2-naphthyl)-1-methoxyethene (1.0 mmol, 0.187 g). The mixture was stirred at 80 °C for 12 h and then was quenched by 1 M HCl aq. The mixture was extracted with diethyl ether (10 x 3 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm) (0.149 g, 59%). IR: (neat) 1732 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.87-7.79 (m, 2H, 5'-H and 8'-H), 7.77 (d, $J = 8.8$ Hz, 1H, 4'-H), 7.62 (d, $J = 1.6$ Hz, 1H, 1'-H), 7.52-7.43 (m, 2H, 6'-H and 7'-H), 7.30 (dd, $J = 8.8, 1.6$ Hz, 1H, 3'-H), 5.43 (s, 1H, 4-C*H*H), 5.26 (s, 1H, 4-CH*H*), 3.71 (s, 3H, OMe), 1.46 (s, 6H, 2-Me_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.0 (s, C-1), 153.0 (s, C-3), 139.1 (s, C-2'), 133.0 (s, C-9'), 132.4 (s, C-10'), 128.0 (d), 127.5 (d), 127.3 (d), 126.6 (d), 126.4 (d), 126.0 (d), 125.8 (d), 115.0 (t, C-4), 52.1 (q, OMe), 47.7 (s, C-2), 25.8 (q, 2-Me_2); MS: (EI, 70 eV) *m/z* 254 (M^+, 60), 239 (M^+ - CH_3, 100), 195 (25), 179 (38), 165 (22), 153 (73), 152 (31), 141 (33); HRMS: (EI, 70 eV) Calculated ($C_{17}H_{18}O_2$) 254.1307 (M^+) Found: 254.1304; Analysis: $C_{17}H_{18}O_2$ (254.32) Calcd: C, 80.28; H, 7.13 Found: C, 79.99; H, 7.27.

Phenethyl 2,2-bis(methyl-d_3)but-3-enoate (Figure2)



To a solution of $GaBr_3$ (0.0169 g, 0.0546 mmol) and trimethyl ((2-(methyl-d_3)-1-phenethoxyprop-1-en-1-yl-3,3,3-d_3)oxy)silane (0.135 g, 0.499 mmol) in dichloroethane (2 mL) was added butyl vinyl ether (0.1237 g, 1.24 mmol). The mixture was stirred at 80 °C for 2 h and then quenched by diethyl ether (2 mL) and sat.Na_2CO_3 solution (2 mL). The mixture was extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 98:2, column length 11 cm, diameter 26 mm, Spherical silica gel) to give the product (0.0938 g, 84%). IR: (neat) 1732 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.31-7.20 (m, 5H, Ar), 5.98 (dd, J = 17.4, 10.6 Hz, 1H, 2-H), 5.05 (d, J = 17.4 Hz, 1H, 1-H^A), 5.04 (d, J = 10.6 Hz, 1H, 1-H^B), 4.28 (t, J = 6.8 Hz, 2H, 5-H_2), 2.93 (t, J = 6.8 Hz, 2H, 6-H_2) ; ^{13}C NMR: (100 MHz, $CDCl_3$) 176.2 (s, C-4), 142.4 (d, C-2), 137.8 (s, *i*), 128.9 (d), 128.4 (d), 126.4 (d, *p*), 112.8 (t, C-1), 65.1 (t, C-5), 35.0 (t, C-6), 23.5 (m, 3-CD_3); MS: (CI, 200 eV) *m/z* 225 (M+1, 100), 105 (CH_2CH_2Ph, 83); HRMS: (CI, 200 eV) Calculated ($C_{14}H_{13}D_6O_2$) 225.1762 (M + 1) Found: 225.1758.

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26 The injection of Me_3SiBr had no influence on the rate (Experimental Section), which suggested that Me_3SiBr does not take part in the *syn* elimination step unlike the mechanism we proposed in the primary report.

27 See Experimental Section for the derivation of rate equations.

28 See Experimental Section for the details of Arrhenius plot.

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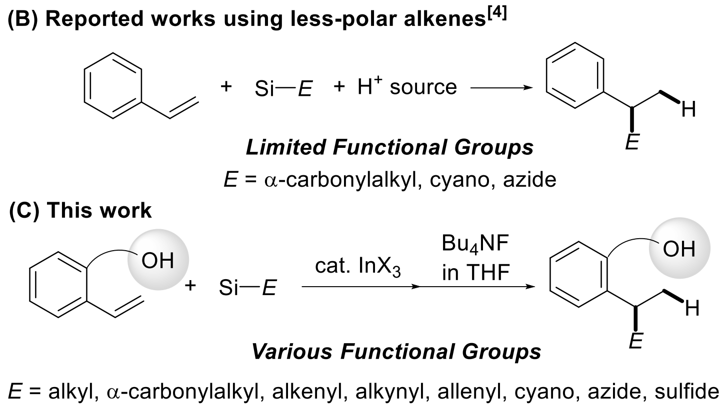
Chapter 2

Indium Catalyzed Hydrofunctionalization of Styrene Derivatives Bearing a Hydroxy Group with Organosilicon Nucleophiles

2-1. Introduction

Alkenes are important fundamental materials in organic synthesis and industrial chemistry, and many useful transformations of alkenes have been established.[1] Therefore, the direct addition reaction of alkenes with various reagents such as electrophilic, nucleophilic, and radical ones to give functionalized alkanes with high selectivity and high step economy is highly desired even now. In this context, many examples for hydrofunctionalization of alkenes through the addition of E-H (E = C, O, N, P, and S) to alkenes have already been reported.[2] One example involves the hydrofunctionalization of Michael acceptors such as α,β-unsaturated carbonyl compounds or nitriles with a variety of organosilicon nucleophiles, which is a well-developed method[3] (Scheme 1-A). However, the application of less-polar alkenes to the process of hydrofunctionalization has been insufficiently developed, and available organosilicon nucleophiles are limited to silyl enolates, silyl cyanides and silyl azides[4] (Scheme 1-B). Our group also reported the regioselective hydrofunctionalization of simple alkenes with silyl ketene acetals and a stoichiometric amount of indium[4g] or bismuth salts[4f] through carboindation or carbobismuthination, respectively. Herein, the regioselective hydrofunctionalization of less-polar alkenes bearing a hydroxy group with organosilicon nucleophiles was accomplished in the presence of catalytic amount of indium trihalide (Scheme 1-C). The present reaction proceeded through a unique reaction mechanism including Brønsted acid-catalyzed hydroalkoxylaiton of alkenes followed by InI_3-catalyzed substitution reaction of cyclic ether intermediates, which is quite different from our previously reported method through carbometalation. In the present hydrofunctionalization, various organosilicon nucleophiles as well as silyl ketene acetals were allowed to use. Moreover, not only mono-substituted alkenes but also di- and tri-substituted alkenes, which often showed low reactivity for previously developed hydrofunctionalization,[4c,4f,4g,4j] were applicable. It is noted that a wide range of functional groups could be introduced into alkenes via a single synthetic operation.[5]



Scheme 1. (A) Michael addition. (B) Hydrofunctionalization by organosilicon nucleophiles with less-polar alkenes. (C) This work allows the introduction of versatile functional groups to alkenes.

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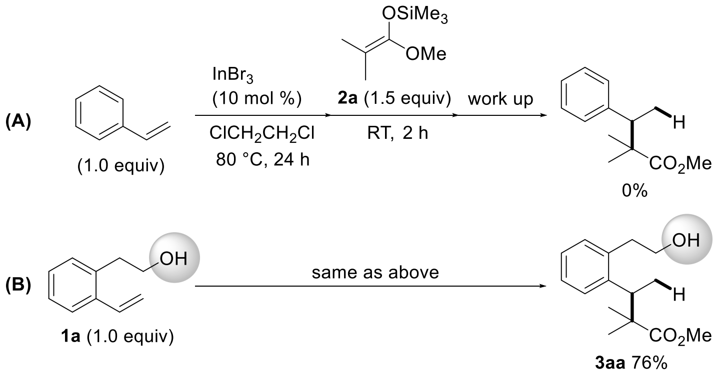
2-2. Results and Discussion

Optimization of Reaction Conditions

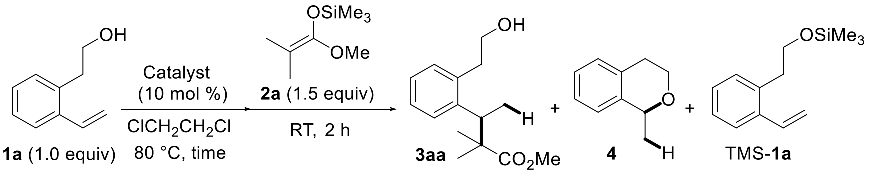
The reaction of styrene with silyl ketene acetal **2a** was attempted in the presence of a catalytic amount of indium tribromide, but instead of obtaining the hydrofunctionalization product, the polymerization of styrene occurred (Scheme 2-A). Interestingly, we found that *o*-(2-hydroxyethyl)styrene (**1a**) afforded the target product **3aa** in a high yield (Scheme 2-B).



Scheme 2. Investigation of indium bromide catalyzed reaction of silyl ketene acetal with styrene (A) or styrene derivative **1a** (B).

That result prompted us to investigate the effect of acid catalysts on the hydrofunctionalization of **1a** with **2a** (Table 1). As shown in Scheme 2-(B), $InBr_3$ gave **3aa** in a 76% yield (entry 1). $GaBr_3$ also afforded **3aa** in approximately the same yield (entry 2). On the other hand, the desired product **3aa** was not obtained, and starting alkene **1a** and TMS-**1a** were recovered in the cases of the reaction using $InCl_3$, $In(OTf)_3$ or BiI_3 (entries 3-5). The reaction catalyzed by InI_3 raised the yield of **3aa** to 92% (entry 6). Without the addition of **2a**, only cyclic ether **4** was produced in a high yield (entry 7). Thus, the hydrofunctionalization product could be obtained via **4**. Typical Lewis acids such as $ZnCl_2$, $AlCl_3$, and $TiCl_4$ were ineffective for the desired hydrofunctionalization and either gave the cyclic ether **4** or recovered the starting material (entries 8-10). The reaction using $BF_3{\cdot}OEt_2$ resulted in complicated mixture (entry 11). A cationic gold catalyst, which is often used to functionalize alkenes,[6] was ineffective (entry 12). The reaction catalyzed by HI aq. would not afford the product **3aa**, but did produce cyclic ether **4** in a high yield (entry 13).

Table 2. The effect of acid catalysts on the hydrofunctionalization of styrene derivative **1a** with organosilicon nucleophile **2a**.[a]



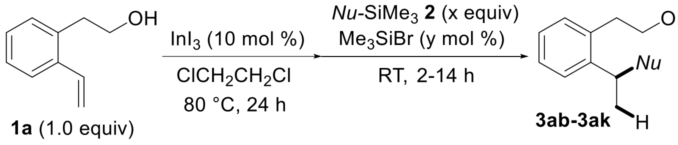
Entry	Catalyst	Time (h)	Yield (%)[b]			Recovery of **1a** (%)
			3aa	4	TMS-**1a**	
1	$InBr_3$	24	76	0	0	0
2	$GaBr_3$	24	72	0	0	0
3	$InCl_3$	96	0	16	33	15
4	$In(OTf)_3$	24	0	40	3	5
5	BiI_3	72	0	0	91	0
6	InI_3	24	92 (71)[c]	0	0	0
7[d]	InI_3	24	0	90	0	0
8	$ZnCl_2$	96	0	0	45	8
9	$AlCl_3$	24	1	56	0	0
10	$TiCl_4$	48	0	57	0	0
11	$BF_3{\cdot}OEt_2$	24	0	0	0	0
12	$AuCl_3$/AgOTf	24	0	52	0	0
13	HI aq.	24	0	77	0	0

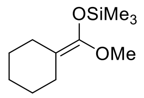
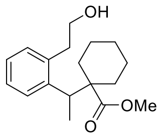
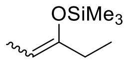
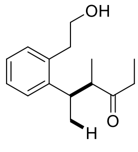
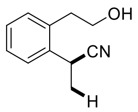
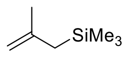
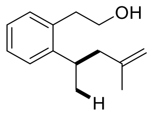
[a] 1st step: **1a** (0.5 mmol), catalyst (0.05 mmol), $ClCH_2CH_2Cl$ (1 mL), 80 ˚C, 24 h. 2nd step: **2a** (0.75 mmol), RT, 2 h. The reaction was quenched with Bu_4NF (1 M in THF). [b] Yields were determined by ^1H NMR using internal standards (bromoform). [c] Isolated yield. [d] The 2nd step was not carried out.

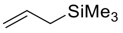
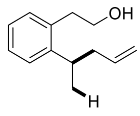
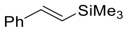
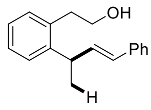
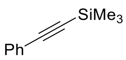
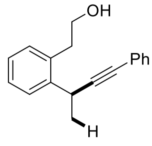
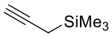
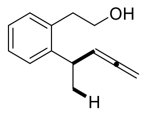
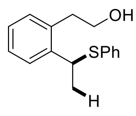
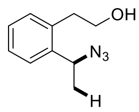
Substrate Scope of Organosilicon Nucleophiles

Reactions of **1a** with various organosilicon nucleophiles **2** catalyzed by InI_3 were carried out (Table 2). The bulky silyl ketene acetal **2b** was suitable for this reaction system to provide the cyclohexane derivative **3ab** in high yield (entry 1). The silyl enol ether **2c** afforded the target product **3ac** (entry 2). Hydrofunctionalization with the silyl cyanide **2d** occurred (entry 3), but the reported method[4b] that uses a Brønsted acid for hydrocyanation of styrene gave only cyclic ether **4** (see Scheme S1 in Supporting Information for detail). Methallylsilane **2e** also provided the hydrofunctionalization product in moderate yield (entry 4).[7] Reactions using allylsilane **2f**, alkenylsilane **2g**, alkynylsilane **2h**, and propargylsilane **2i** proceeded efficiently in the presence of a catalytic amount of InI_3/Me_3SiBr (entries 5-8). The addition of Me_3SiBr was necessary for the reactions using nucleophiles **2f-2i**, which have a relatively low level of nucleophilicity. In these cases, the combination of InX_3 with Me_3SiX showed high Lewis acidity.[8] To the best of our knowledge, the reaction using **2i** is the first example of an intermolecular Markovnikov hydroallenylation toward less-polar alkenes.[9] Heteroatom nucleophiles such as silyl sulfide **2j** and silyl azide **2k** were applicable to this reaction system (entries 9 and 10).[10]

Table 2. Scope of hydrofunctionalization using various organosilicon nucleophiles.[a]



Entry	*Nu*-$SiMe_3$ (x equiv)	Me_3SiBr (y mol%)	Yield of **3** (%)[b]
1[c]	 **2b** (3.0 equiv)	none	 **3ab** 74
2	 **2c** (3.0 equiv)	none	 **3ac** 69
3[d]	Me_3SiCN **2d** (5.0 equiv)	none	 **3ad** 31
4	 **2e** (1.5 equiv)	none	 **3ae** 55

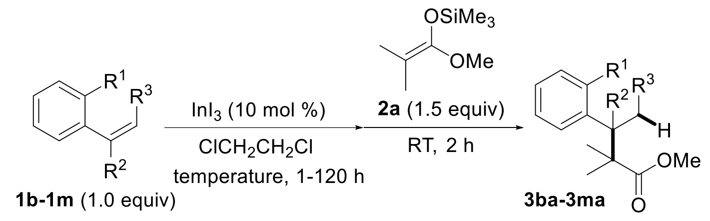
5	 **2f** (1.5 equiv)	10	 **3af** 86
6	 **2g** (3.0 equiv)	20	 **3ag** 59
7	 **2h** (3.0 equiv)	20	 **3ah** 54
8[e]	 **2i** (3.0 equiv)	20	 **3ai** 68
9	Me_3SiSPh **2j** (3.0 equiv)	none	 **3aj** 59
10[f]	Me_3SiN_3 **2k** (3.0 equiv)	none	 **3ak** 54

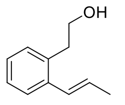
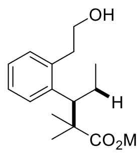
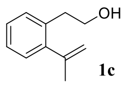
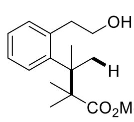
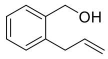
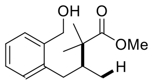
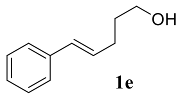
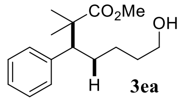
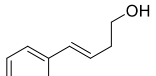
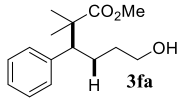
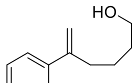
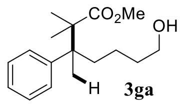
[a] 1st step: **1a** (0.5 mmol), InI_3 (0.05 mmol), $ClCH_2CH_2Cl$ (1 mL), 80 ˚C, 24 h. 2nd step: **2** (0.75-2.5 mmol), Me_3SiBr (0-0.1 mmol), RT, 2-14 h (See Experimental Section for detail). The reaction was quenched with Bu_4NF (1 M in THF). [b] Isolated yield. [c] InI_3 (20 mol%) [d] InI_3 (20 mol%), 70 ˚C at the second step. [e] 35 ˚C at the second step. [f] 50 ˚C at the second step.

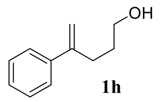
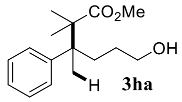
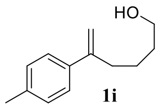
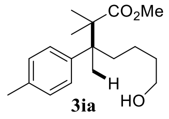
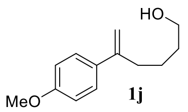
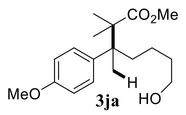
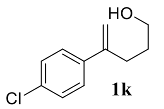
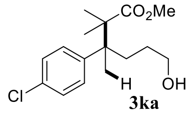
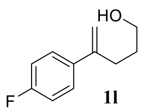
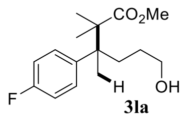
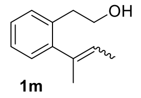
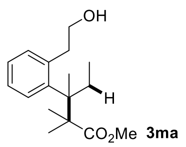
Substrate Scope and Limitation of Styrene Derivatives

The scope of styrene derivatives with a hydroxy moiety is shown in Table 3. In all cases, the nucleophilic attack of **2a** took place at a benzylic position exclusively and other regioisomers were not formed. The β-methylstyrene derivative **1b** gave the product **3ba**, and the reaction of the α-methylstyrene derivative **1c** formed vicinal quaternary carbon atoms efficiently (entries 1 and 2). The reaction using the alkene **1d**, which is not a styrene derivative, provided no hydrofunctionalized product **3da** and complicated mixture was obtained (entry 3). The result suggested that the present reaction system was limited to styrene derivatives. The styrene derivatives **1e-1l**, which have different carbon frameworks, were also suitable to this reaction system. The reaction of β-(hydroxyalkyl)-substituted styrenes **1e** and **1f** afforded the target products in modest yields (entries 4 and 5) while α-(hydroxyalkyl)-substituted substrates **1g** and **1h** gave higher yields (entries 6 and 7). A variety of α-(hydroxyalkyl)-substituted styrenes were applicable to this reaction system. The reaction of styrene derivatives bearing electron donating groups **1i** and **1j**, as well as electron withdrawing groups **1k** and **1l**, proceeded smoothly to give target products **3ia**-**3la** in moderate to high yields (entries 8-11). The trisubstituted alkene **1m** was suitable for this reaction system (entry 12). The intermolecular addition of silyl enolates to trisubstituted alkenes without electron-withdrawing group has not been reported and the use of disubstituted alkenes usually resulted in low yields due to their steric hindrance.[4f,4g] Therefore, it is advantage of this work that trisubstituted substrate was applicable and disubstituted alkenes gave moderate to high yield.

Table 3. Scope of hydrofunctionalization using various styrene derivatives.[a],[b]



Entry	1	3	Temp (°C)	Yield (%)[c]
1[d]	 **1b**	 **3ba**	80	52
2	 **1c**	 **3ca**	80	53
3	 **1d**	 **3da**	80	0
4	 **1e**	 **3ea**	80	28
5	 **1f**	 **3fa**	80	30
6[d]	 **1g**	 **3ga**	RT	59

7	 **1h**	 **3ha**	RT	66
8	 **1i**	 **3ia**	RT	70
9	 **1j**	 **3ja**	RT	57
10	 **1k**	 **3ka**	RT	45
11	 **1l**	 **3la**	RT	77
12[c]	 **1m**	 **3ma**	70	56

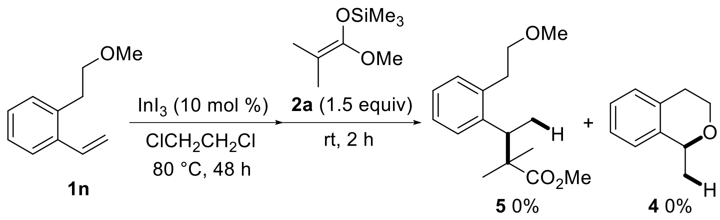
[a] 1st step: **1** (0.5 mmol), InI_3 (0.05 mmol), $ClCH_2CH_2Cl$ (1 mL), RT-80 °C, 1-120 h (See Experimental Section for detail). 2nd step: **2a** (0.75 mmol), RT, 2 h. The reaction was quenched with Bu_4NF (1 M in THF). [b] Corresponding cyclic ethers were obtained without addition of **2a** (see Table S1 in Experimental Section for detail). [c] Isolated yield. [d] **2a** (3 equiv). [e] **2a** (4 equiv).

Mechanistic Investigation

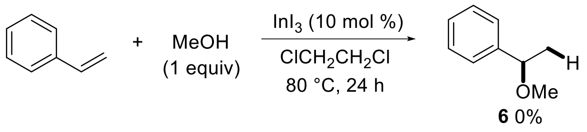
Hydrofunctionalization with styrene derivative **1n**, including a methoxyalkyl group, was attempted, but gave neither the target product **5** nor the cyclic ether **4** (Scheme 3-A). Moreover, the hydroalkoxylation of styrene with methanol as an external alcohol in the presence of a catalytic amount of InI_3 afforded no benzyl ether **6** (Scheme 3-B). These control experiments suggested that the intramolecular hydroxy group is necessary for this type of hydrofunctionalization. Taking into account the result of entry 13 in Table 1, the hydroalkoxylation of **1a** can be catalyzed by a Brønsted acid, which can be generated via the alcoholysis of InI_3 with **1a** *in situ*.[11] Thus, control experiments were carried out as shown in Scheme 4 to identify the active catalyst species for hydroalkoxylation. InI_3 or HI aq. efficiently catalyzed the hydroalkoxylation while the addition of K_2CO_3, or 2,6-di(*tert*-butyl)-4-

methylpyridine[12] as a proton scavenger, entirely prevented the InI_3-catalyzed hydroalkoxylation of **1a**. Therefore, these results indicated that *in situ*-generated Brønsted acid promoted the formation of the cyclic ether **4**.

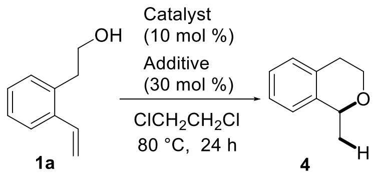
(A) Hydrofunctionalization with styrene derivative with a methoxyalkyl group

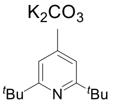


(B) Hydroalkoxylation of styrene with methanol as an external alcohol



Scheme 3. Investigation of styrene derivatives without OH group.

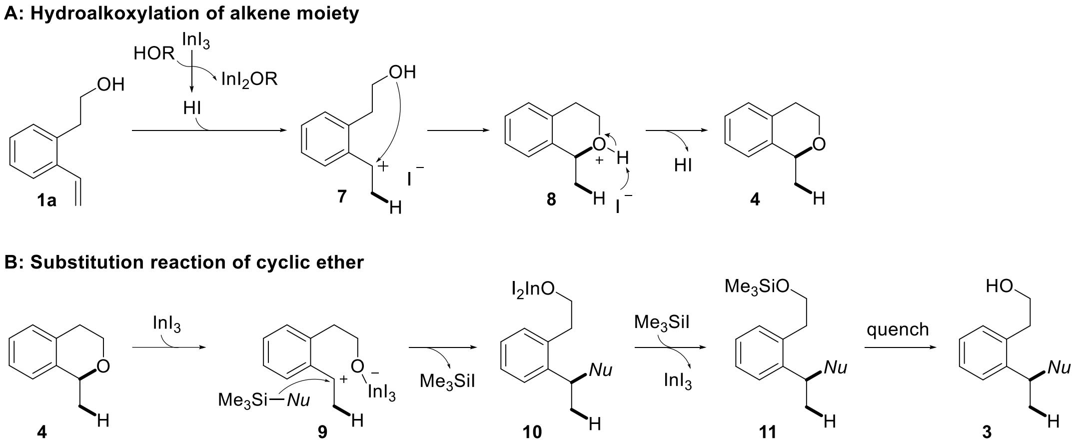


Catalyst	Additive	Yield
InI_3	none	90%
HI aq.	none	100%
InI_3	K_2CO_3	0%
InI_3		0%

Scheme 4. Hydroalkoxylation in the presence of a proton scavenger.

Proposed Mechanism

A proposed mechanism for the InI_3-catalyzed hydrofunctionalization of **1a** with an organosilicon nucleophile (Me_3Si*Nu*) is shown in Scheme 5. A trace amount of InI_3 undergoes alcoholysis with **1a** to give HI. The alkene moiety of **1a** is protonated and then alkoxylation occurs to afford cyclic ether **4**. The interaction between InI_3 and the ethereal oxygen of **4** cleaves the oxygen-carbon bond to generate carbocation **9**. A nucleophilic attack of the organosilicon compound to **9** occurs to produce the hydrofunctionalization product **10**. Transmetalation of the alkoxyindium moiety of **10** with Me_3SiI regenerates the InI_3 catalyst. The indium trihalide catalyzed substitution reaction of ethers by an organosilicon nucleophile (Me_3Si*Nu*) has been previously reported by our group.[13] Target alcohol product **3** is obtained after quenching by Bu_4NF.[14] In our previous reports[4f,4g], an indium trihalide coordinated to a carbon-carbon double bond and acted as a π Lewis acid to activate alkenes. Contrastively, in the present reaction, InI_3 mainly contributes to the generation of a Brønsted acid to transform an alkene into a cyclic ether intermediate and the substitution reaction of the intermediate with nucleophiles.

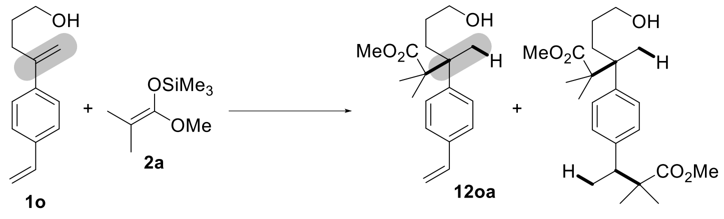


Scheme 5. Proposed mechanism.

Selective Functionalization of Alkenes

We demonstrated the selective functionalization of substrate **1o** with two types of alkene moieties (Scheme 6).[15] When **1o** underwent our developed hydrofunctionalization using silyl ketene acetal **2a**, hydroalkylation took place selectively at the alkene moiety with a hydroxyalkyl group to afford product **12oa** (Scheme 6-A). By contrast, when utilizing the $BiBr_3$-mediated hydrofunctionalization conditions,[4f] polymerization of **1o** just occurred. Moreover, the selective hydroazidation proceeded in the InI_3-mediated reaction of **1o** with silyl azide **2k** to give **12-N$_3$** (Scheme 6-B). On the other hand, the reported iron-mediated hydroazidation[16] using NaN_3 occurred at both alkene moieties of **1o** to give product **13-N$_3$**. The other reported system using Brønsted acid catalyst and Me_3SiN_3 as an azide source[17] was employed to afford no hydroazidation product but a hydroalkoxylation intermediate and starting material **1o**. The selective hydrocyanation of **1o** with silyl cyanide **2d** was also observed under InI_3-catalyzed conditions to give **12od** exclusively, while the reported method[4b] resulted in polymerization of **1o** (Scheme 6-C). These results showed the advantage of the InI_3-catalyzed system for selective functionalization of the complex molecules.

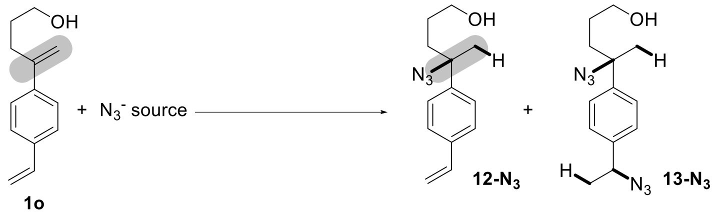
(A) Hydroalkylation of **1o**



1o **2a** **12oa** **13oa**

		Yield	Ratio of Products		
Our method	cat. InI_3[a]	46%	**100**	**:**	**0**
Reported method	$BiBr_3$ (ref. 4f)[b]	Polymerization			

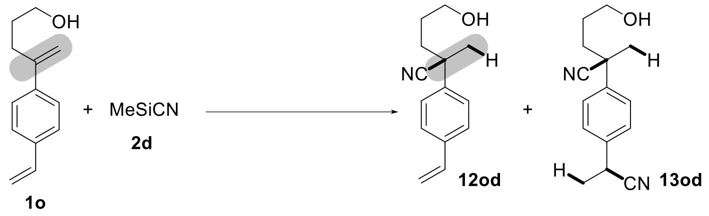
(B) Hydroazidation of **1o**



1o **12-N_3** **13-N_3**

		Yield	Ratio of Products		
Our method	cat. InI_3[c]	20%	**100**	**:**	**0**
Reported method	$Fe_2(ox)_3{\cdot}6H_2O$ (ref. 14)[d]	28%	0	:	100
Reported method	cat. TfOH (ref. 15)[e]	0%			

(C) Hydrocyanation of **1o**



1o **2d** **12od** **13od**

		Yield	Ratio of Products		
Our method	cat. InI_3[f]	50%	**100**	**:**	**0**
Reported method	TfOH (ref. 4b)[g]	Polymerization			

Scheme 6. Selective hydrofunctionalization of the substrate **1o** with two types of alkene moieties. Reaction conditions: [a] 1) **1o** (0.5 mmol), InI_3 (10 mol %), $ClCH_2CH_2Cl$ (10 mL), 5 ˚C, 17 h. 2) **2a** (1.5 mmol), RT, 12 h. [b] **1o** (0.2 mmol), $BiBr_3$ (0.3 mmol), **2a** (0.3 mmol) and CH_2Cl_2 (0.2 mL), RT, 8 h. [c] 1) **1o** (0.5 mmol), InI_3 (10 mol %), $ClCH_2CH_2Cl$ (10 mL), 5 ˚C, 5 h. 2) Me_3SiN_3 (**2k**, 1.5 mmol), RT, 17 h. [d] **1o** (0.5 mmol), NaN_3 (4.0 mmol), $Fe_2(ox)_3{\cdot}6H_2O$ (2.5 mmol), $NaBH_4$ (3.2 mmol), THF (20 mL) and H_2O (20 mL), 0 ˚C, 0.5 h. [e] **1o** (0.5 mmol), TfOH (25 mol %), Me_3SiN_3 (**2k**, 1.5 mmol), SiO_2 (1.25 g), CH_2Cl_2 (2.5 mL), RT, 1 h. [f] 1) **1o** (0.5 mmol), InI_3 (10 mol %), $ClCH_2CH_2Cl$ (10 mL), 5 ˚C, 19 h. 2) Me_3SiCN (**2d**, 2.5 mmol), RT, 35 h. [g] **1o** (0.5 mmol), TfOH (2.2 mmol), Me_3SiCN (**2d**, 2.1 mmol), $PhCF_3$ (4.5 mL), -5 ˚C, 1 h.

2-3. Conclusion

We have developed an InI_3 catalyzed hydrofunctionalization of alkenes with a hydroxyalkyl group using organosilicon nucleophiles such as silyl enolate, allylsilane, alkenylsilane, alkynylsilane, propargylsilane, silyl cyanide, silyl sulfide and silyl azide. Many functional groups that would be used for further elaboration were added to the alkene moiety in a single step. Various styrene derivatives were suitable for this reaction. It is noted that addition reaction of silyl enolate proceeded efficiently for not only monosubstituted alkenes but also multi-substituted ones compared with previously reported hydrofunctionalization. The selective functionalization of styrene derivatives with two alkene moieties was accomplished to show the preference of an alkene moiety with a hydroxyalkyl group. Mechanistic investigation showed that this hydrofunctionalization is composed of two steps: the hydroalkoxylation of an alkene catalyzed by a Brønsted acid and a sequential substitution reaction of cyclic ether catalyzed by InI_3. This transformation of alkene to ether allowed us to synthesize alkenes with many types of functional groups, which cannot be introduced into alkenes in our previous works. Therefore, this work provides a novel method for functionalization of alkenes.

2-4. Experimental Section

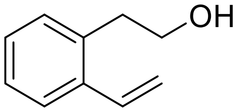
General

New compounds were characterized by ^1H and ^{13}C NMR, ^{13}C off-resonance techniques, COSY, HMQC, HMBC, IR, MS, HRMS. ^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained with TMS as internal standard. IR spectra were recorded as thin films. Bulb-to-bulb distillation (Kugelrohr) was accomplished at the oven temperature and pressure indicated. High-resolution mass spectra were obtained by magnetic sector type mass spectrometer. All reactions were carried out under nitrogen. All products were obtained as racemic mixtures.

Materials

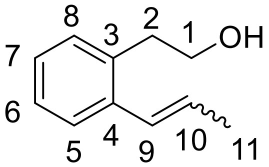
Dehydrated $ClCH_2CH_2Cl$ was purchased and used without further purification. Organosilicon nucleophiles **2a**, **2d**, **2e**, **2f,** **2h** and **2k** are commercially available. Styrene derivatives **1a**, **1d**, **1e**, **1f**, **1g**, **1h**, **1l** and organosilicon nucleophiles **2b**, **2c**, **2g**, **2i** and **2j** were synthesized by literature procedures and spectral data of these compounds were shown below. Styrene derivatives **1b**, **1c**, **1i**, **1j**, **1k**, **1m**, **1n** and **1o** are new compounds, and synthetic method and spectral data of these compounds were shown below. All metal salt and Me_3SiBr are commercially available.

(**1a**) 2-(2-vinylphenyl)ethan-1-ol[18]



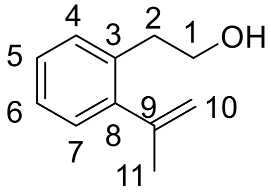
To a three necked flask, THF (56 mL) and 1-bromo-2-vinylbenzene (4.15 g, 20 mmol) were added. This solution was cooled at -78 °C and *n*-BuLi (1.6 M hexane solution, 14 mL, 22 mmol) was dropped over 15 minutes. After stirring for 1.5 h at -78 °C, to the reaction mixture was dropped ethylene oxide (1.1 M in THF, 25 mL, 30 mmol) and the reaction mixture was stirred for 0.5 h at -78 °C. The mixture was warm to room temperature and quenched by sat. NH_4Cl aq. (25 mL). This solution was extracted with diethyl ether (20 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (1.36 g, 45%). This is known compound and spectroscopic data were identical with those from literature.

(**1b**) 2-(2-(prop-1-en-1-yl)phenyl)ethan-1-ol



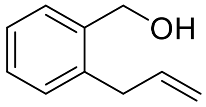
To a three necked flask, THF (56 mL) and 1-bromo-2-(prop-1-en-1-yl)benzene (4.15 g, 20 mmol) were added. This solution was cooled at -78 °C and n-BuLi (1.6 M hexane solution, 14 mL, 22 mmol) was dropped over 15 minutes. After stirring for 1.5 h at -78 °C, to the reaction mixture was dropped ethylene oxide (1.1 M in THF, 25 mL, 30 mmol) and the reaction mixture was stirred for 0.5 h at -78 °C. The mixture was warm to room temperature and quenched by sat. NH_4Cl aq. (25 mL). This solution was extracted with diethyl ether (20 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (*E*/*Z* = 99: 1, 1.67 g, 51%). IR: (neat) 3359 (OH) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.43 (d, *J* = 5.5 Hz, 1H, 5-H), 7.23-7.11 (m, 3H, 6-H, 7-H and 8-H), 6.65 (dq, *J* = 15.6, 1.4 Hz, 1H, 9-H), 6.11 (dq, *J* = 15.6, 6.9 Hz, 1H, 10-H), 3.80 (t, *J* = 6.9 Hz, 2H, 1-H_2), 2.94 (t, *J* = 6.9 Hz, 2H, 2-H_2), 1.90 (dd, *J* = 6.9, 1.4 Hz, 3H, 11-H_3), 1.41 (s, 1H, OH); ^{13}C NMR: (100 MHz, $CDCl_3$) 137.3 (s, C-3), 134.9 (s, C-4), 130.2 (d, C-8), 128.3 (d, C-9), 127.9 (d, C-10), 126.9 (d), 126.8 (d), 126.2 (d, C-5), 63.1 (t, C-1), 36.4 (t, C-2), 18.9 (q, C-11); MS: (CI, 70 eV) *m*/*z* 163 ([M + 1]$^+$, 43); HRMS: (EI, 70 eV); Calculated ($C_{11}H_{14}O$) 162.1045 (M); Found: 162.1046.

(**1c**) 2-(2-(prop-1-en-2-yl)phenyl)ethan-1-ol



To a three necked flask, THF (56 mL) and 1-bromo-2-(prop-1-en-2-yl)benzene (3,49 g, 20 mmol) were added. This solution was cooled at -78 °C and n-BuLi (1.6 M hexane solution, 14 mL, 22 mmol) was dropped over 15 minutes. After stirring for 1.5 h at -78 °C, to the reaction mixture was dropped ethylene oxide (1.1 M in THF, 25 mL, 30 mmol) and the mixture was stirred for 0.5 h at -78 °C. The reaction mixture was warm to room temperature and quenched by sat. NH_4Cl aq. (25 mL). This solution was extracted with diethyl ether (20 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (1.53 g, 47%). IR: (neat) 3359 (OH) cm^{-1}, 1639 (C=C) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.29-7.15 (m, 3H), 7.15-7.09 (m, 1H, 7-H), 5.23-5.17 (m, 1H, 10-H^{A}), 4.89-4.82 (m, 1H, 10-H^{B}), 3.81 (t, J = 7.2 Hz, 2H, 1-H_2), 2.92 (t, J = 7.2 Hz, 2H, 2-H_2), 2.05 (s, 3H, 11-H_3), 1.39 (s, 1H, OH); ^{13}C NMR: (100 MHz, $CDCl_3$) 145.4 (s, C-9), 144.3 (s, C-8), 134.6 (s, C-3), 129.6 (d, C-4), 128.4 (d, C-7), 126.9 (d), 126.3 (d), 115.2 (t, C-10), 63.7 (t, C-1), 36.1 (t, C-2), 25.3 (q, C-11); MS: (CI, 70 eV) m/z 163 ($[M + 1]^+$, 100); HRMS: (EI, 70 eV) Calculated ($C_{11}H_{14}O$) 162.1045 (M) Found: 162.1043.

(**1d**) (2-allylphenyl)methanol[19]

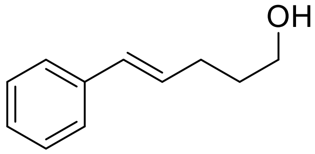


To a three necked flask, (2-bromophenyl)methanol (9.45 g, 50 mmol), hexane (50 mL), Et2O (5 mL), 3,4-dihydro-*2H*-pyran (5.12 g, 60 mmol) and Amberlyst15 (6.3 g) were added. After stirring for 45 minutes, the reaction mixture was purified by column chromatography (hexane, column length 11 cm, diameter 26 mm, silica 75 g and Amberlyst15 6.2 g) to give 2-((2-bromobenzyl)oxy)tetrahydro-2H-pyran (7.2 g, 53%).

To a three necked flask, magnesium turning (0.73 g, 30 mmol) and THF (10 mL) were added. Three drops of a solution of 2-((2-bromobenzyl)oxy)tetrahydro-2H-pyran (7.2 g, 27 mmol) in THF (12 mL) was dropped into the vessel, and then ten drops of 1,2-dibromoethane was added to the reaction mixture. The reminding THF solution of 2-((2-bromobenzyl)oxy)tetrahydro-2H-pyran was dropped into the reaction mixture over 10 minutes. After stirring for 15 minutes, the mixture was refluxed for 1 hour, and then cooled at 30 °C. A solution of allyl bromide (4.4 g, 36 mmol) in THF (10 mL) was dropped over 5 minutes. After stirring for 17 hours, the reaction mixture was quenched by sat. NH_4Cl aq. (30 mL) under ice bath. The solution was extracted by ethyl acetate (30 mL x 4). The collected organic layer was dried ($MgSO_4$) and the solvent was evaporated to give 2-((2-allylbenzyl)oxy)tetrahydro-2H-pyran (6.35 g, 100%).

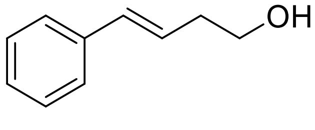
To a three necked flask, 2-((2-allylbenzyl)oxy)tetrahydro-2H-pyran (6.27 g, 27 mmol), MeOH (38 mL) and 1N HCl aq. (38 mL) were added. After stirring for 20 hours at 50 °C, the reaction mixture was quenched by Et_2O (100 mL). The mixture was extracted by Et_2O (50 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 60:40, column length 11 cm, diameter 26 mm, spherical silica gel) to give (2-allylphenyl)methanol as the target product (4.0 g, 100%). This is known compound and spectroscopic data were identical with those from literature.

(**1e**) (*E*)-5-phenylpent-4-en-1-ol[20]



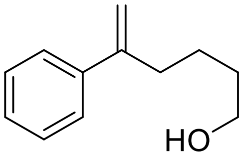
To a three necked flask, THF (250 mL) and $LiAlH_4$ (5.1 g, 130 mmol) were added. This solution was cooled at 0 °C and 5-phenylpent-4-yn-1-ol (4.28 g, 26 mmol) was added to the mixture and the reaction mixture was stirred for 1 h at 0 °C. After refluxing for 2 days, to the reaction mixture was dropped sat. potassium sodium tartrate aq. (100 mL) at 0 °C. This solution was extracted with diethyl ether (100 mL x 3) and the collected organic layer was washed by sat. NaCl aq. (100 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (3,24 g, 77%). This is known compound and spectroscopic data were identical with those from literature.

(**1f**) (*E*)-4-phenylbut-3-en-1-ol [21]



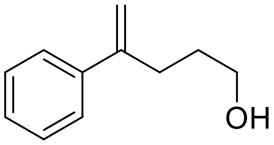
To a three necked flask, THF (21 mL) and $LiAlH_4$ (1.78 g, 47 mmol) were added. This solution was cooled at 0 °C and 4-phenylbut-3-yn-1-ol (2.34 g, 16 mmol) in THF (21 mL) was dropped to the mixture over 10 minutes. After refluxing for 15 h, the reaction mixture was quenched by $Na_2SO_4 \cdot 10H_2O$ at 0 °C. This mixture was filtered and the filtrate was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (2.21 g, 93%). This is known compound and spectroscopic data were identical with those from literature.

(**1g**) 5-phenylhex-5-en-1-ol[22]



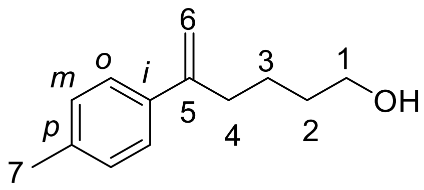
To a two necked flask, $Pd(PPh_3)_4$ (0.695 g, 0.6 mmol), 1,4-dioxane (40 mL), phenyl boronic acid (3.05 g, 24 mmol), 5-hexyne-1-ol (2.10 g, 20 mmol) and acetic acid (0.13 g, 2.0 mmol) were added. After stirring for 10 minutes at rt, the reaction mixture was stirred for 16 h at 80 °C. The reaction mixture was filtered and the solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (3.17 g, 90%). This is known compound and spectroscopic data were identical with those from literature.

(**1h**) 4-phenylpent-4-en-1-ol[22]



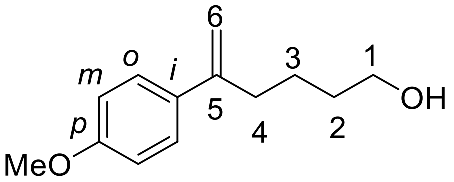
To a two necked flask, $Pd(PPh_3)_4$ (0.692 g, 0.6 mmol), 1,4-dioxane (60 mL), phenyl boronic acid (3.04 g, 24 mmol), 4-pentyne-1-ol (1.65 g, 20 mmol) and acetic acid (0.22 mL, 4.0 mmol) were added. The reaction mixture was stirred for 16 h at 80 °C. The mixture was filtered and the solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (2.60 g, 80%). This is known compound and spectroscopic data were identical with those from literature.

(**1i**) 5-(p-tolyl)hex-5-en-1-ol



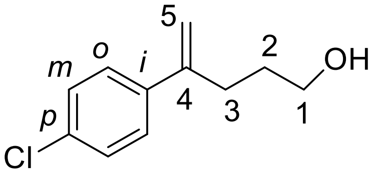
To a two necked flask, $Pd(PPh_3)_4$ (0.343 g, 0.297 mmol), 1,4-dioxane (20 mL), *p*-tolyl boronic acid (1.70 g, 12.5 mmol), 5-hexyn-1-ol (0.981 g, 0.999 mmol) and acetic acid (0.101 g, 1.68 mmol) were added. After stirring for 24 h at 80 °C, the reaction mixture was filtered through a short pad of celite and the filtrate was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (1.17 g, 61%). IR: (neat) 3444 (OH) cm^{-1}, 1624 (C=C) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.29 (d, *J* = 8.2 Hz, 2H, *o*), 7.13 (d, *J* = 8.2 Hz, 2H, *m*), 5.24 (d, *J* = 1.4 Hz, 1H, 6-H^A), 5.01 (d, *J* = 1.4 Hz, 1H, 6-H^B), 3.62 (t, *J* = 6.3 Hz, 2H, 1-H_2), 2.51 (t, *J* = 7.7 Hz, 2H, 4-H_2), 2.34 (s, 3H, 7-H_3), 1.67-1.54 (m, 2H, 2-H_2), 1.54-1.41 (m, 2H, 3-H_2), 1.67-1.41 (br, 1H, OH); ^{13}C NMR: (100 MHz, $CDCl_3$) 148.0 (s, C-5), 138.1 (s, *p*), 137.0 (s, *i*), 128.9 (d, *m*), 125.9 (d, *o*), 111.6 (t, C-6), 62.7 (t, C-1), 35.0 (t, C-4), 32.3 (t, C-2), 24.3 (t, C-3), 21.0 (q, C-7); MS: (EI, 70 eV) *m*/*z* 190 (M, 28); HRMS: (EI, 70 eV) Calculated ($C_{13}H_{18}O$) 190.1358 (M) Found: 190.1355.

(**1j**) 5-(4-methoxyphenyl)hex-5-en-1-ol



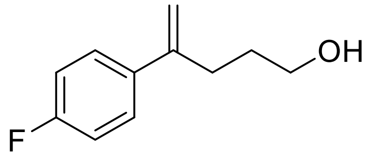
To a two necked flask, $Pd(PPh_3)_4$ (0.352 g, 0.305 mmol), 1,4-dioxane (20 mL), *p*-methoxy phenyl boronic acid (1.85 g, 12.2 mmol), 5-hexyn-1-ol (0.977 g, 9.95 mmol) and acetic acid (0.117 g, 1.95 mmol) were added. After stirring for 24 h at 80 °C, the reaction mixture was filtered through a short pad of celite and the filtrate was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.993 g, 48%). IR: (neat) 3400 (OH) cm^{-1}, 1608 (C=C) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.35 (d, *J* = 8.9 Hz, 2H, *o*), 6.86 (d, *J* = 8.9 Hz, 2H, *m*), 5.21 (s, 1H, 6-H^A), 4.98 (s, 1H, 6-H^B), 3.81 (s, 3H, OMe), 3.65 (t, *J* = 6.0 Hz, 2H, 1-H_2), 2.51 (t, *J* = 7.5 Hz, 2H, 4-H_2), 1.66-1.46 (m, 4H, 2-H_2 and 3-H_2), 1.39 (s, 1H, OH); ^{13}C NMR: (100 MHz, $CDCl_3$) 158.9 (s, *p*), 147.5 (s, C-5), 133.5 (s, *i*), 127.1 (d, *o*), 113.6 (d, *m*), 110.9 (t, C-6), 62.8 (t, C-1), 55.2 (q, OMe), 35.0 (t, C-4), 32.3 (t, C-3), 24.3 (t, C-2); MS: (EI, 70 eV) *m*/*z* 206 (M, 24); HRMS: (EI, 70 eV) Calculated ($C_{13}H_{18}O_2$) 206.1307 (M) Found: 206.1308.

(**1k**) 4-(4-chlorophenyl)pent-4-en-1-ol



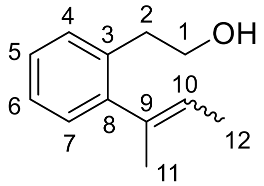
To a two necked flask, $Pd(PPh_3)_4$ (0.352 g, 0.305 mmol), 1,4-dioxane (20 mL), *p*-chloro phenyl boronic acid (1.81 g, 11.6 mmol), 4-pentyn-1-ol (0.811 g, 9.64 mmol) and acetic acid (0.125 g, 2.08 mmol) were added. After stirring for 24 h at 80 °C, the reaction mixture was filtered through a short pad of celite and the filtrate was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.715 g, 36%). IR: (neat) 3433 (OH) cm^{-1}, 1716 (C=C) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.34 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 8.9 Hz, 2H), 5.28 (d, J = 0.92 Hz, 1H, 5-H^A), 5.10 (d, J = 0.92 Hz, 1H, 5-H^B), 3.65 (t, J = 6.4 Hz, 2H, 1-H_2), 2.57 (t, J = 7.8 Hz, 2H, 3-H_2), 1.70 (tt, J = 7.8, 6.4 Hz, 2H, 2-H_2), 1.29 (s, 1H, OH); ^{13}C NMR: (100 MHz, $CDCl_3$) 146.8 (s, C-4), 139.4 (s, *i*), 133.2 (s, *p*), 128.4 (d), 127.4 (d), 113.0 (t, C-5), 62.2 (t, C-1), 31.4 (t, C-3), 30.9 (t, C-2); MS: (EI, 70 eV) *m*/*z* 196 (M, 2); HRMS: (EI, 70 eV) Calculated ($C_{11}H_{13}ClO$) 196.0655 (M) Found: 196.0654.

(**1l**) 4-(4-fluorophenyl)pent-4-en-1-ol[22]



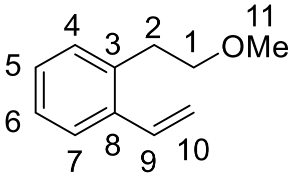
To a two necked flask, $Pd(PPh_3)_4$ (0.328 g, 0.3 mmol), 1,4-dioxane (20 mL), *p*-fluorophenyl boronic acid (1.69 g, 12 mmol), 4-pentyne-1-ol (0.839 g, 10 mmol) and acetic acid (0.13 g, 2.0 mmol) were added. The reaction mixture was stirred for 24 h at 80 °C. The mixture was filtered and the solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.341 g, 19%). This is known compound and spectroscopic data were identical with those from literature.

(**1m**) 2-(2-(but-2-en-2-yl)phenyl)ethan-1-ol



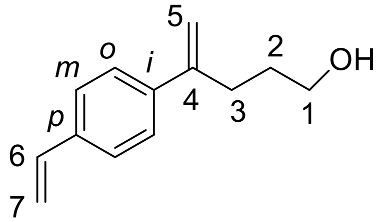
To a three necked flask, THF (35 mL) and 1-bromo-2-(but-2-en-2-yl)benzene (2.55 g, 12 mmol) were added. This solution was cooled at -78 °C and n-BuLi (1.6 M hexane solution, 9 mL, 13 mmol) was dropped over 15 minutes. After stirring for 1.5 h at -78 °C, to the reaction mixture was dropped ethylene oxide (1.1 M in THF, 16 mL,18 mmol) and the mixture was stirred for 0.5 h at -78 °C. The reaction mixture was warm to room temperature and quenched by sat. NH_4Cl aq. (15 mL). This solution was extracted with diethyl ether (20 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.368 g, 17%, ratio of stereoisomer = 85:15). IR: (neat) 3352 (OH) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) major stereoisomer 7.30-7.19 (m, 3H, 4-H, 5-H and 6-H), 7.03 (dd, *J* = 5.6, 3.6 Hz, 1H, 7-H), 5.58 (qq, *J* = 6.5, 1.7 Hz, 1H, 10-H), 3.80 (dd, *J* = 7.0, 12.8 Hz, 2H, 1-H_2), 2.91-2.76 (m, 2H, 2-H_2), 1.96 (m, 3H, 11-H_3), 1.41-1.33 (br, 1H, OH), 1.37 (d, *J* = 6.5 Hz, 3H, 12-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) major stereoisomer 142.3 (s, C-8), 136.7 (s, C-9), 135.3 (s, C-3), 129.5 (d, C-4), 128.8 (d, C-7), 126.8 (d), 126.6 (d), 122.4 (d, C-10), 63.4 (t, C-1), 36.1 (t, C-2), 26.0 (q, C-11), 14.8 (q, C-12); MS: (CI, 70 eV) *m/z* 176 (M, 5); HRMS: (EI, 70 eV) Calculated ($C_{12}H_{16}O$) 176.1201 (M) Found: 176.1205.

(**1n**) 1-(2-methoxyethyl)-2-vinylbenzene



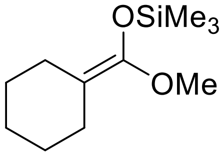
To a branched reactor vessel, NaOH aq. (50 wt%, 1g), benzene (2 mL), 2-(2-vinylphenyl)ethan-1-ol (0.737 g, 5 mmol), tributylamine (0.0492 g, 0.27 mmol) and dimethyl sulfate (0.962 g, 8 mmol) were added. After stirring for 3 h at 40 °C, the reaction mixture was quenched by diethyl ether (4 mL) and H_2O (4 mL). This solution was extracted with diethyl ether (5 mL x 3), and washed by H_2O (4 mL) and sat. NaCl aq. (5 mL). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane) column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.649 g, 81%). IR: (neat) 1115 (OMe) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.49 (dd, *J* = 3.6, 5.3 Hz, 1H), 7.24-7.15 (m, 3H), 7.01 (dd, *J* = 17.4, 11.1 Hz, 1H, 9-H), 5.64 (dd, *J* = 17.4, 1.4 Hz, 1H, 10-H^A), 5.30 (dd, *J* = 11.1, 1.4 Hz, 1H, 10-H^B), 3.53 (t, *J* = 7.7 Hz, 2H, 1-H_2), 3.34 (s, 3H, 11-H_3), 2.97 (t, *J* = 7.7 Hz, 2H, 2-H_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 136.9 (s, C-8), 135.9 (s, C-3), 134.4 (d, C-9), 130.0 (d, C-4), 127.7 (d), 126.7 (d), 125.8 (d), 115.7 (t, C-10), 73.0 (t, C-1), 58.6 (q, C-11), 33.5 (t, C-2); MS: (CI, 70 eV) *m/z* 163 ($[M + 1]^+$, 100), 131 (52); HRMS: (EI, 70 eV) Calculated ($C_{11}H_{14}O$) 162.1045 (M^+) Found: 162.1046; Analysis: $C_{11}H_{14}O$ (162.10) Calculated: C, 81.44; H, 8.70 Found: C, 81.16; H, 8.52.

(**1o**) 2-(2-(prop-1-en-2-yl)phenyl)ethan-1-ol



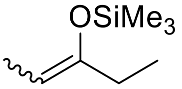
To a two necked flask, Pd(PPh$_3$)$_4$ (0.420 g, 0.363 mmol), 1,4-dioxane (20 mL), *p*-vinyl boronic acid (2.20 g, 14.9 mmol), 4-pentyn-1-ol (1.05 g, 12.5 mmol) and acetic acid (0.13 mL, 2.40 mmol) were added. After stirring for 29 h at 80 °C, the reaction mixture was filtered through a short pad of celite and the filtrate was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (1.77 g, 75%). IR: (neat) 3359 (OH) cm^{-1}, 1628 (C=C) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.42-7.36 (m, 4H), 6.71 (dd, *J* = 18.4, 10.6 Hz, 1H, 6-H), 5.76 (d, *J* = 18.4 Hz, 1H, 7-H^A), 5.33 (s, 1H, 5-H^A), 5.25 (d, *J* = 10.6 Hz, 1H, 7-H^B), 5.10 (s, 1H, 5-H^B), 3.66 (t, *J* = 6.3 Hz, 2H, 1-H$_2$), 2.61 (t, *J* = 7.7 Hz, 2H, 3-H$_2$), 1.73 (tt, *J* = 6.3, 7.7 Hz, 2H, 2-H$_2$), 1.51 (br, 1H, OH); ^{13}C NMR: (100 MHz, CDCl$_3$) 147.4 (s, C-4), 140.2 (s, *i*), 136.7 (s, *p*), 136.3 (d, C-6), 126.2 (d), 126.1 (d), 113.7 (t, C-7), 112.5 (t, C-5), 62.4 (t, C-1), 31.4 (t, C-3), 31.1 (t, C-2); MS: (CI, 70 eV) *m/z* 189 ([M + 1]$^+$, 100); HRMS: (EI, 70 eV) Calculated ($C_{13}H_{16}O$) 188.1201 (M) Found: 188.1199.

(**2b**) (cyclohexylidene(methoxy)methoxy)trimethylsilane[4g]



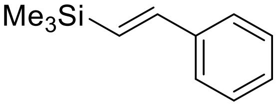
To a solution of diisopropylamine (11.5 g, 110 mmol) in THF (80 mL) was added *n*-BuLi (63 mL, 1.6 M in hexane) at 0 ºC. The resulted solution was stirred for 10 min at room temperature. Then, a solution of methyl cyclohexanecarboxyrate (11.4 g, 80 mmol) in THF (30 mL) was slowly added to the LDA solution at -78 ºC. After the solution was stirred for 2 h at -78 ºC, trimethylsilylchloride (10.8 g, 100 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 20 h at room temperature. The reaction mixture was poured into ice water and hexane, which was extracted with hexane. The organic phase was washed with brine, dried (MgSO$_4$) and concentrated. The obtained crude oil was purified by distillation (bp. 100-102 ºC, 20 mmHg) to give the desired product (14.3 g, 83%). This is known compound and spectroscopic data were identical with those from literature.

(**2c**) 3-trimetylsilyloxy-2-pentene[23]



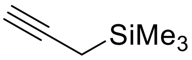
To a solution of diisopropylamine (10.1 g, 100 mmol) in THF (100 mL) was added *n*-BuLi (1.6 M in hexane, 63 mL, 100 mmol) at 0 °C. After stirring at 0 °C for 15 min, then to reaction mixture was added 3-pentanone (6.89 g, 80 mmol) dropwise at -78 °C. After stirred for 30 min at -78 °C, Me_3SiCl (10.9 g, 100 mmol) was added dropwise at -78 °C. The reaction mixture was allowed to reach room temperature and stirred for 30 min. Then, sat. $NaHCO_3$ aq. (50 mL) was added and the solution was extracted with pentane (50 mL x 3). The organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by distillation under reduced pressure (76 °C, 85 mmHg) to give the product (12.0 g, 76% yield, E/Z = 5:1). This is known compound and spectroscopic data were identical with those from literature.

(**2g**) (*E*)-trimethyl(styryl)silane[24,25]



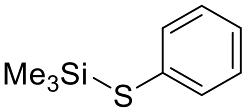
To a three necked flask, trimethyl(phenylethynyl)silane (3.63 g, 20.8 mmol) and dry hexane (5 mL) were added. To the reaction mixture was dropped DIBAL-H (1.0 M in hexane, 24 mL, 24 mmol). After stirring for 13 h at rt, the reaction mixture was quenched by 4 N HCl aq. (17 mL) at 0 °C. The mixture was extracted by Et_2O (20 mL x 3) and the collected organic layer was washed with sat. NaCl aq. (60 mL x 3). The organic layer was dried ($MgSO_4$) and the solvent was evaporated and the residue was purified by distillation under reduced pressure (112 °C, 23 mmHg) to give the product (2.23 g, 60%). This is known compound and spectroscopic data were identical with those from literature.

(**2i**) trimethyl(prop-2-yn-1-yl)silane[26]



To a three necked flask, Mg (1.82 g, 75 mmol), Et_2O (16 mL) and $HgCl_2$ (0.255 g, 0.94 mmol) were added. After vigolously stirring for 30 minutes at rt, propargyl bromide (1.1 M in Et_2O, 2 mL, 2.2 mmol) was dropped to the mixture. The reaction mixture was cooled into 0 °C and propargyl bromide (1.1 M in Et_2O, 31 mL, 34.1 mmol) was dropped to the reaction mixture. After stirring for 30 minutes at rt, the reaction mixture was cooled into 0 °C and Me_3SiCl (3.34 g, 30.7 mmol) was dropped to the reaction mixture. After vigolously stirring for 9 h at rt, the reaction mixture was filtered through a celite pad and the filtrate was purified by column chromatography (Et_2O, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (51wt% in Et_2O, 2.91 g, 36%). This is known compound and spectroscopic data were identical with those from literature.

(**2j**) trimethyl(phenylthio)silane[27,28]



To a three necked flask, Et_2O (32 mL) and benzenethiol (3.60 g, 33 mmol) were added. This solution was cooled at -78 °C and *n*-BuLi (1.6 M hexane solution, 52 mL, 82.5 mmol) was dropped to the mixture over 15 minutes, followed by Me_3SiCl was dropped over 4 minutes. After stirring for 2 hours, the reaction mixture was quenched by dry hexane (18 mL). The solvent was evaporated and the residue was filtered and the residue was washed by hexane. The solvent was evaporated and the residue was purified by distillation under reduced pressure (110 °C, 20 mmHg) to give the product (4.82 g, 81%). This is known compound and spectroscopic data were identical with those from literature.

General procedure for InI_3 catalyzed hydrofunctionalization of styrene derivatives 1 using organosilicon nucleophiles 2 (Table 1-3, Scheme 3A and Scheme 6)

To a solution of acid catalyst (10 mol %) in 1,2-dichloroethane (1 mL) was added styrene derivatives **1** (0.5 mmol). The mixture was stirred at 80 °C for 24 h and then cooled to rt. Organosilicon nucleophiles **2** (0.75 mmol) was added to the reaction mixture. After stirring at RT for 2 h, the mixture was quenched by diethyl ether (2 mL), Bu_4NF (1 M in THF, 1 mL) and sat. Na_2CO_3 aq. (2 mL) and then extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (column length 11 cm, diameter 26 mm, spherical silica gel).

Experimental procedure for InI_3 catalyzed hydroalkoxylation of styrene derivative 1a (Entry 7 in Table 1)

To a solution of InI_3 (0.0250 g, 0.0504 mmol) in 1,2-dichloroethane (1 mL) was added 2-(2-vinylphenyl)ethan-1-ol **1a** (0.0777 g, 0.524 mmol). After stirring at 80 °C for 24 h, the mixture was quenched by diethyl ether (2 mL) and sat. Na_2CO_3 aq. (2 mL), and then extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the yield of cyclic ether **4** was determined by ^{1}H-NMR.

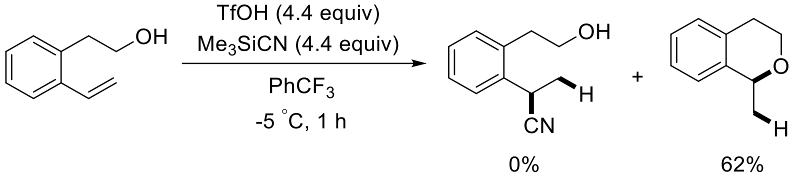
Experimental procedure for InI_3 catalyzed hydroalkoxylation of styrene with methanol (Scheme 3-B)

To a solution of InI_3 (0.0241 g, 0.050 mmol) in 1,2-dichloroethane (1.0 mL) and methanol (20 μL, 0.50 mmol) was added styrene (56 μL, 0.50 mmol). After stirring at 80 °C for 24 h, the mixture was quenched by diethyl ether (2 mL) and sat. Na_2CO_3 aq. (2 mL), and then extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the yield of benzyl ether **6** was determined by ^{1}H-NMR.

Experimental procedure for InI_3 catalyzed hydroalkoxylation of styrene derivative 1a in the presence of proton scavenger (Scheme 4)

To a solution of InI_3 (0.05 mmol) and proton scavenger (0.15 mmol) in 1,2-dichloroethane (1 mL) was added 2-(2-vinylphenyl)ethan-1-ol **1a** (0.50 mmol). After stirring at 80 °C for 24 h, the mixture was quenched by diethyl ether (2 mL) and sat. Na_2CO_3 aq. (2 mL), and then extracted with diethyl ether (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the yield of the cyclic ether **4** was determined by ^{1}H-NMR.

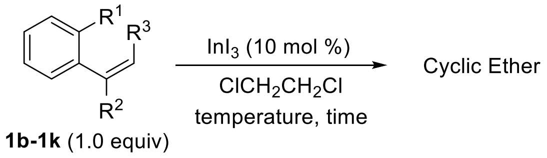
Hydrocyanation of styrene derivative with reported method

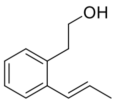
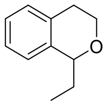
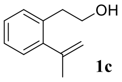
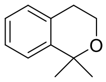


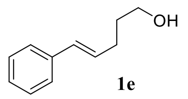
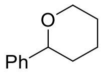
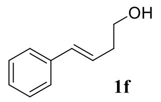
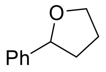
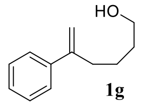
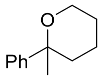
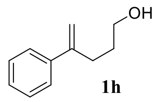
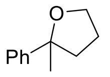
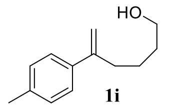
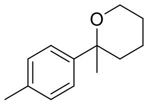
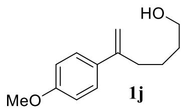
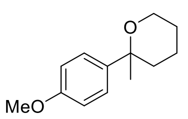
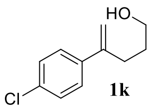
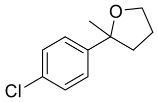
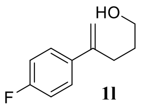
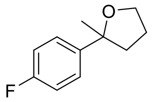
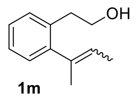
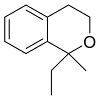
Scheme S1. Hydrocyanation of styrene derivative **1a** with reported method.[4b]

Hydroalkoxylation of various types of styrene derivaives

Table S1. Hydroalkoxylation of various types of styrene derivatives.[a]



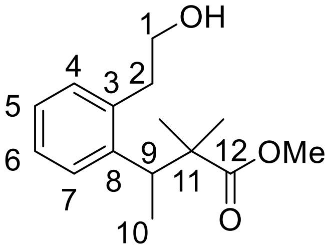
Entry	1	Temp (°C)	Time (h)	Cyclic ether	Yield (%)[b]
1	 **1b**	80 °C	96		64
2	 **1c**	80 °C	89		80

3	 **1e**	80 °C	89		71
4	 **1f**	80 °C	72		45
5	 **1g**	RT	45		92
6	 **1h**	RT	14		80
7	 **1i**	RT	7		98
8	 **1j**	RT	7		58
9	 **1k**	RT	23		63
10	 **1l**	RT	21		87
11	 **1m**	70	4		91

[a] **1** (0.5 mmol), catalyst (0.05 mmol), $ClCH_2CH_2Cl$ (1 mL), RT -80 °C, 7-96 h. [b] Yields were determined by NMR analysis.

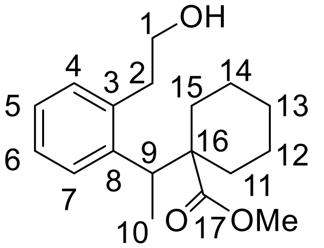
Product date

Methyl 3-[2-(2-hydroxyethyl)phenyl]-2,2-dimethylbutanoate (**3aa**)



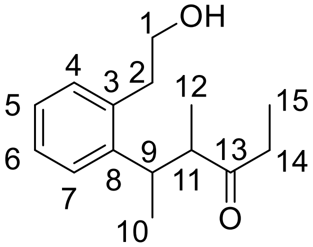
From InI_3 (0.0254 g, 0.0513 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0740 g, 0.499 mmol), and dimethylketene methyl trimethylsilylacetal (0.141 g, 0.809 mmol) following general procedure, **3aa** (0.089 g, 71%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3440 (OH) cm^{-1}, 1728 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.25-7.10 (m, 4H, 4-H, 5-H, 6-H and 7-H), 3.87-3.69 (m, 2H, 1-H$_2$), 3.63 (s, 3H, OMe), 3.54 (q, J = 7.2 Hz, 1H, 9-H), 3.27 (ddd, J = 13.5, 7.2, 6.8 Hz, 1H, 2-H^A), 2.79 (ddd, J = 13.5, 7.7, 7.2 Hz, 1H, 2-H^B), 1.47 (s, 1H, OH), 1.23 (d, J = 7.2 Hz, 3H, 10-H$_3$), 1.18 (s, 3H, 11-Me^A), 1.11 (s, 3H, 11-Me^B);^{13}C NMR: (100 MHz, $CDCl_3$) 178.3 (s, C-12), 141.5 (s, C-8), 136.8 (s, C-3), 130.1 (d, C-4), 128.0 (d), 126.3 (d), 126.2 (d), 63.6 (t, C-1), 51.7 (q, C-13), 47.0 (s, C-11), 39.9 (d, C-9), 36.6 (t, C-2), 24.0 (q, 11-Me^B), 21.2 (q, 11-Me^A), 17.5 (q, C-10); MS: (CI, 70 eV) *m/z* 251 ([M + 1]$^+$, 100); HRMS: (EI, 70 eV) Calculated ($C_{15}H_{22}O_3$) 250.1569 (M$^+$) Found: 250.1571.

Methyl 1-(1-(2-(2-hydroxyethyl)phenyl)ethyl)cyclohexane-1-carboxylate (**3ab**)



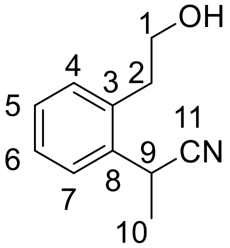
From InI_3 (0.0495 g, 0.10 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0755 g, 0.509 mmol), and (cyclohexylidene(methoxy)methoxy)trimethylsilane (0.327 g, 1.53 mmol) following general procedure (rt, 3 h at 2nd step), **3ab** (0.109 g, 74%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3440 (OH) cm^{-1}, 1716 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.19-7.11 (m, 4H, Ar), 3.78-3.67 (m, 2H, 1-H$_2$), 3.60 (s, 3H, OMe), 3.32-3.19 (m, 2H, 9-H and 2-H^A), 2.75 (dt, J = 14.0, 6.8 Hz, 1H, 2-H^B), 2.34-2.28 (br, 1H), 2.21 (s, 1H, OH), 2.08-2.00 (br, 1H), 1.65-1.51 (br, 3H), 1.33-1.21 (m, 2H), 1.24 (d, J = 7.2 Hz, 3H, 10-H$_3$), 1.21-0.95 (m, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) 176.4 (s, C-17), 141.6 (s, C-8), 136.6 (s, C-3), 129.9 (d, C-4), 128.2 (d, C-7), 126.2 (d), 125.9 (d), 63.5 (t, C-1), 52.2 (s, C-11), 51.2 (q, OMe), 41.9 (d, C-9), 36.6 (t, C-2), 32.7 (t), 30.7 (t), 25.5 (t), 23.8 (t), 23.6 (t), 17.0 (q, C-10); MS: (EI, 70 eV) *m/z* 290 (M, 1); HRMS: (CI, 70 eV) Calculated ($C_{18}H_{27}O_3$) 291.1960 ($[M + 1]^+$) Found: 291.1957.

5-[2-(2-Hydroxyethyl)phenyl]-4-methylhexan-3-one (**3ac**)



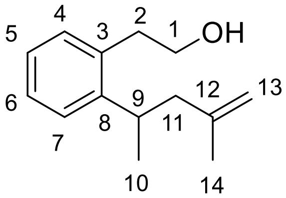
From InI_3 (0.0226 g, 0.0456 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0765 g, 0.516 mmol), and (*Z*)-trimethyl(pent-2-en-3-yloxy)silane (0.216 g, 1.36 mmol) following general procedure (rt, 5 h at 2nd step), **3ac** (0.0837 g, 69%, d.r. = 54:46) was obtained after column chromatography (hexane/ethyl acetate = 80:20). IR: (neat) 3433 (OH) cm^{-1}, 1709 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) diastereo mixture: 7.26-7.07 (m, 4H), 3.97-3.88 (m, 0.46H), 3.88-3.75 (m, 1.54H), 3.39-3.25 (m, 1H), 3.07 (dt, *J* = 13.5, 6.8 Hz, 0.46H), 3.02-2.78 (m, 2.54H), 2.61 (dq, J = 18.4, 7.2 Hz, 0.54H), 2.53-2.32 (m, 1H), 2.03 (dq, *J* = 17.8, 7.2 Hz, 0.46H), 1.82 (s, 0.54H), 1.20 (t, *J* = 6.8 Hz, 3H), 1.11 (t, *J* = 6.8 Hz, 1.62H), 1.10 (t, *J* = 7.2 Hz, 1.38H), 0.806 (t, *J* = 7.2 Hz, 1.62H), 0.788 (t, *J* = 6.8 Hz, 1.38H); ^{13}C NMR: (100 MHz, $CDCl_3$) diastereo mixture: 215.9 (s), 215.7 (s), 144.7 (s), 143.4 (s), 136.2 (s), 136.1 (s), 130.6 (d), 130.4 (d), 127.1 (d), 126.7 (d), 126.1 (d), 126.0 (d), 125.5 (d), 63.8 (t), 63.4 (t), 52.7 (d), 52.0 (d), 36.6 (d), 36.5 (d), 36.4 (t), 36.3 (t), 36.2 (t), 36.0 (t), 21.4 (q), 19.8 (q), 16.2 (q), 15.6 (q), 7.64 (q), 7.41 (q); MS: (CI, 70 eV) m/z 235 ($[M + 1]^+$, 100); HRMS: (CI, 70 eV) Calculated ($C_{15}H_{23}O_2$) 235.1698 ($[M + 1]^+$) Found: 235.1698.

5-[2-(2-Hydroxyethyl)phenyl]-4-methylhexan-3-one (**3ad**)



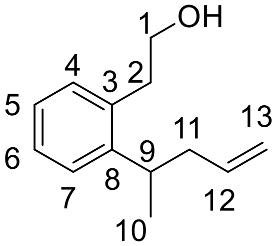
From InI_3 (0.0565 g, 0.114 mmol, 20 mol %), 2-(2-vinylphenyl)ethan-1-ol (0.0765 g, 0.516 mmol), and trimethylsilyl cyanide (0.3 mL, 2.5 mmol) following general procedure (70 °C, 14 h at 2nd step), **3ad** (0.0284 g, 31%) was obtained after column chromatography (hexane/ethyl acetate = 80:20). IR: (neat) 3429 (OH) cm^{-1}, 2241 (CN) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.54-7.47 (m, 1H), 7.34-7.20 (m, 3H, 4-H, 5-H and 6-H), 4.24 (q, *J* = 6.8 Hz, 1H, 9-H), 3.92-3.81 (m, 2H, 1-H_2), 2.89 (t, *J* = 6.8 Hz, 2H, 2-H_2), 1.71 (s, 1H, OH), 1.62 (d, *J* = 6.8 Hz, 3H, 10-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 136.0 (s), 135.6 (s), 130.5 (d, C-4), 128.3 (d), 127.6 (d), 127.3 (d), 122.2 (s, C-11), 63.2 (t, C-1), 35.2 (t, C-2), 27.7 (d, C-9), 21.0 (d, C-10); MS: (CI, 70 eV) *m/z* 176 ([M + 1]$^+$, 25), 158 (M – OH, 100); HRMS: (EI, 70 eV) Calculated ($C_{11}H_{13}NO$) 175.0997 (M^+) Found: 175.0998.

2-(2-(4-Methylpent-4-en-2-yl)phenyl)ethan-1-ol (**3ae**)



From InI_3 (0.0244 g, 0.0492 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0744 g, 0.502 mmol) and trimethyl(2-methylallyl)silane (0.115 g, 0.896 mmol) following general procedure (rt, 4 h at 2nd step), **3ae** (0.056 g, 55%) was obtained after column chromatography (hexane/ethyl acetate = 80:20). IR: (neat) 3410 (OH) cm^{-1}, 1647 (C=C) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.27 (d, *J* = 7.2 Hz, 1H, 7-H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H, 4-H), 7.13 (t, *J* = 7.2 Hz, 1H), 4.74 (s, 1H, 13-H^A), 4.68 (s, 1H, 13-H^B), 3.83 (t, *J* = 6.8 Hz, 2H, 1-H_2), 3.27-3.16 (m, 1H, 9-H), 3.03-2.88 (m, 2H, 2-H_2), 2.32 (dd, *J* = 13.5, 6.3 Hz, 11-H^A), 2.23 (dd, *J* = 13.5, 8.7 Hz, 11-H^B), 1.70 (s, 3H, 14-H_3), 1.50 (s, 1H, OH), 1.20 (d, *J* = 6.8 Hz, 3H, 10-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 146.0 (s, C-8), 144.0 (s, C-12), 135.0 (s, C-3), 130.1 (d, C-4), 126.9 (d), 126.1 (d, C-7), 125.8 (d), 112.2 (t, C-13), 63.5 (t, C-1), 46.6 (t, C-11), 35.9 (t, C-2), 32.1 (d, C-9), 22.4 (q, C-14), 21.6 (q, C-10); MS: (EI, 70 eV) *m/z* 204 (M, 2); HRMS: (CI, 70 eV) Calculated ($C_{14}H_{21}O$) 205.1592 ([M + 1]$^+$) Found: 205.1589.

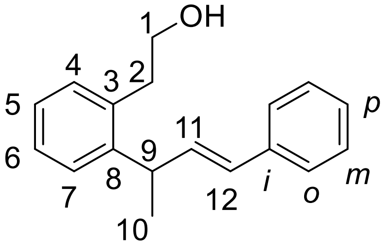
2-[2-(Pent-4-en-2-yl)phenyl]ethan-1-ol (**3af**)



From InI_3 (0.0303 g, 0.0611 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0745 g, 0.503 mmol), allyltrimethylsilane (0.0834 g, 0.730 mmol) and Me_3SiBr (0.0097 g, 0.0634 mmol) following general procedure (rt, 3 h at 2nd step), **3af** (0.082 g, 86%) was obtained after column chromatography (hexane/ethyl acetate = 80:20). IR: (neat) 3344 (OH) cm^{-1}, 1666 (C=C) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.29-7.10 (m, 4H, 4-H, 5-H, 6-H and 7-H), 5.77-5.64 (m, 1H, 12-H), 5.01 (d, *J* = 14.0 Hz, 1H, 13-H^A), 4.95 (d, *J* = 10.1 Hz, 1H, 13-H^B), 3.80 (t, *J* = 7.2 Hz, 2H, 1-H_2), 3.09 (sextet, *J* = 7.0 Hz, 1H, 9-

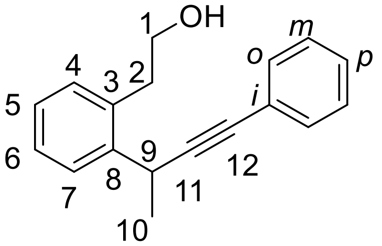
H), 3.00-2.85 (m, 2H, 2-H_2), 2.43-2.24 (m, 2H, 11-H_2), 1.59 (s, 1H, OH), 1.23 (d, J = 7.0 Hz, 3H, 10-H_3) ^{13}C NMR: (100 MHz, $CDCl_3$) 145.4 (s, C-8), 137.0 (d, C-12), 135.1 (s, C-3), 130.1 (d, C-4), 126.9 (d), 126.0 (d), 125.8 (d), 116.1 (t, C-13), 63.5 (t, C-1), 42.4 (t, C-11), 36.0 (t, C-2), 34.1 (d, C-9), 21.8 (q, C-10); MS: (CI, 70 eV) *m/z* 191 ([M + 1]$^+$, 30), 173 (M - OH, 100), 149 (M – CH_2CHCH_2, 35); HRMS: (EI, 70 eV) Calculated ($C_{13}H_{18}O$) 190.1358 (M$^+$) Found: 190.1357.

(*E*)-2-[2-(4-Phenylbut-3-en-2-yl)phenyl]ethan-1-ol (**3ag**)



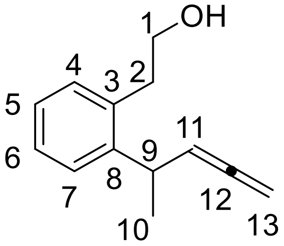
From InI_3 (0.0229 g, 0.0462 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0743 g, 0.501 mmol), (*E*)-trimethyl(styryl)silane (0.2687 g, 1.52 mmol) and Me_3SiBr (0.016 g, 0.105 mmol) following general procedure (rt, 10 h at 2nd step), **3ag** (0.0742 g, 59%) was obtained after column chromatography (hexane/ethyl acetate = 80:20). IR: (neat) 3402 (OH) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.35-7.14 (m, 9H, Ar), 6.37 (dd, J = 4.3, 15.9 Hz, 1H, 11-H), 6.35 (d, J = 15.9 Hz, 1H, 12-H), 3.94 (dq, J = 4.3, 6.8 Hz, 1H, 9-H), 3.85 (t, J = 6.8 Hz, 2H, 1-H_2), 2.98 (t, J = 6.8 Hz, 2H, 2-H_2), 1.58 (s, 1H, OH), 1.45 (d, J = 6.8 Hz, 3H, 10-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 143.9 (s, C-8), 137.4 (s, *i*), 135.4 (s, C-3), 135.2 (d, C-11), 130.2 (d, C-4), 128.5 (d), 127.2 (d), 127.04 (d), 127.01, 126.2 (d), 126.1 (d), 63.5 (t, C-1), 37.4 (d, C-9), 35.9 (t, C-2), 21.4 (q, C-10); MS: (CI, 70 eV) *m/z* 253 ([M + 1]$^+$, 5), 235 (M – OH, 100); HRMS: (EI, 70 eV) Calculated ($C_{18}H_{20}O$) 252.1514 (M$^+$) Found: 252.1514.

2-(2-(4-Phenylbut-3-yn-2-yl)phenyl)ethan-1-ol (**3ah**)



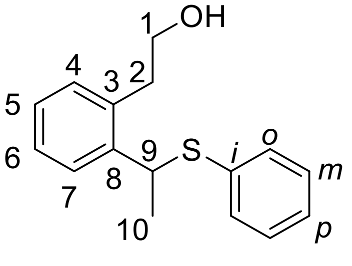
From InI_3 (0.0257 g, 0.0519 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0751 g, 0.507 mmol), trimethyl(phenylethynyl)silane (0.270 g, 1.55 mmol) and Me_3SiBr (0.0143 g, 0.0934 mmol) following general procedure (rt, 1 h at 2nd step), **3ah** (0.0684 g, 54%) was obtained after column chromatography (hexane/ethyl acetate = 80:20). IR: (neat) 3301 (OH) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.64 (d, J = 7.2 Hz, 1H, Ar), 7.43-7.38 (m, 2H, Ar), 7.30-7.22 (m, 4H, Ar), 7.22-7.17 (m, 2H, Ar), 4.24 (q, J = 6.8 Hz, 1H, 9-H), 3.88 (t, *J* = 7.2 Hz, 2H, 1-H_2), 3.04-2.92 (m, 2H, 2-H_2), 1.72 (s, 1H, OH), 1.56 (d, *J* = 6.8 Hz, 3H, 10-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 141.8 (s, C-8), 134.9 (s, C-3), 131.5 (d), 130.1 (d, C-4), 128.2 (d), 127.7 (d), 127.5 (d), 127.2 (d), 126.9 (d), 123.6 (s, *i*), 93.1 (s, C-11), 81.7 (s, C-12), 63.4 (t, C-1), 35.6 (t, C-2), 28.5 (d, C-9), 23.8 (q, C-10); MS: (CI, 70 eV) *m/z* 251 ([M + 1]$^+$, 20), 233 (M - OH, 100); HRMS: (CI, 70 eV) Calculated ($C_{18}H_{19}O$) 251.1436 ([M + 1]$^+$) Found: 251.1436.

2-[2-(Penta-3,4-dien-2-yl)phenyl]ethan-1-ol (**3ai**)



From InI_3 (0.0274 g, 0.0553 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0745 g, 0.503 mmol), trimethyl(prop-2-yn-1-yl)silane (51 wt % in Et_2O, 0.1653 g, 1.50 mmol) and Me_3SiBr (0.0170 g, 0.111 mmol) following general procedure (35 °C, 2 h at 2nd step), **3ai** (0.07 g, 68%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3394 (OH) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.31 (d, *J* = 7.7 Hz, 1H, 7-H), 7.25-7.21 (m, 1H), 7.20-7.14 (m, 2H), 5.30 (dt, *J* = 6.8, 6.5 Hz, 1H, 11-H), 4.83-4.74 (m, 2H, 13-H_2), 3.85 (dt, *J* = 6.3, 6.8 Hz, 2H, 1-H_2), 3.82-3.74 (m, 1H, 9-H), 2.972 (t, *J* = 6.8 Hz, 1H, 2-H^A), 2.966 (t, *J* = 6.8 Hz, 1H, 2-H^B), 1.41 (t, *J* = 6.3 Hz, 1H, OH), 1.34 (d, *J* = 7.0 Hz, 3H, 10-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 207.8 (s, C-12), 144.3 (s, C-8), 135.2 (s, C-3), 130.1 (d, C-4), 127.1 (d), 127.0 (d), 126.2 (d), 96.0 (d, C-11), 76.7 (t, C-13), 63.5 (t, C-1), 35.9 (t, C-2), 33.6 (d, C-9), 21.5 (q, C-10); MS: (CI, 70 eV) *m/z* 189 ([M + 1]$^+$, 10); HRMS: (EI, 70 eV) Calculated ($C_{13}H_{16}O$) 188.1201 (M^+) Found: 188.1199.

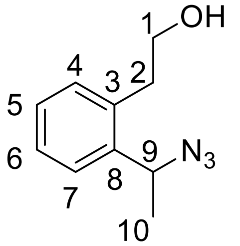
2-[2-(1-(Phenylthio)ethyl)phenyl]ethan-1-ol (**3aj**)



From InI_3 (0.0245 g, 0.0494 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0739 g, 0.499 mmol) and trimethyl(phenylthio)silane (0.278 g, 1.52 mmol) following general procedure (rt, 13 h at 2nd step), **3aj** (0.0758 g, 59%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3394 (OH) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.51 (d, *J* = 7.7 Hz, 1H, 7-H), 7.42-7.36 (m, 2H), 7.32-

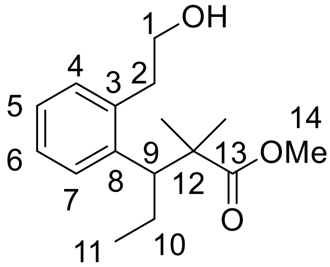
7.15 (m, 6H), 4.66 (q, 1H, 9-H), 3.88-3.73 (m, 2H, 1-H_2), 3.03-2.82 (m, 2H, 2-H_2), 1.77 (s, 1H, OH), 1.63 (d, *J* = 7.2 Hz, 3H, 10-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 141.1 (s, C-8), 135.7 (s), 134.7 (s), 133.2 (d), 130.1 (d, C-4), 128.8 (d), 127.6 (d), 127.2 (d), 127.1 (d), 127.0 (d), 63.4 (t, C-1), 43.3 (d, C-9), 35.7 (t, C-2), 22.3 (q, C-10); MS: (CI, 70 eV) *m*/*z* 259 ($[M + 1]^+$, 1), 149 (M – SPh, 100); HRMS: (EI, 70 eV) Calculated ($C_{16}H_{18}OS$) 258.1078 (M^+) Found: 258.1081.

2-[2-(1-Azidoethyl)phenyl]ethan-1-ol (**3ak**)



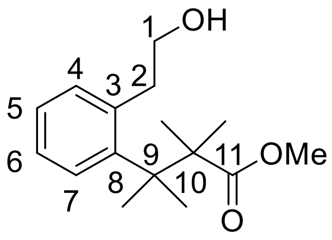
From InI_3 (0.0288 g, 0.0581 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0776 g, 0.524 mmol) and azidotrimethylsilane (0.2 mL, 1.5 mmol) following general procedure (50 °C, 4 h at 2nd step), **3ak** (0.0612 g, 54%) was obtained after column chromatography (hexane/ethyl acetate = 80:20). IR: (neat) 3437 (OH) cm^{-1}, 2102 (N=N=N) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.35 (d, *J* = 7.2 Hz, 1H, 7-H), 7.26-7.12 (m, 3H, 4-H, 5-H and 6-H), 4.89 (q, *J* = 6.8 Hz, 1H, 9-H), 3.77 (t, *J* = 6.8 Hz, 2H, 1-H_2), 2.87 (t, *J* = 6.8 Hz, 2H, 2-H_2), 1.65 (s, 1H, OH), 1.47 (d, *J* = 6.8 Hz, 3H, 10-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 139.2 (s, C-8), 135.7 (s, C-3), 130.3 (d, C-4), 128.1 (d), 127.2 (d), 126.1 (d, C-7), 63.5 (t, C-1), 56.7 (d, C-9), 35.4 (t, C-2), 21.1 (q, C-10); MS: (CI, 70 eV) *m*/*z* 164 ($[M + 1]^+ - N_2$, 30); HRMS: (CI, 70 eV) Calculated ($C_{10}H_{14}N_3O$) 192.1137 ($[M + 1]^+$) Found: 192.1134.

Methyl 3-[2-(2-hydroxyethyl)phenyl)]-2,2-dimethylpentanoate (**3ba**)



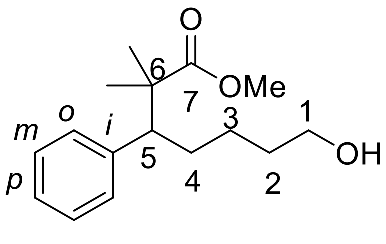
From InI_3 (0.0286 g, 0.0577 mmol), (*E*)-2-(2-(prop-1-en-1-yl)phenyl)ethan-1-ol (0.0799 g, 0.493 mmol) and dimethylketene methyl trimethylsilylacetal (0.2819 g, 1.62 mmol) following general procedure (80 °C, 15 h at 1st step), **3ba** (0.068 g, 52%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3452 (OH) cm^{-1}, 1728 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.24-7.14 (m, 4H, 4-H, 5-H, 6-H and 7-H), 3.93-3.93 (m, 1H, 1-H^A), 3.83-3.73 (m, 1H, 1-H^B), 3.65 (s, 3H, 14-H_3), 3.34 (dd, J = 11.8, 3.4 Hz, 1H, 9-H), 3.25 (dt, J = 14.0, 7.2 Hz, 1H, 2-H^A), 2.83 (ddd, J = 14.0, 7.7, 7.5 Hz, 1H, 2-H^B), 1.84-1.73 (m, 1H, 10-H^A), 1.66-1.58 (m, 1H, 10-H^B), 1.49-1.41 (m, 1H, OH), 1.16 (s, 3H, 12-Me^A), 1.03 (s, 3H, 12-Me^B), 0.677 (t, J = 7.2 Hz, 3H, 11-H$_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) 178.6 (s, C-13), 138.7 (s, C-8), 138.4 (s, C-3), 130.0 (d), 127.7 (d), 126.3 (d), 126.1 (d), 63.5 (t, C-1), 51.8 (q, C-14), 47.3 (s, C-12), 47.2 (d, C-9), 36.3 (t, C-2), 24.5 (q, 12-Me^B), 24.1 (t, C-10), 20.7 (q, 12-Me^A), 12.8 (q, C-11); MS: (CI, 70 eV) *m/z* 265 ([M + 1]$^+$, 100); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{25}O_3$) 265.1804 ([M + 1]$^+$) Found: 265.1803.

Methyl 3-[2-(2-hydroxyethyl)phenyl)]-2,2-dimethylpentanoate (**3ca**)



From InI_3 (0.0264 g, 0.0533 mmol), 2-(2-(prop-1-en-2-yl)phenyl)ethan-1-ol (0.0822 g, 0.507 mmol) and dimethylketene methyl trimethylsilylacetal (0.135 g, 0.774 mmol) following general procedure (80 °C, 6 h at 1st step), **3ca** (0.1047 g, 72%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3425 (OH) cm^{-1}, 1720 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.39-7.30 (m, 1H, 7-H), 7.21-7.08 (m, 3H, 4-H, 5-H and 6-H), 3.87 (t, J = 7.2 Hz, 2H, 1-H$_2$), 3.56 (s, 3H, OMe), 3.11 (t, J = 7.2 Hz, 2H, 2-H$_2$), 1.59 (s, 4H, 9-Me and OH), 1.16 (s, 3H, 10-Me); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.3 (s, C-11), 144.1 (s, C-8), 137.3 (s, C-3), 132.4 (d, C-4), 130.9 (d, C-7), 126.3 (d), 125.4 (d), 64.8 (t, C-1), 51.4 (q, OMe), 49.9 (s, C-10), 45.4 (s, C-9), 39.6 (t, C-2), 28.2 (q, 9-Me), 22.5 (q, 10-Me); MS: (EI, 70 eV) *m/z* 232 (M - MeOH, 5); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{25}O_3$) 265.1804 ([M + 1]$^+$) Found: 265.1801.

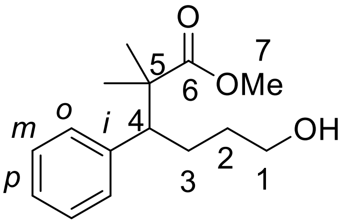
Methyl 7-hydroxy-2,2-dimethyl-3-phenylheptanoate (**3ea**)



From InI_3 (0.0278 g, 0.0561 mmol), (E)-5-phenylpent-4-en-1-ol (0.0864 g, 0.532 mmol) and dimethylketene methyl trimethylsilylacetal (0.149 g, 0.855 mmol) following general procedure (80 °C, 65 h at 1st step), **3ea** (0.040 g, 28%) was obtained after column chromatography (hexane/ethyl acetate =

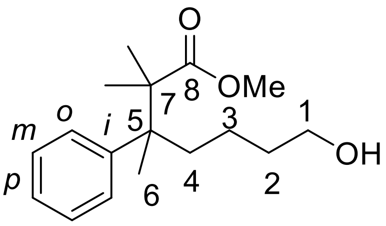
80:20). IR: (neat) 3444 (OH) cm^{-1}, 1728 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.25 (t, 2H, *m*), 7.22 (d, 1H, *p*), 7.15 (d, 2H, *o*), 3.64 (s, 3H, OMe), 3.51 (t, J = 6.8 Hz, 2H, 1-H_2), 2.96 (dd, J = 12.6, 3.4 Hz, 1H, 5-H), 1.89-1.77 (m, 1H, 4-H^A), 1.59-1.39 (m, 3H, 4-H^B and 2-H_2), 1.34 (s, 1H, OH), 1.18-1.05 (m, 2H, 3-H_2), 1.14 (s, 3H, 6-Me^A), 1.01 (s, 3H, 6-Me^B); ^{13}C NMR: (100 MHz, $CDCl_3$) 178.3 (s, C-7), 140.1 (s, *i*), 129.7 (d, *m*), 127.8 (d, *o*), 126.6 (d, *p*), 62.7 (t, C-1), 52.8 (d, C-5), 51.7 (q, OMe), 46.7 (s, C-6), 32.5 (t, C-2), 29.7 (t, C-4), 24.5 (q, 6-Me^A), 24.2 (t, C-3), 20.7 (q, 6-Me^B); MS: (CI, 70 eV) *m/z* 265 ([M + 1]$^+$, 74); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{25}O_3$) 265.1804 ([M + 1]$^+$) Found: 265.1805.

Methyl 6-hydroxy-2,2-dimethyl-3-phenylhexanoate (**3fa**)



From InI_3 (0.0338 g, 0.068 mmol), (*E*)-4-phenylbut-3-en-1-ol (0.0762 g, 0.514 mmol) and dimethylketene methyl trimethylsilylacetal (0.120 g, 0.688 mmol) following general procedure (80 °C, 120 h at 1st step), **3fa** (0.038 g, 30%) was obtained after column chromatography (hexane/ethyl acetate = 80:20). IR: (neat) 3437 (OH) cm^{-1}, 1728 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.38 (t, J = 7.2 Hz, 2H, *m*), 7.23 (t, J = 7.2 Hz, 1H, *p*), 7.16 (d, J = 7.2 Hz, 2H, *o*), 3.64 (s, 3H, 7-H_3), 3.55 (t, J = 6.8 Hz, 2H, 1-H_2), 2.99 (dd, J = 12.6, 2.9 Hz, 1H, 4-H), 1.92-1.79 (m, 1H, 3-H^A), 1.66-1.47 (m, 2H, 3-H^B and OH), 1.37-1.24 (m, 2H, 2-H_2), 1.16 (s, 3H, 5-Me^A), 1.02 (s, 3H, 5-Me^B); ^{13}C NMR: (100 MHz, $CDCl_3$) 178.4 (s, C-6), 139.9 (s, *i*), 129.7 (d, *o*), 127.9 (d, *m*), 126.7 (d, *p*), 62.5 (t, C-1), 52.4 (d, C-4), 51.7 (q, C-7), 46.7 (s, C-5), 31.1 (t, C-2), 26.2 (t, C-3), 24.6 (q, 5-Me^B), 20.6 (q, 5-Me^A); MS: (CI, 70 eV) *m/z* 251 ([M + 1]$^+$, 100); HRMS: (CI, 70 eV) Calculated ($C_{15}H_{23}O_3$) 251.1647 ([M + 1]$^+$) Found: 251.1649.

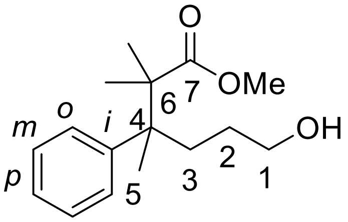
Methyl 7-hydroxy-2,2,3-trimethyl-3-phenylheptanoate (**3ga**)



From InI_3 (0.0253 g, 0.0511 mmol), 2-(2-vinylphenyl)ethan-1-ol (0.0911 g, 0.615 mmol) and dimethylketene methyl trimethylsilylacetal (0.125 g, 0.717 mmol) following general procedure (rt, 3 h at 1st step), **3ga** (0.084 g, 59%) was obtained after column chromatography (hexane/ethyl acetate =

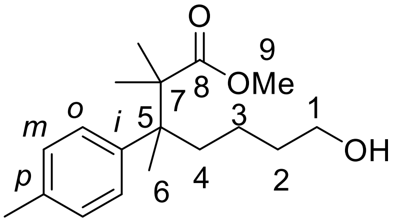
70:30). IR: (neat) 3444 (OH) cm^{-1}, 1720 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.32-7.15 (m, 5H, Ar), 3.55 (t, J = 7.0 Hz, 2H, 1-H$_2$), 3.50 (s, 3H, OMe), 2.24 (td, J = 13.0, 4.8 Hz, 1H, 4-H^A), 1.77 (s, 1H, OH), 1.63 (td, J = 13.0, 4.8 Hz, 1H, 4-H^B), 1.54 (tt, J = 7.7, 7.0 Hz, 2H, 2-H$_2$), 1.39 (s, 3H, 6-H$_3$), 1.28-1.15 (m, 1H, 3-H^A), 1.12 (s, 3H, 7-Me^A), 1.02 (s, 3H, 7-Me^B), 0.993-0.836 (m, 1H, 3-H^B); ^{13}C NMR: (100 MHz, CDCl$_3$) 177.2 (s, C-8), 143.0 (s, *i*), 128.2 (d), 127.3 (d), 125.9 (d, *p*), 62.7 (t, C-1), 51.2 (q, OMe), 49.7 (s, C-7), 45.9 (s, C-5), 34.8 (t, C-4), 33.5 (t, C-2), 22.1 (q, 7-Me^A), 21.7 (q, 7-Me^B), 21.2 (q, C-6), 20.8 (t, C-3); MS: (CI, 70 eV) *m/z* 279 ([M + 1]$^+$, 1), 247 (M - OMe, 3); HRMS: (CI, 70 eV) Calculated (C$_{17}$H$_{27}$O$_3$) 279.1960 ([M + 1]$^+$) Found: 279.1958.

Methyl 6-hydroxy-2,2,3-trimethyl-3-phenylhexanoate (**3ha**)



From InI$_3$ (0.0213 g, 0.0430 mmol), 4-phenylpent-4-en-1-ol (0.0862 g, 0.531 mmol) and dimethylketene methyl trimethylsilylacetal (0.139 g, 0.797 mmol) following general procedure (rt, 8 h at 1st step), **3ha** (0.092 g, 66%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3448 (OH) cm^{-1}, 1720 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.32-7.22 (m, 4H, *o* and *m*), 7.22-7.16 (m, 1H, *p*), 3.59 (td, J = 6.8, 1.9 Hz, 2H, 1-H$_2$), 3.50 (s, 3H, OMe), 2.31 (ddd, J = 14.0, 13.0, 3.38 Hz, 1H, 3-H^A), 1.73-1.59 (m, 2H, 3-H^B and OH), 1.48-1.34 (m, 1H, 2-H^A), 1.40 (s, 3H, 5-H$_3$) 1.22-1.09 (m, 1H, 2-H^B), 1.13 (s, 3H, 6-Me^A), 1.03 (s, 3H, 6-Me^B); ^{13}C NMR: (100 MHz, CDCl$_3$) 177.2 (s, C-7), 142.8 (s, *i*), 128.2 (d), 127.3 (d), 126.0 (d, *p*), 63.4 (t, C-1), 51.2 (q, OMe), 49.7 (s, C-6), 45.6 (s, C-4), 31.0 (t, C-3), 28.0 (t, C-2), 22.1 (q, 6-Me^B), 21.7 (q, 6-Me^A), 21.3 (q, C-5); MS: (CI, 70 eV) *m/z* 265 ([M + 1]$^+$, 100); HRMS: (EI, 70 eV) Calculated (C$_{16}$H$_{24}$O$_3$) 264.1725 (M$^+$) Found: 264.1724.

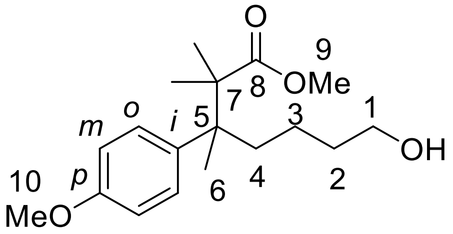
Methyl 7-hydroxy-2,2,3-trimethyl-3-(p-tolyl)heptanoate (**3ia**)



From InI$_3$ (0.0253 g, 0.0511 mmol), 5-phenylhex-5-en-1-ol (0.0908 g, 0.477 mmol) and dimethylketene methyl trimethylsilylacetal (0.123 g, 0.706 mmol) following general procedure (rt, 4 h at 1st step), **3ia**

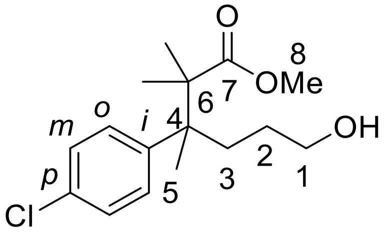
(0.097 g, 70%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3444 (OH) cm^{-1}, 1720 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.11 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 3.56 (t, *J* = 6.8 Hz, 2H, 1-H$_2$), 3.52 (s, 3H, 9-H$_3$), 2.31 (s, 3H, *p*-Me), 2.22 (td, *J* = 13.0, 3.9 Hz, 1H, 4-H^A), 1.61 (td, *J* = 12.6, 4.8 Hz, 1H, 4-H^B), 1.54 (tt, *J* = 6.8, 7.3 Hz, 2H, 2-H$_2$), 1.37 (s, 3H, 6-H$_3$), 1.30 (s, 1H, OH), 1.27-1.15 (m, 1H, 3-H^A), 1.10 (s, 3H, 7-Me^A), 1.01 (s, 3H, 7-Me^B), 0.99-0.87 (m, 1H, 3-H^B); ^{13}C NMR: (100 MHz, CDCl$_3$) 177.3 (s, C-8), 139.9 (s, *i*), 135.4 (s, *p*), 128.1 (d), 128.0 (d), 62.8 (t, C-1), 51.2 (q, C-9), 49.7 (s, C-7), 45.6 (s, C-5), 34.8 (t, C-4), 33.6 (t, C-2), 22.2 (q, 7-Me^A), 21.8 (q, 7-Me^B), 21.3 (q, C-6), 20.9 (t, C-3), 20.8 (q, *p*-Me); MS: (CI, 70 eV) *m/z* 293 ([M + 1]$^+$, 24); HRMS: (CI, 70 eV) Calculated ($C_{18}H_{29}O_3$) 293.2117 ([M + 1]$^+$) Found: 293.2114.

Methyl 7-hydroxy-3-(4-methoxyphenyl)-2,2,3-trimethylheptanoate (**3ja**)



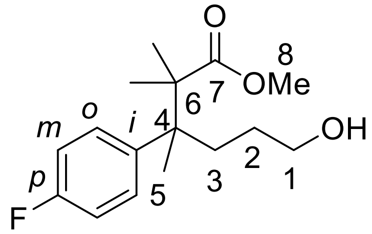
From InI$_3$ (0.0266 g, 0.0537 mmol), 5-(4-methoxyphenyl)hex-5-en-1-ol (0.1075 g, 0.521 mmol) and dimethylketene methyl trimethylsilylacetal (0.121 g, 0.692 mmol) following general procedure (rt, 1 h at 1st step), **3ja** (0.092 g, 57%) was obtained after column chromatography (hexane/ethyl acetate = 60:40). IR: (neat) 3440 (OH) cm^{-1}, 1720 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.14 (d, *J* = 8.7 Hz, 2H, *o*), 6.81 (d, *J* = 8.7 Hz, 2H, *m*), 3.79 (s, 3H, 10-H$_3$), 3.55 (t, *J* = 7.2 Hz, 2H, 1-H$_2$), 3.52 (s, 3H, 9-H$_3$), 2.19 (ddd, *J* = 14.5, 13.5, 3.4 Hz, 1H, 4-H^A), 1.66-1.50 (m, 3H, 4-H^B and 2-H$_2$), 1.36 (s, 3H, 6-H$_3$), 1.27-1.13 (m, 2H, 3-H^A and OH), 1.10 (s, 3H, 7-Me^A), 1.01 (s, 3H, 7-Me^B), 0.98-0.87 (m, 1H, 3-H^B); ^{13}C NMR: (100 MHz, CDCl$_3$) 177.3 (s, C-8), 157.5 (s, *p*), 134.9 (s, *i*), 129.2 (d, *o*), 112.5 (d, *m*), 62.7 (t, C-1), 55.0 (q, C-10), 51.2 (q, C-9), 49.7 (s, C-7), 45.3 (s, C-5), 34.9 (t, C-4), 33.5 (t, C-2), 22.0 (q, 7-Me^B), 21.7 (q, 7-Me^A), 21.3 (q, C-6), 20.8 (t, C-3); MS: (EI, 70 eV) *m/z* 277 (M - OMe, 0.5), 207 (M - Me$_2$CHCO$_2$Me, 100); HRMS: (CI, 70 eV) Calculated ($C_{18}H_{29}O_4$) 309.2066 ([M + 1]$^+$) Found: 309.2064.

Methyl 3-(4-chlorophenyl)-6-hydroxy-2,2,3-trimethylhexanoate (**3ka**)



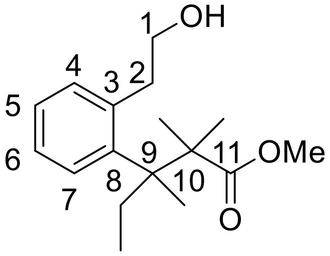
From InI_3 (0.0267 g, 0.0539 mmol), 4-(4-chlorophenyl)pent-4-en-1-ol (0.1014 g, 0.481 mmol) and dimethylketene methyl trimethylsilylacetal (0.137 g, 0.786 mmol) following general procedure (rt, 12 h at 1st step), **3ka** (0.064 g, 45%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3444 (OH) cm^{-1}, 1724 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.25 (d, J = 8.7 Hz, 2H, *m*), 7.17 (d, J = 8.7 Hz, 2H, *o*), 3.64-3.56 (m, 2H, 1-H_2), 3.52 (s, 3H, 8-H_3), 2.27 (ddd, J = 14.5, 13.0, 3.4 Hz, 1H, 3-H^A), 1.54 (ddd, J = 13.5, 13.0, 5.3 Hz, 1H, 3-H^B), 1.45-1.34 (m, 1H, 2-H^A), 1.38 (s, 3H, 5-H_3), 1.32 (s, 1H, OH), 1.19-1.06 (m, 1H, 2-H^B), 1.12 (s, 3H, 6-Me^A), 1.04 (s, 3H, 6-Me^B); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.0 (s, C-7), 141.5 (s, *i*), 132.0 (s, *p*), 129.7 (d, *o*), 127.5 (d, *m*), 63.4 (t, C-1), 51.3 (q, C-8), 49.7 (s, C-6), 45.5 (s, C-4), 31.1 (t, C-3), 28.0 (t, C-2), 22.1 (q, 6-Me^B), 21.8 (q, 6-Me^A), 21.3 (q, C-5); MS: (CI, 70 eV) *m/z* 301 ($[M + 1]^+ + 2$, 34), 299 ($[M + 1]^+$, 100); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{24}ClO_3$) 299.1414 ($[M + 1]^+$) Found: 299.1410.

Methyl 3-(4-fluorophenyl)-6-hydroxy-2,2,3-trimethylhexanoate (**3la**)



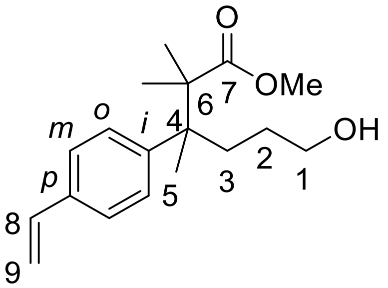
From InI_3 (0.0229 g, 0.046 mmol), 4-(4-fluorophenyl)pent-4-en-1-ol (0.0905 g, 0.481 mmol) and dimethylketene methyl trimethylsilylacetal (0.139 g, 0.797 mmol) following general procedure (rt, 22 h at 1st step), **3la** (0.101 g, 77%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3456 (OH) cm^{-1}, 1720 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.21 (dd, J^4_{HF} = 5.3 Hz, J^3_{HH} = 8.7 Hz, 2H, *o*), 6.98 (dd, J^3_{HF} = 9.2 Hz, J^3_{HH} = 8.7 Hz, 2H, *m*), 3.65-3.53 (m, 2H, 1-H_2), 3.51 (s, 3H, 8-H_3), 2.27 (ddd, J = 14.5, 13.5, 3.4 Hz, 1H, 3-H^A), 1.67 (ddd, J = 13.5, 13.5, 5.3 Hz, 1H, 3-H^B), 1.52 (s, 1H, OH), 1.46-1.34 (m, 1H, 2-H^A), 1.39 (s, 3H, 5-H_3), 1.22-1.13 (m, 1H, 2-H^B), 1.12 (s, 3H, 6-Me^A), 1.03 (s, 3H, 6-Me^B); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.1 (s, C-7), 161.2 (d, J = 255 Hz, *p*), 138.6 (d, J = 3.3 Hz, *i*), 129.8 (d, J = 7.4 Hz, *o*), 114.0 (d, J = 20.5 Hz, *m*), 63.3 (t, C-1), 51.3 (q, C-8), 49.8 (s, C-6), 45.3 (s, C-4), 31.1 (t, C-3), 27.9 (t, C-2), 22.0 (q, 6-Me^B), 21.7 (q, 6-Me^A), 21.4 (q, C-5); MS: (CI, 70 eV) *m/z* 283 ($[M + 1]^+$, 100); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{24}FO_3$) 283.1709 ($[M + 1]^+$) Found: 283.1708.

Methyl 3-(2-(2-hydroxyethyl)phenyl)-2,2,3-trimethylpentanoate (**3ma**)



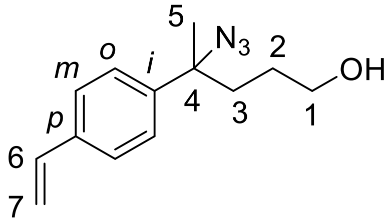
From InI_3 (0.0298 g, 0.0601 mmol), 2-(2-(but-2-en-2-yl)phenyl)ethan-1-ol (0.0482 g, 0.273 mmol) and dimethylketene methyl trimethylsilylacetal (0.203 g, 1.16 mmol) following general procedure (70 °C, 4 h at 1st step), **3ma** (0.043 g, 56%) was obtained after column chromatography (hexane/ethyl acetate = 50:50). IR: (neat) 3417 (OH) cm^{-1}, 1716 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.23 (dd, J = 7.3, 1.8 Hz, 1H, 7-H), 7.19 (dd, J = 6.9, 2.3 Hz, 1H, 4-H), 7.17-7.10 (m, 2H, 5-H and 6-H), 3.94-3.83 (m, 2H, 1-H_2), 3.55 (s, 3H, OMe), 3.28 (dt, J = 13.7, 6.0 Hz, 1H, 2-H^A), 2.91 (dt, J = 13.7, 6.8 Hz, 1H, 2-H^B), 2.51 (dq, J = 14.7, 7.3 Hz, 1H, 10-H^A), 1.60 (s, 3H, 9-Me), 1.60-1.51 (m, 1H, 10-H^B), 1.25 (s, 1H, OH), 1.15 (s, 3H, 12-Me^A), 1.13 (s, 3H, 12-Me^B), 0.719 (t, J = 7.3 Hz, 3H, 11-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 177.4 (s, C-13), 140.6 (s, C-8), 138.6 (s, C-3), 132.2 (d, C-4), 131.6 (d, C-7), 126.2 (d), 125.1 (d), 64.6 (t, C-1), 51.4 (q, OMe), 50.8 (s, C-12), 49.2 (s, C-9), 39.1 (t, C-2), 31.3 (t, C-10), 24.4 (q, 9-Me), 22.5 (q, 12-Me^A), 22.2 (q, 12-Me^B), 9.3 (q, C-11); MS: (EI, 70 eV) m/z 249 (M – CH_2CH_3, 12); HRMS: (CI, 70 eV) Calculated ($C_{17}H_{27}O_3$) 279.1960 ([M + 1]$^+$) Found: 279.1958.

Methyl 6-hydroxy-2,2,3-trimethyl-3-(4-vinylphenyl)hexanoate (**12oa**)



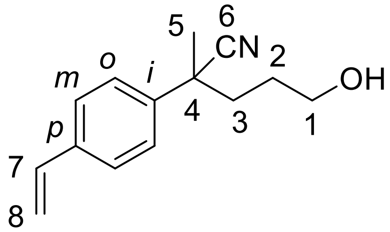
From InI_3 (0.0251 g, 0.0507 mmol) in 1,2-dichloroethane (10 mL), 4-(4-vinylphenyl)pent-4-en-1-ol (0.080 g, 0.425 mmol) and dimethylketene methyl trimethylsilylacetal (0.302 g, 1.73 mmol) following general procedure (5 °C, 17 h at 1st step and rt, 12 h at 2nd step), **12oa** (0.0568 g, 46%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3487 (OH) cm^{-1}, 1716 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.33 (d, J = 8.6 Hz, 2H, *m*), 7.20 (d, J = 8.6 Hz, 2H, *o*), 6.69 (dd, J = 17.7, 10.9 Hz, 1H, 8-H), 5.73 (d, J = 17.7 Hz, 1H, 9-H^A), 5.22 (d, J = 10.9 Hz, 1H, 9-H^B), 3.62-3.55 (m, 2H, 1-H_2), 3.52 (s, 3H, OMe), 2.30 (ddd, J = 14.0, 12.7, 3.2 Hz, 1H, 3-H^A), 1.76-1.60 (br, 1H, OH), 1.66 (ddd, J = 13.1, 12.7, 5.0 Hz, 1H, 3-H^B), 1.45-1.35 (m, 1H, 2-H^A), 1.39 (s, 3H, 5-H_3), 1.21-1.10 (m, 1H, 2-H^B), 1.13 (s, 3H, 6-Me^A), 1.04 (s, 3H, 6-Me^B); ^{13}C NMR: (100 MHz, CDCl$_3$) 177.2 (s, C-7), 142.6 (s, *i*), 136.3 (d, C-8), 135.1 (s, *p*), 128.4 (d, *o*), 125.1 (d, *m*), 113.4 (t, C-9), 63.4 (t, C-1), 51.2 (q, OMe), 49.7 (s, C-6), 45.6 (s, C-4), 31.0 (t, C-3), 28.0 (t, C-2), 22.1 (q, 6-Me^B), 21.7 (q, 6-Me^A), 21.2 (q, C-5); MS: (EI, 70 eV) *m/z* 290 (M, 2); HRMS: (CI, 70 eV) Calculated ($C_{18}H_{27}O_3$) 291.1960 ($[M + 1]^+$) Found: 291.1958.

4-Azido-4-(4-vinylphenyl)pentan-1-ol (**12-N$_3$**)



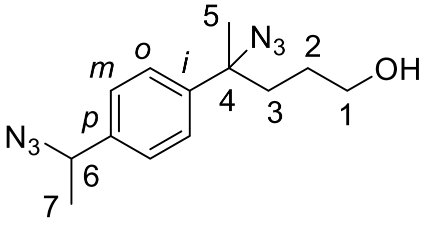
From InI$_3$ (0.0261 g, 0.0527 mmol) in 1,2-dichloroethane (10 mL), 4-(4-vinylphenyl)pent-4-en-1-ol (0.0964 g, 0.512 mmol) and trimethylsilyl azide (0.167 g, 1.45 mmol) following general procedure (5 °C, 5 h at 1st step and rt, 17 h at 2nd step), **12-N$_3$** (0.0228 g, 20%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3398 (OH) cm^{-1}, 2106 (N$_3$) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.41 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 6.71 (dd, J = 17.9, 10.6 Hz, 1H, 6-H), 5.76 (d, J = 17.9 Hz, 1H, 7-H^A), 5.26 (d, J = 10.6 Hz, 1H, 7-H^B), 3.53 (t, J = 6.3 Hz, 2H, 1-H$_2$), 1.96-1.85 (m, 2H, 3-H$_2$), 1.69 (s, 3H, 5-H$_3$), 1.57-1.32 (m, 3H, 2-H$_2$ and OH); ^{13}C NMR: (100 MHz, CDCl$_3$) 142.8 (s, *i*), 136.6 (s, *p*), 136.0 (d, C-6), 126.3 (d), 125.7 (d), 114.2 (t, C-7), 66.6 (s, C-4), 62.6 (t, C-1), 38.5 (t, C-3), 27.5 (t, C-2), 25.7 (q, C-5); MS: (EI, 70 eV) *m/z* 171 (M – N$_3$ – H$_2$O, 69); HRMS: (CI, 70 eV) Calculated ($C_{13}H_{18}N_3O$) 232.1450 ($[M + 1]^+$) Found: 232.1455.

5-Hydroxy-2-methyl-2-(4-vinylphenyl)pentanenitrile (**12od**)



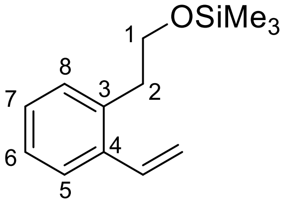
From InI$_3$ (0.0256 g, 0.0517 mmol) in 1,2-dichloroethane (10 mL), 4-(4-vinylphenyl)pent-4-en-1-ol (0.0949 g, 0.504 mmol) and trimethylsilyl cyanide (0.3 mL, 2.5 mmol) following general procedure (5 °C, 19 h at 1st step and rt, 35 h at 2nd step), **12od** (0.055 g, 50%) was obtained after column chromatography (hexane/ethyl acetate = 70:30). IR: (neat) 3433 (OH) cm^{-1}, 2237 (CN) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.42 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 6.70 (dd, J = 17.4, 10.6 Hz, 1H, 7-H), 5.76 (d, *J* = 17.4 Hz, 1H, 8-H^{A}), 5.28 (d, *J* = 10.6 Hz, 1H, 8-H^{B}), 3.61 (t, *J* = 6.3 Hz, 2H, 1-H$_2$), 2.08-1.94 (m, 2H, 3-H$_2$), 1.78-1.65 (m, 1H, 2-H^{A}), 1.73 (s, 3H, 5-H$_3$), 1.57-1.38 (m, 2H, 2-H^{B} and OH); ^{13}C NMR: (100 MHz, CDCl$_3$) 139.3 (s, *i*), 137.1 (s, *p*), 135.8 (d, C-7), 126.7 (d), 125.6 (d), 123.3 (s, C-6), 114.6 (t, C-8), 62.0 (t, C-1), 42.1 (s, C-4), 38.3 (t, C-3), 28.6 (t, C-2), 27.8 (q, C-5); MS: (EI, 70 eV) *m*/*z* 215 (M, 21); HRMS: (CI, 70 eV) Calculated ($C_{14}H_{18}NO$) 216.1388 ([M + 1]$^+$) Found: 216.1391.

4-Azido-4-(4-(1-azidoethyl)phenyl)butan-1-ol (**13-N$_3$**)



To a branched reaction vessel, $Fe_2(ox)_3{\cdot}6H_2O$ (1.19 g, 2.46 mmol) and H_2O (20 mL) was added. After stirring for 1 h, the solution was cooled to 0 °C and degassed for 10 minutes. NaN_3 (0.26 g, 4.0 mmol) and THF (10 mL) were added and the vessel was purged by N_2. To the mixture, 2-(2-(prop-1-en-2-yl)phenyl)ethan-1-ol (0.0987 g, 0.524 mmol) in THF (10 mL) was slowly added at 0 °C, and then $NaBH_4$ (0.06 g, 1,60 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 5 minutes and $NaBH_4$ (0.06 g, 1,60 mmol) was added. After stirring for 50 minutes at 0 °C, the mixture was quenched by sat. NH_4Cl aq. (8 mL) and then extracted with MeOH (10 wt % in CH_2Cl_2 x 2). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 60:40, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product **13-N$_3$** (0.035 g, 28%). IR: (neat) 3401 (OH) cm^{-1}, 2106 (N$_3$) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 7.40 (d, *J* = 7.7 Hz, 2H, *o*), 7.32 (d, *J* = 7.7 Hz, 2H, *m*), 4.62 (q, *J* = 7.0 Hz, 1H, 6-H), 3.58 (t, *J* = 6.0 Hz, 2H, 1-H$_2$), 1.91 (t, *J* = 7.7 Hz, 2H, 3-H$_2$), 1.70 (s, 3H, 5-H$_3$), 1.60-1.46 (m, 1H, 2-H^{A}), 1.54 (d, *J* = 7.0 Hz, 3H, 7-H$_3$), 1.46-1.31 (m, 1H, 2-H^{B}), 1.31-1.18 (br, 1H, OH); ^{13}C NMR: (100 MHz, CDCl$_3$) 143.2 (s, *i*), 139.9 (s, *p*), 126.5 (d, *m*), 125.9 (d, *o*), 66.5 (s, C-4), 62.6 (t, C-1), 60.6 (d, C-6), 38.5 (t, C-3), 27.5 (t, C-2), 25.7 (q, C-5), 21.5 (q, C-7); MS: (EI, 70 eV) m/z 232 (M – N$_3$, 15); HRMS: (EI, 70 eV) Calculated ($C_{13}H_{18}N_6O$) 274.1542 (M) Found: 274.1546.

Trimethyl(2-vinylphenethoxy)silane (TMS-**1a**)



TMS-**1a** in a crude product was identified by ^{1}H NMR of an authentic sample of TMS-**1a** (Table 1). The authentic sample was prepared by the following procedure.[7b] The solution of $HN(SiMe_3)_2$ (0.80 mmol, 0.129 g) in CH_2Cl_2 (0.5 mL) was slowly added to the solution of **1a** (0.99 mmol, 0.147 g) and I_2 (0.010 mmol, 0.0025 g) at room temperature. After stirring for 1 hour at room temperature, $Na_2S_2O_3$ (1 g) was added to the reaction mixture and the resulting precipitation was stirred for 30 min. The supernatant liquid was directly purified by silica gel column chromatography (only CH_2Cl_2 was used as a mobile-phase) to obtain trimethyl(2-vinylphenethoxy)silane TMS-**1a** (0.88 mmol, 0.194 g, 89%). IR: (neat) 3087, 3062, 3027, 1627, 1484, 1450, 1412, 1383 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.49 (dd, J = 5.6, 4.1 Hz, 1H), 7.23-7.15 (m, 3H), 7.02 (dd, J = 17.4, 10.9 Hz, 1H), 5.65 (dd, J = 17.4, 1.2 Hz, 1 H), 5.30 (dd, J = 10.9, 1.2 Hz, 1H), 3.72 (t, J = 7.3 Hz, 2H), 2.93 (t, J = 7.3 Hz, 2H), 0.06 (s, 9H); ^{13}C NMR: (100 MHz, $CDCl_3$) 137.0 (s), 136.0 (s), 134.5 (d), 130.4 (d), 127.7 (d), 126.7 (d), 125.7 (d), 115.7 (t), 63.2 (t), 36.7 (t), -0.61 (q); MS: (EI, 70 eV) m/z; HRMS: (EI, 70 eV) 220.1283 (M) Calculated Found: 220.1285.

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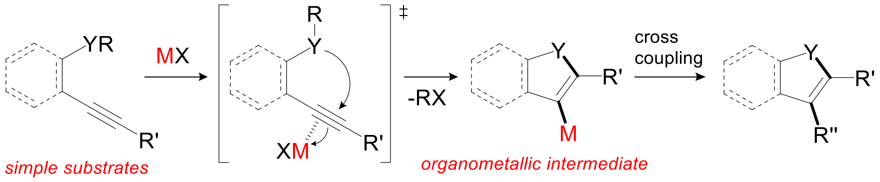
Chapter 3

Selective Oxymetalation of Terminal Alkynes *via* 6-*Endo* Cyclization: Mechanistic Investigation and Application to the Efficient Synthesis of 4-Substituted Isocoumarins

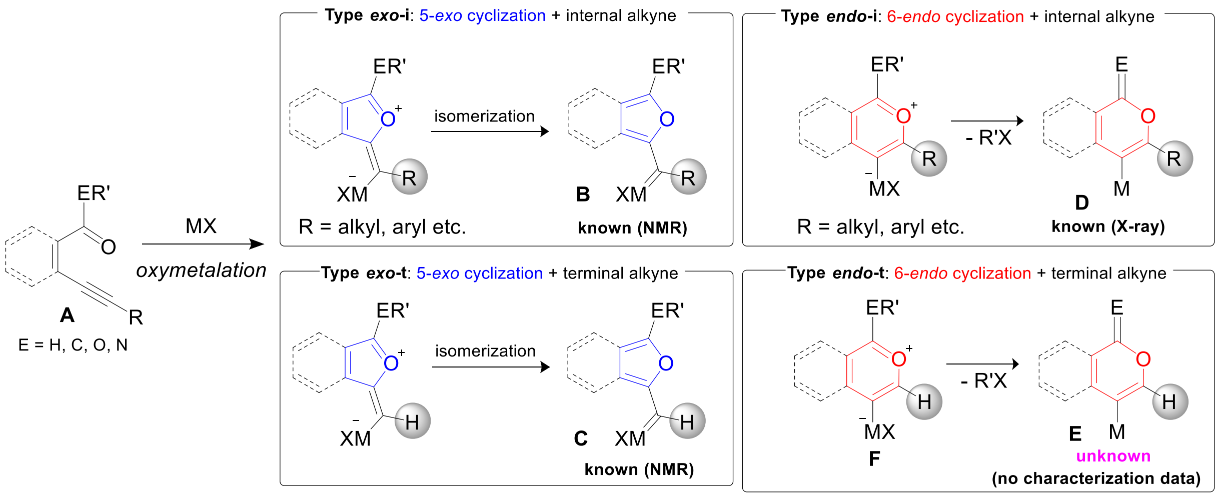
3-1. Introduction

Heterocyclic compounds have attracted much attention in pharmaceutical chemistry as well as in photochemistry, and also play a pivotal role as building blocks in organic synthetic transformation.[1] Therefore, a novel efficient synthetic method for heterocyclic frameworks is highly desired in various fields of chemistry. Many well-established methods are available in the literature.[2] Heterocyclization of ω-heteroatom-substituted alkynes using π acidic metal salts is undoubtedly a powerful strategy for the preparation of heterocycles (Scheme 1).[3] This addition reaction uses readily available alkynes as a starting material. Furthermore, metal salt-mediated cyclization spontaneously forms a carbon-metal bond and a heterocyclic framework and produces organometallic intermediates leading to target heterocycles via appropriate synthetic reactions such as cross coupling. These features allowed us to directly access various substituted heterocycles from simple organic substrates.

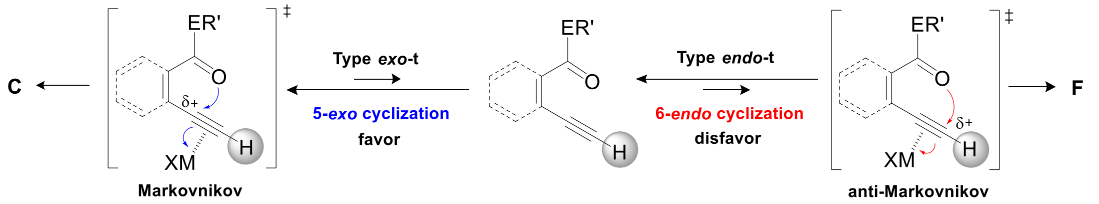


Scheme 1. Metal salt-mediated heterocyclization of ω-heteroatom-substituted alkynes.

Various heteroatom-containing alkynes have been investigated for use in the synthesis of heterocyclic compounds using π acidic metal salts. Alkyne **A** includes a carbonyl moiety and is a feasible and beneficial substrate to obtain 5- or 6-membered oxacyclic alkenylmetals (Scheme 2A). When **A** is treated with a metal salt (MX), oxymetalation proceeds to afford heterocyclic compounds through either 5-*exo* or 6-*endo* cyclization (Type *exo* or *endo*). Considering that the structure of **A** bears either an internal (R = alkyl, aryl etc.) or a terminal alkyne (R = H), oxymetalation can be distinguished by four types of reaction courses: Type *exo*-i, Type *exo*-t, Type *endo*-i, and Type *endo*-t. In Type *exo*-i and *exo*-t, the furan frameworks **B** and **C** have a metal carbenoid moiety and are obtained via the isomerization of zwitterion intermediates.[4,5] On the other hand, Type *endo*-i and *endo*-t lead to 1*H*-isochromen derivatives **D** and **E** via elimination of R'X from zwitterion intermediates.[6,7] Among these four types, only Type *endo*-t is kinetically unfavorable due to an unstable cationic transition state via an *anti*-Markovnikov addition manner (Scheme 2B). Furthermore, recent theoretical researches about the regioselectivity of cyclization revealed that nucleophilic cyclization of alkynes displays *exo* selectivity intrinsically.[8] On the other hand, Lewis acidic metals can promote *endo* cyclization by decrease of the stereoelectronic penalty, but the *exo* cyclization was not disturbed, and, thus, the cyclization showed low selectivity.[7,9] For the above reasons, there is no report of a preparation method for species **E** via Type *endo*-t in contrast to the cases of Types *exo*-i, *exo*-t, and *endo*-i, for which target organometallic compounds (**B**, **C**, **D**) are well established.[4b,5a,6c,6e] If the reaction course of oxymetalation is realized from **A** to **E** in Type *endo*-t,[10] various 6-membered heterocycles based on **E**, which have been difficult to obtain and remain unknown, should be synthesized. Therefore, the establishment of a strategy for Type *endo*-t is an important challenge in heterocyclic chemistry.

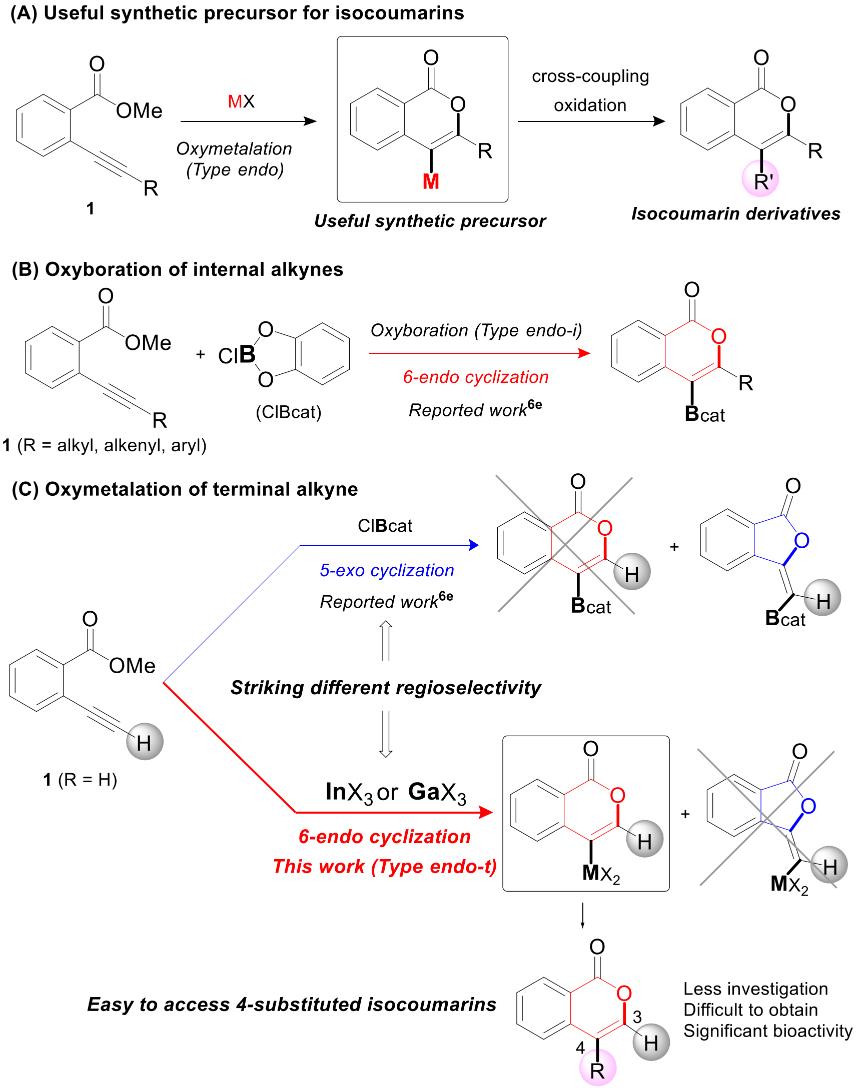


(B) Comparison of transition states of Type *exo*-t with Type *endo*-t



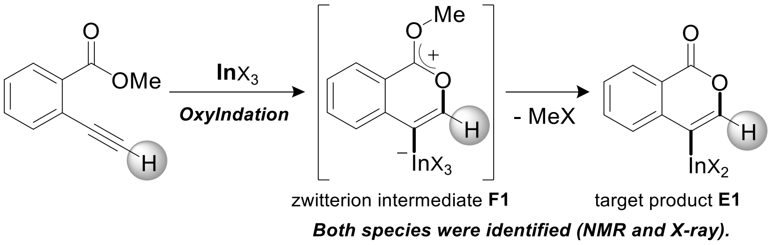
Scheme 2. (A) Four types of metalated heterocycles from oxymetalation of alkyne **A** including carbonyl moiety. (B) Comparison of transition states of type *exo*-t with type *endo*-t.

Isocoumarins are an important class of oxygen-containing heterocycles that exhibit a wide range of pharmacological properties.[11] Thus, the development of their general synthetic method has attracted much attention. The reaction of Type *endo* would be a powerful tool for the synthesis of isocoumarins (Scheme 3A). In fact, reports have described the oxymetalation of 2-alkynylbenzoate **1** (R = alkyl, alkenyl, aryl) for Type *endo*-i and application to the synthesis of isocoumarins.[6a,6b,6e] Recently, Blum reported an excellent method for the construction of 4-borylated isocoumarins by oxyboration of the internal alkynes **1** in the Type *endo*-i reaction course (Scheme 3B).[6e] However, terminal alkyne **1** (R = H) gave only a 5-*exo* cyclization product according to the Markovnikov rule (blue path in Scheme 3C).[6e] This result prompted us to explore oxymetalation of the terminal alkynes **1** for Type *endo*-t. Oxymetalation of Type *endo*-t provides 3-unsubstituted and 4-substituted isocoumarins that are seldom investigated due to the lack of synthetic methods,[12] and limited substituents have been introduced at the 4-position despite well-known beneficial significant bioactivity characteristics such as antitumor,[13] antiangiogenic,[14] antifungal,[15] and antibiotic.[16]



Scheme 3. (A) Oxymetalation of 2-alkynylbenzoate **1** followed by transformation for the construction of isocoumarins. (B) Previously reported oxyboration of internal alkynes to generate 4-borylated isocoumarins. (C) Oxymetalation of terminal alkynes, reported oxyboration for 5-membered compounds (blue path), and our developed oxymetalation for 6-membered compounds (red path).

Our group developed the indium or gallium salt-mediated carbometalation of simple terminal alkynes with silyl ketene acetals by utilizing their high π electron affinity and moderate Lewis acidity.[17] In this context, we investigated the Type *endo*-t reaction of 2-ethynylbenzoate using indium or gallium trihalides for the synthesis of corresponding metalated isocoumarins. In this report, we successfully achieved a 6-*endo* selective oxymetalation of terminal alkynes and fully characterized the target organometallic species **E1** via NMR study and X-ray crystallographic analysis. Furthermore, the intermediate **F1** was isolated, which revealed that oxymetalation proceeds via the zwitterion intermediate **F1**, and elimination of the alkyl halide gives the target product **E1** (Scheme 4). While benzopyrylium species such as **F** are known as highly reactive intermediates in the proposed catalytic oxymetalation cycle,[10a,18] the isolation of species **F** is a challenge issue.[10e,10f,19] To the best of our knowledge, **F1** is the first example of a fully characterized benzopyrylium intermediate **F**. In addition, we performed full disclosure of the mechanism by combining experimental data and theoretical calculation. These mechanistic investigations were consistent with the achievement of isolation of the zwitterion intermediate and demonstrated that its stability is a crucial point in this remarkable cyclization regioselectivity.



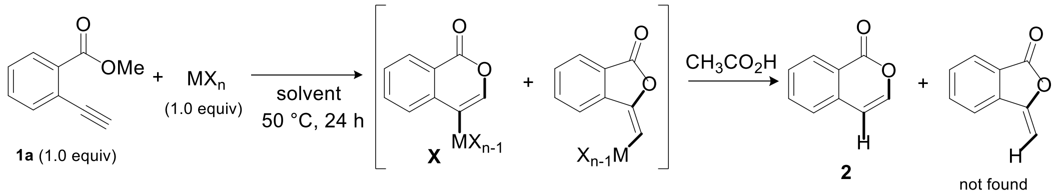
Scheme 4. Oxyindation of alkynes for synthesis of isocoumarin framework *via* a zwitterion intermediate.

3-2. Results and Discussion

Optimization of reaction conditions

First, we examined the effect of Lewis acids on oxymetalation using methyl 2-ethynylbenzoate **1a** (Table 1). The reaction of **1a** with metal halides was carried out in toluene at 50 °C, and the reaction mixture was quenched with acetic acid. The reaction using $InCl_3$ afforded the target isocoumarin **2** via 6-*endo* cyclization, albeit in a low yield (entry 1). Gratifyingly, $InBr_3$ and InI_3 mediated oxymetalation smoothly proceeded in 6-*endo* cyclization fashion to give **2** in high yields (entries 2 and 3). In these cases, the reaction mixture was quenched by deuterated acetic acid to afford **2** bearing deuterium at the 4-position. We did not observe an isocoumarin bearing deuterium at the 3- position which could be produced through the generation of indium acetylide[20] followed by Lewis acid mediated cycloaddition. The reaction using InI_3 showed a higher ratio of D/H than the case of $InBr_3$. This result suggested the more efficient generation of the alkenylmetal intermediate **X** in the case of InI_3. Gallium salts were also suitable for the 6-*endo* cyclization of **1a**, and GaI_3 gave a high yield (entries 4 and 5). On the other hand, typical Lewis acids such as $AlCl_3$, AlI_3, BBr_3 and $TiCl_4$ were ineffective (entries 6-9). Transition metal salts such as $PdCl_2$, $CuBr_2$ and $FeBr_3$ provided no target product and resulted in a decomposition of **1a** (entries 10-12). Alkynophilic π-acids such as gold and silver salts were subjected into the present cyclization. It was found that $AuCl_3$, AlCl, AgOTf and AuCl/AgOTf resulted in low yields (entries 13-16). A decrease in yield was observed at lower temperature (entry 17). The solvent effect was examined on oxyindation using InI_3. Dichloroethane as a solvent provided a good yield while chlorobenzene and hexane afforded only moderate yields (entries 18-20). The yields were appreciably decreased in CH_3CN and THF (entries 21 and 22) probably because the coordination of these solvents to InI_3 decreased the Lewis acidity. Finally, InI_3 was the most effective Lewis acid, and, therefore, we chose entry 3 to represent the optimal conditions.

Table 1. Effect of Lewis Acids on the Oxymetalation of 2-Ethynylbenzoate **1a**.[a]

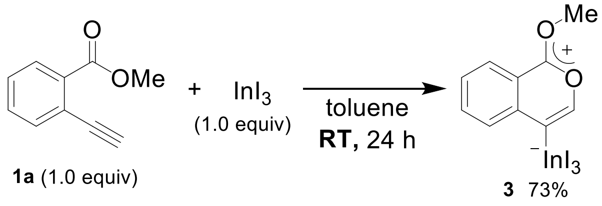


Entry	MX_n	Solvent	Yield of **2** (%)^b
1	$InCl_3$	toluene	13
2^c	$InBr_3$	toluene	82 (77% D)
3^c	InI_3	toluene	79 (91% D)
4	$GaBr_3$	toluene	30
5	GaI_3	toluene	77
6	$AlCl_3$	toluene	0
7	AlI_3	toluene	0
8	BBr_3	toluene	0
9	$TiCl_4$	toluene	0
10	$PdCl_2$	toluene	0
11	$CuBr_2$	toluene	0
12	$FeBr_3$	toluene	0
13	$AuCl_3$	toluene	7
14	AuCl	toluene	5
15	AgOTf	toluene	31
16	AuCl/AgOTf	toluene	18
17^d	InI_3	toluene	61
18	InI_3	$ClCH_2CH_2Cl$	78
19	InI_3	ClC_6H_5	57
20	InI_3	hexane	57
21	InI_3	CH_3CN	17
22	InI_3	THF	0

[a] Reaction conditions: **1a** (0.5 mmol), Lewis acid MX_n (0.5 mmol), solvent (1 mL), 50 °C, 24 h. [b] The yield of **2** was determined by ^1H NMR. [c] The reaction mixture was quenched by CH_3CO_2D (30 equiv, 5 min) and a subsequent addition of H_2O (10 mL). [d] 35 °C.

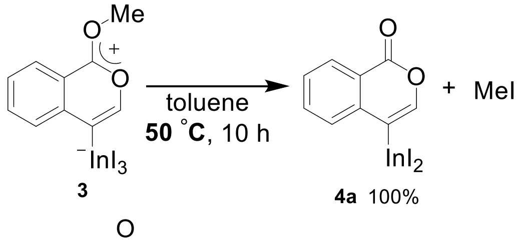
Mechanistic Investigation

To gain insight into the reaction mechanism, we used ^{1}H NMR spectroscopy to monitor the oxyindation. When 2-alkynylbenzoate **1a** was mixed with InI_3 in $CDCl_3$ at -30 °C, no reaction occurred. At -5 °C, some amount of a new product was observed (See Fig. S1 and S2 in Experimental Section). At room temperature, a large amount of white precipitation was formed. This white solid was also obtained in the reaction of **1a** with InI_3 in toluene at room temperature (Eq. 1). X-ray crystallographic analysis revealed that the white solid was a 6-membered oxacycle zwitterion **3** bearing a carbon-indium bond (Fig. 1). The bond lengths of two carbon-oxygen bonds (C1-O1 = 1.267 Å, C1-O2 = 1.298 Å) in the zwitterion **3** existed between a C-O double bond (1.203 Å) and the single bond (1.377 Å) of a typical isocoumarin derivative,[21] and, thus, the positive charge was delocalized in an ester moiety. The indium atom was coordinated with three iodines and showed a distorted tetrahedral structure with a formal negative charge. The formed zwitterionic alkenyl indium **3** was heated at 50 °C in toluene to give a neutral alkenylindium product **4a**, quantitatively by elimination of MeI (Eq. 2). Although a suitable single crystal of **4a** for X-ray analysis was not obtained, we successfully conducted X-ray diffraction analysis of nitro-substituted alkenylindium **4b** produced from the 2-ethynyl-5-nitrobenzoate **1b** (Eq. 3 and Fig. 2). The bond lengths of C1-O1 (1.211 Å) and C1-O2 (1.367 Å) were similar to those of reported isocoumarin framework.[21] The indium complex **4b** displayed trigonal bipyramidal coordination with two THF ligands in axial positions. These results indicated a two-step pathway including a fast cyclization and a slow elimination of MeI during the 6-*endo* oxyindation processing from **1** to **4**.



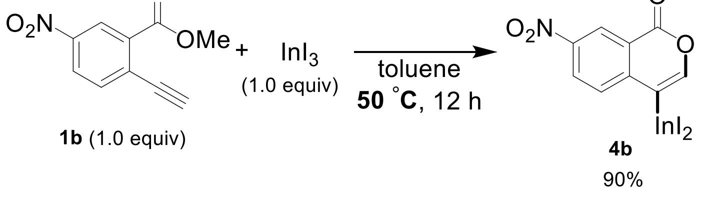
1a (1.0 equiv) **3** 73%

(1)



3 **4a** 100%

(2)



1b (1.0 equiv) **4b** 90%

(3)

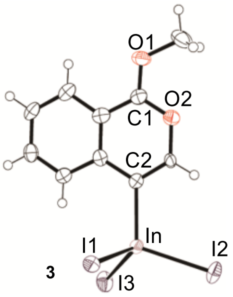


Figure 1. The X-ray crystallographic structure of zwitterion intermediate **3** with the thermal ellipsoids shown at 50% probability (CCDC 1579824). Selected bond lengths (Å): C1-O1 = 1.267(9), C1-O2 = 1.298(11), C2-In = 2.171(7), In-I1 = 2.7392(8), In-I2 = 2.7219(8), In-I3 = 2.6915(7).

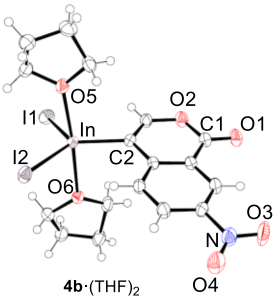
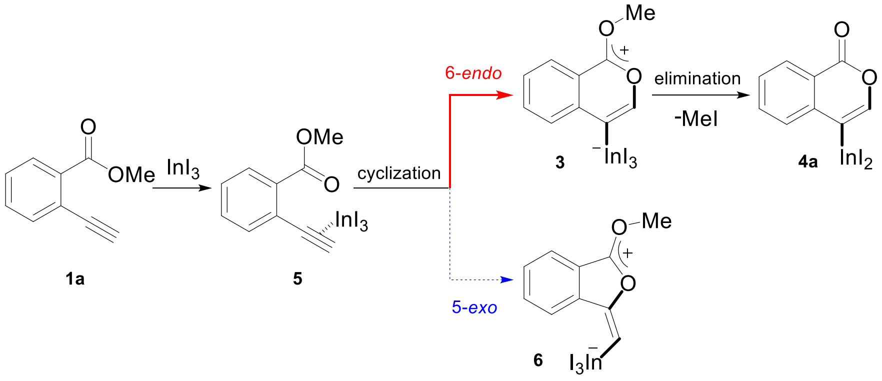


Figure 2. The X-ray crystallographic structure of isocoumarin including a carbon-indium bond at the 4-position, **4b**·(THF)$_2$, with the thermal ellipsoids shown at 50% probability (CCDC 1576342). Selected bond lengths (Å) and angles (deg): C1-O1 = 1.211(4), C1-O2 = 1.367(5). C2-In = 2.162(3), In-I1 = 2.7148(4), In-I2 = 2.7005(4), In-O5 = 2.318(3), In-O6 = 2.371(3), O5-In-O6 = 175.44(10), I1-In-C2 = 116.70(11), C2-In-I2 = 125.51(11), I2-In-I1 = 117.621(12).

Theoretical Calculation for Oxyindation

A mechanism for the formation of the target isocoumarin **4a** using InI_3 is proposed in Scheme 5 wherein InI_3 is coordinated by the alkyne moiety in **5**, oxyindation proceeds via 6-*endo* cyclization to give the zwitterion intermediate **3**, and, finally, the elimination of MeI affords **4a**.



Scheme 5. A proposed mechanism for formation of the isocoumarin **4a**.

Density functional theory (DFT) calculations were performed to more thoroughly consider the reaction mechanism. Calculation of the potential energy profile for 6-*endo* cyclization (red) shows in Fig. 3. We selected **1a** and In_2I_6 as starting materials because InI_3 exists in a dimer fashion.[22] The coordination of two **1a** to In_2I_6 dissociates the aggregation of InI_3 to give the complex **7**, in which InI_3 is chelated by the alkyne moiety and carbonyl group of **1a** (Fig. S3 in Experimental Section shows detail mechanism of generating the complex **7** from **1a** and In_2I_6). Dissociation of the carbonyl oxygen atom generates complex **5**, in which InI_3 directly activates the alkyne moiety. In this pathway, the anti-addition of InI_3 and the ester moiety into the alkyne moiety proceeds in a concerted mechanism to provide a stable 6-membered zwitterion intermediate **3**. Elimination of MeI proceeds in an intermolecular fashion, because the intramolecular elimination of MeI requires a very unstable intermediate (Fig. S4 in Experimental Section shows the potential energy profile for the intramolecular elimination of MeI). Two zwitterions aggregate in a head-to-tail fashion to give complex **8**, and then the elimination step starts from **8**. Intermolecular nucleophilic substitution of the methyl group by I^- proceeds in an S_N2-mechanism to give complex **10** and MeI, and then a subsequent elimination of MeI affords the target product **4a**.[23] A carbonyl group of **4a** coordinates to the indium atom of another **4a** to give the stable dimeric product **13**. The activation energy of the elimination step (**8** to TS2-6-*endo*, 28.7 kcal/mol) is much higher than that of the cyclization step (**7** to TS1-6-*endo*, 19.7 kcal/mol).[24] Therefore, the elimination of MeI is a rate-determining step. We also calculated the 5-*exo* cyclization pathway (blue) to investigate the regioselectivity. This process proceeds via concerted cyclization wherein the 5-membered zwitterion **6** is much more unstable than the 6-membered version **3**. Intermolecular elimination of MeI takes place in an S_N2-manner (**9** to **11**). The energy level of the transition state (TS2-5-*exo*) shows the highest energy level, and it is higher even than the energy profile of the 6-*endo* cyclization process (red) due to the instability of the 5-membered zwitterion **6**.

In order to clarify the unique 6-*endo* cyclization selectivity of oxyindation, the energy profiles of the two cyclization manners were compared. The activation energy of 5-*exo* cyclization is lower (**7** to TS1-5-*exo*, 15.5 kcal/mol) than that of 6-*endo* cyclization (**7** to TS1-6-*endo*, 19.7 kcal/mol). However, 5-*exo* cyclization is reversible because the activation energy for the elimination of MeI (**9** to TS2-5-*exo*, 21.9 kcal/mol) is much higher than that of retro-cyclization (**6** to TS1-5-*exo*, 9.3 kcal/mol) due to the instability of the zwitterion **6**. On the other hand, during 6-*endo* cyclization, both activation energies of elimination (**8** to TS2-6-*endo*, 28.7 kcal/mol) and retro-cyclization (**3** to TS1-6-*endo*, 23.0 kcal/mol) are high because the 6-membered zwitterion intermediate **3** is thermodynamically stable. This result indicates that 6-*endo* cyclization is irreversible and the most thermodynamically stable form of intermediate **8** is exclusively generated to provide the target product **4a**, which is consistent with the successful isolation of the zwitterion intermediate **3** (Fig. 1). Therefore, oxyindation proceeds under thermodynamic control to afford the stable 6-membered product **4a**. We also calculated an energy profile of $InCl_3$-mediated oxyindation and found the same pathway with the case of InI_3 (See Fig. S5 in Experimental Section). The activation energy of elimination step in the cases of $InCl_3$ is higher than that of InI_3 because of low nucleophilicity of Cl^-, and it caused much less reactivity of $InCl_3$ (entry 1, Table 1).

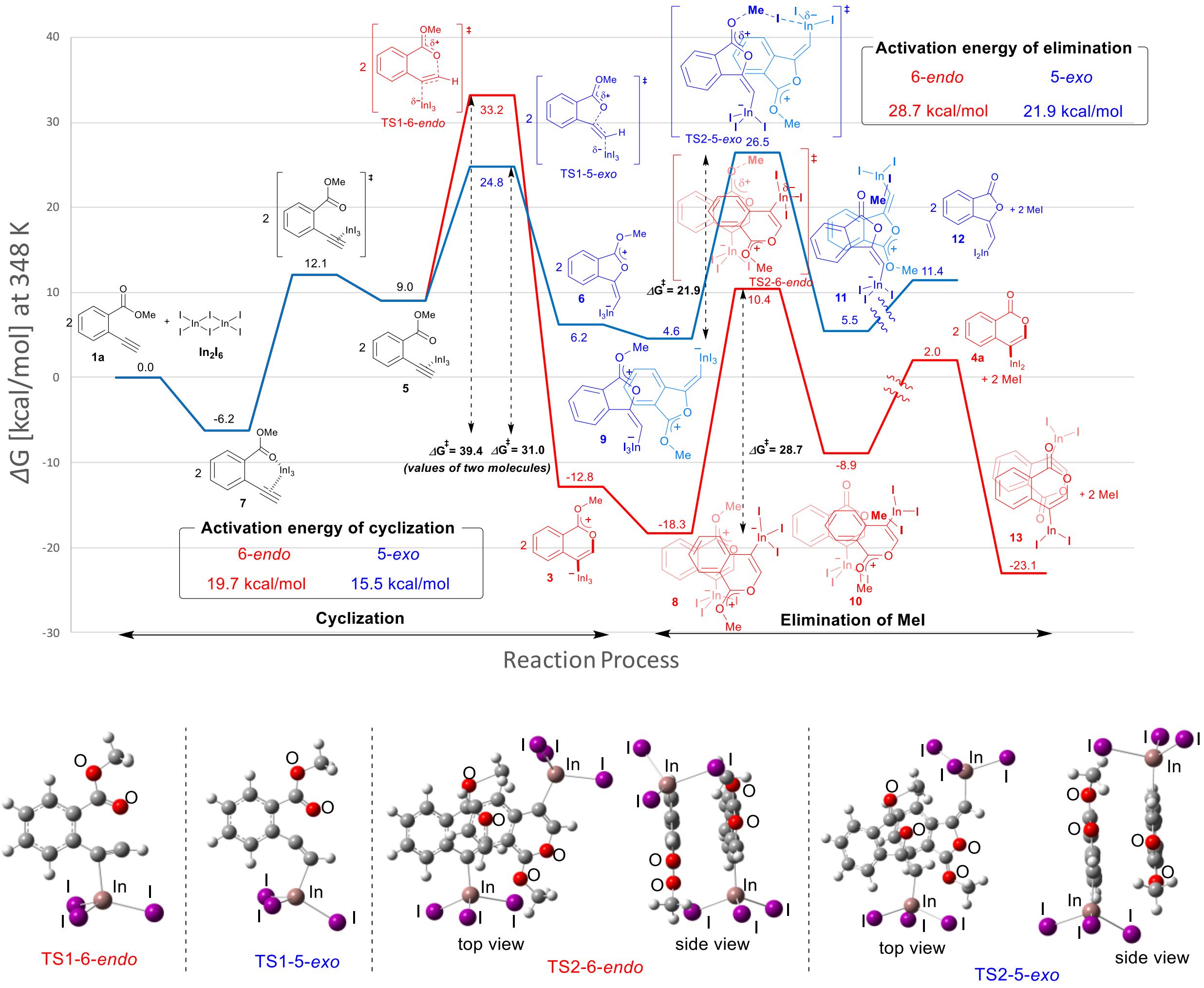
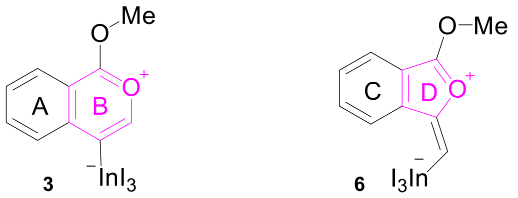


Figure 3. The energy profiles of 6-*endo* and 5-*exo* oxyindations and 3D molecular structures of transition states. DFT calculation was performed using wB97XD/6-31+G (d,p) for C, H, and O and using DGDZVP for In and I. Solvation effect was introduced using the IEFPCM model, and toluene was used as a solvent.

The remarkable regioselectivity of oxyindation is ascribed to the differences in stability between the 6-membered zwitterion **3** and the 5-membered **6**. Zwitterion **3** is much more stable than **6**, and this difference in stability originates from the aromaticity of these compounds, although ring strain is also a consideration. To verify this possibility, the aromaticity of zwitterions was evaluated via NICS(1)[25] (Fig. 4), and the 6-membered compound **3** showed a higher level of aromaticity than that of **6**.



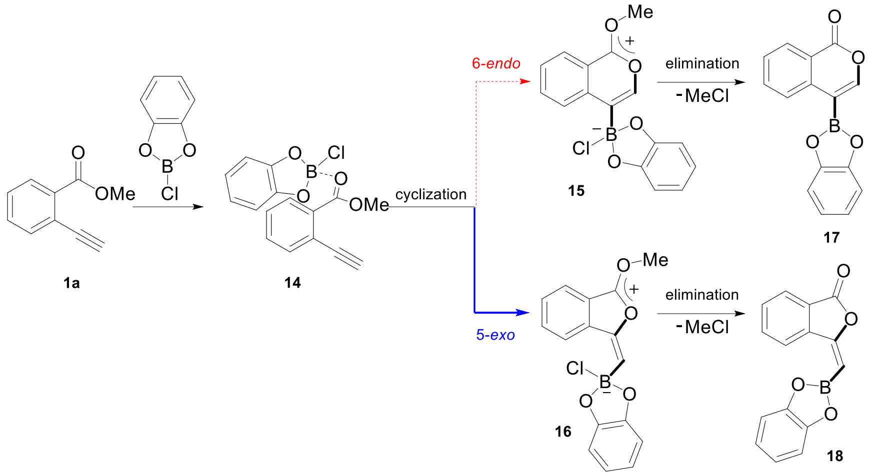
NICS(1) of ring A = -11.0516
NICS(1) of ring B = **-7.0676**

NICS(1) of ring C = -10.4635
NICS(1) of ring D = **-5.0303**

Figure 4. NICS(1) values of 6-membered zwitterion **3** and 5-membered zwitterion **6**. The aromaticity was calculated using B3LYP/6-31G (d,p) for C, H, and O and using DGDZVP for In and I.

Theoretical Calculation for Oxyboration

Blum and co-workers reported that oxyboration of **1a** using *B*-chlorocatecholborane (ClBcat) gave a 5-membered product[6e] rather than the 6-membered version (Scheme 6). ClBcat is coordinated by the carbonyl moiety of **1a**. Then, oxyboration proceeds via 5-*exo* cyclization to give the zwitterion intermediate **16**, and the elimination of MeCl gives the target product **18**. We also performed DFT calculation of oxyboration to investigate the striking change in the regioselectivity between oxyboration and oxyindation. First, the calculation of oxyboration was performed for a similar oxyindation mechanism via concerted cyclization and S_N2-type elimination of MeCl from aggregated zwitterion intermediates (see Fig. S6 in Experimental Section). We considered another possibility for the elimination step, because recent theoretical investigation of ClBcat-mediated heterocyclization has shown other mechanisms,[26] whereby the Me group is attacked either by dissociated chloride[26a] or by $[Cl_2Bcat]^-$[26b]. Thus, we considered these additional two plausible elimination steps assisted either by free Cl^- or $[Cl_2Bcat]^-$ (See Fig. S7 in Experimental Section and Fig. 5 and 6). The result of comparison between these three pathways showed that the most probable path was the use of $[Cl_2Bcat]^-$ (Details of the comparison are shown in Experimental Section).



Scheme 6. A proposed mechanism for oxyboration.

The total reaction profile of oxyboration is described in Fig. 5 and 6. In that profile, 5-*exo* cyclization from **1a** and 2ClBcat to **16** has an activation energy (27.9 kcal/mol) that is lower than that of 6-*endo* cyclization (**1a** and 2ClBcat to **15**, 34.4 kcal/mol). The chloride moiety of zwitterion **16** coordinates to another ClBcat to provide complex **19**. The chloride transfer process (**19** to **20**) has a low energy barrier (5.8 kcal/mol), and [Cl$_2$Bcat]$^-$ is generated rapidly. Cl in [Cl$_2$Bcat]$^-$ approaches the methyl group in the ester moiety (**20**→**21**→**22**), and an elimination of MeCl (**22** to **23**) in the S$_N$2-mechanism occurs to give 5-membered product **18**. The activation energy of the elimination of MeCl (**22** to TS3-5-*exo*) is 20.7 kcal/mol, which allows the elimination of MeCl to proceed smoothly to give the final product **18**. The fast elimination step allows oxyboration to proceed under kinetic control to accomplish the 5-*exo* selective cyclization.

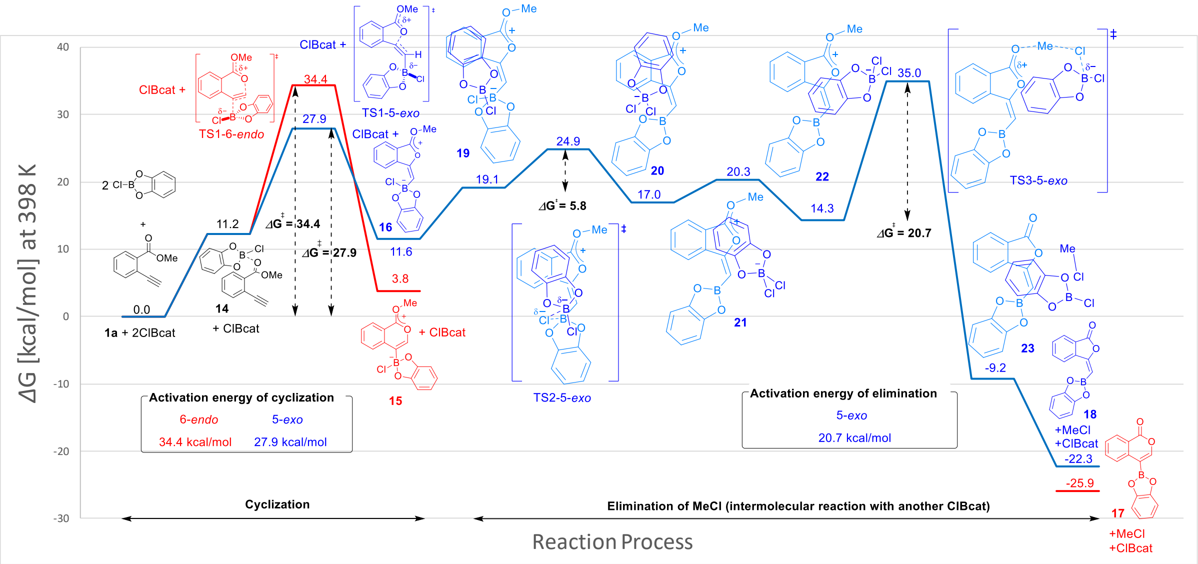


Figure 5. The energy profiles of 5-*exo* and 6-*endo* oxyborations. DFT calculation was performed by wB97XD/6-31+G (d,p) for C, H, O, B, and Cl. Solvation effect was introduced using the IEFPCM model, and toluene was used as a solvent.

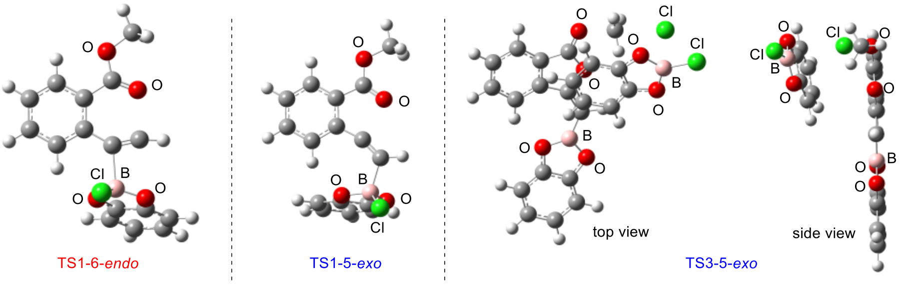


Figure 6. 3D molecular structures of transition states in oxyborations.

Comparing the Transition State of the Cyclization Step in Oxyindation with That in Oxyboration Based on an Electrostatic Potential Map

The significant difference between oxyindation and oxyboration was investigated because each showed a characteristic energy profile, particularly for the cyclization step. The energy barrier of cyclization in oxyindation (6-*endo*: 19.7 kcal/mol, 5-*exo*: 15.5 kcal/mol) is much lower than that of oxyboration (6-*endo*: 34.4 kcal/mol, 5-*exo*: 27.9 kcal/mol). Therefore, the electrostatic potential maps for the transition states of cyclization (TS1-6-*endo* and TS1-5-*exo*) were calculated (Fig. 7). The value of V_{min}, which represents the most negative surface electrostatic potential, was investigated to evaluate the degree of localization for a negative charge.[27] The V_{min} of the organoindium species (left, in Fig. 7) was less negative than that of boron (right, in Fig. 7), which showed that the negative charge was delocalized in the transition state of oxyindation compared with oxyboration. The value of V_{max}, which is the most positive surface electrostatic potential, was also calculated and was less affected by the differences in the metals (see Table S2 in Experimental Section). The polarizability of the indium, boron and heteroatoms binding to a metal explained these results. Indium and iodine atoms have large polarizability ($\alpha_{\mathrm{In}} = 69$ a.u., $\alpha_{\mathrm{I}} = 35.1$ a.u.),[28] and the increasing negative charge in the TS1 of oxyindation was efficiently delocalized to stabilize the zwitterionic TS1-6-*endo*.[29] On the other hand, boron, chlorine and oxygen atoms have smaller polarizability ($\alpha_{\mathrm{B}} = 20.5$ a.u., $\alpha_{\mathrm{Cl}} = 14.7$ a.u., $\alpha_{\mathrm{O}} = 6.04$ a.u.)[28] than indium and iodine atoms, so that TS1-5-*exo* becomes unstable due to the localization of a negative charge. The difference in the fundamental features between indium and boron atoms imparts a significant amount of influence to the regioselectivity of oxymetalation.

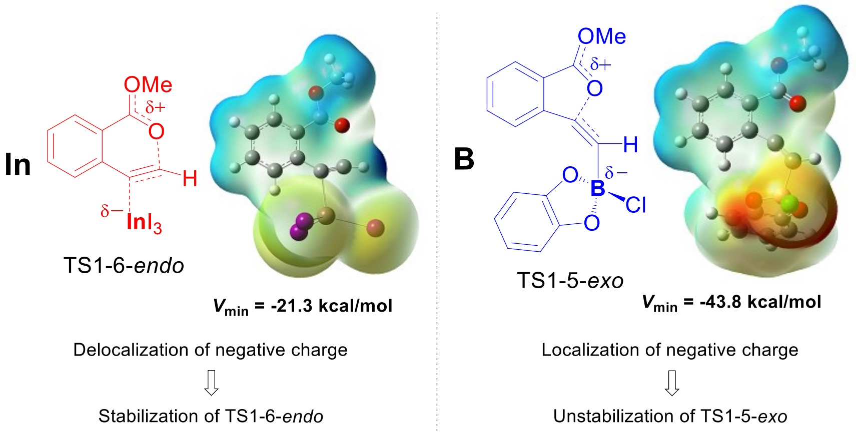


Figure 7. Electrostatic potential maps were calculated on the 0.001 au isosurface of electron density for optimized structures of the transition states of oxyindation (left) and oxyboration (right). The potential is depicted by a color gradient from the most negative (red) to the most positive (blue) value (kcal/mol). V_{min} represents the most negative surface electrostatic potential.

Summary of DFT Calculation

In oxyindation (Fig. 8A), the activation energy of 5-*exo* cyclization is much lower than that required for the elimination of MeI to lead reversible 5-*exo* cyclization. Therefore, the thermodynamically stable 6-membered zwitterion **3** was selectively produced to accomplish the remarkable 6-*endo* selectivity. The elimination step from **3** is a rate-determining step that provides the target metalated isocoumarin **4a**. On the other hand, the energy barrier for cyclization in oxyboration (Fig. 8B) is higher than that for the elimination of MeCl and the cyclization step is a rate-determining step, which leads to irreversible 5-*exo* cyclization to afford the 5-membered product **18** under kinetic control. Therefore, activation energies of cyclization as well as elimination are important factors to determine the regioselectivity in cyclization.

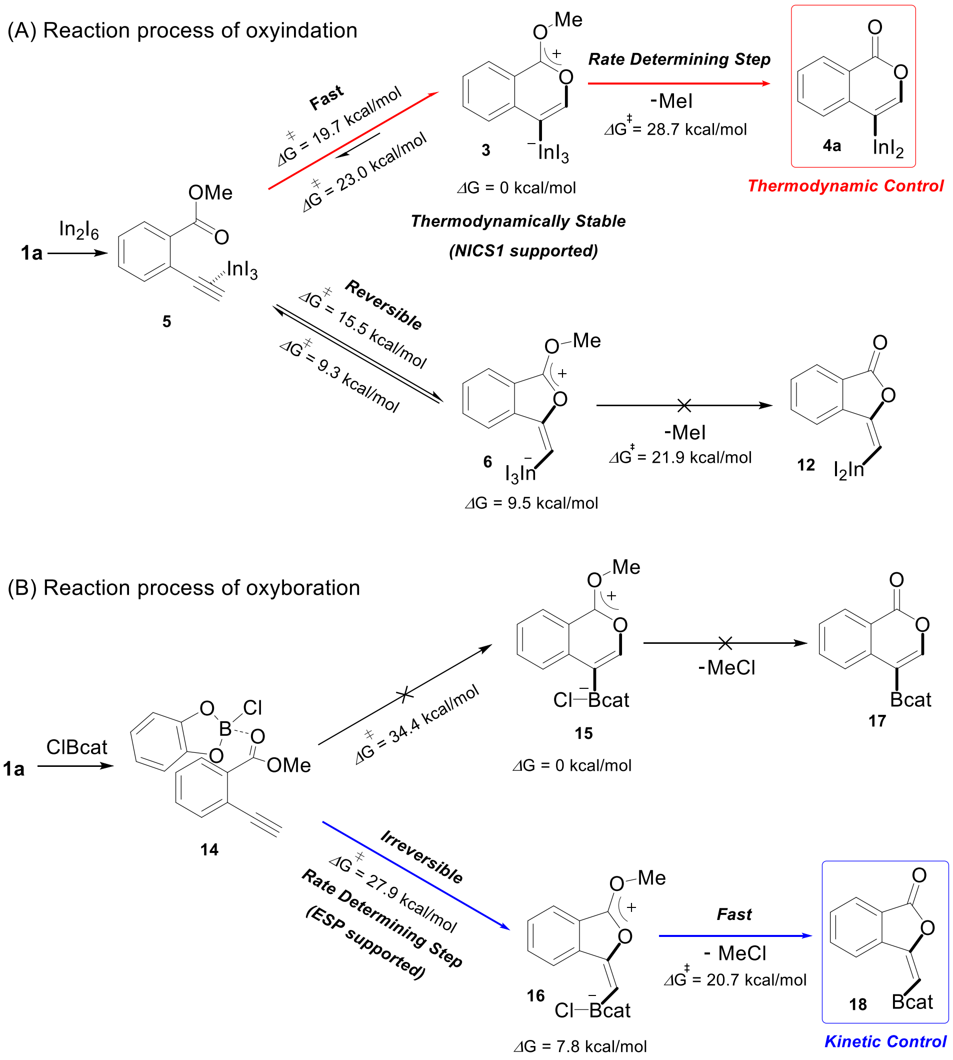
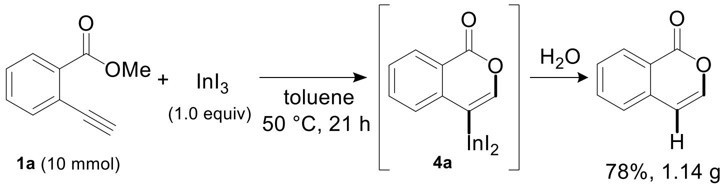


Figure 8. The summarized results of DFT calculation.

Application to the Synthesis of Isocoumarin Derivatives

Our developed oxyindation was applied to the synthesis of isocoumarin derivatives. First, the gram-scale synthesis of an organoindium species was carried out. Methyl ester **1a** (10 mmol) reacted with InI_3 to give organoindium **4a**, and 1.14 g of isocoumarin was isolated by the addition of H_2O (Scheme 7).

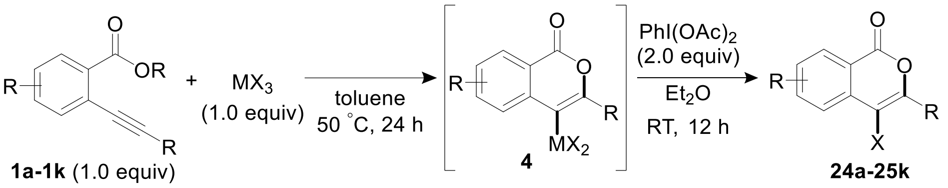


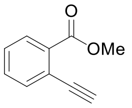
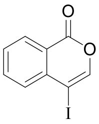
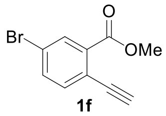
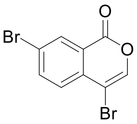
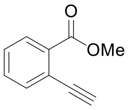
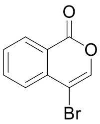
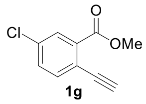
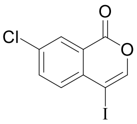
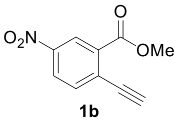
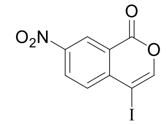
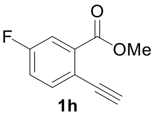
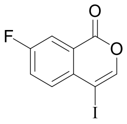
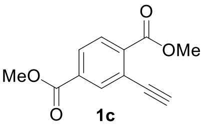
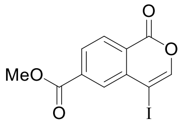
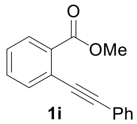
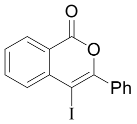
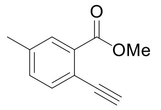
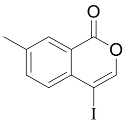
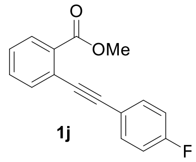
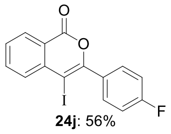
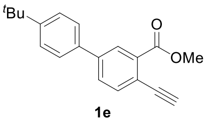
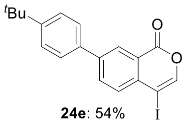
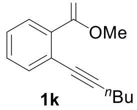
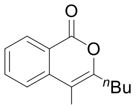
Scheme 7. Gram-scale synthesis of isocoumarin including a carbon-indium bond.

Next, the oxidation of produced alkenylindium compounds was performed (Table 2). An oxyindation of **1a** using InI_3 was carried out, and the organoindium **4a** was oxidized by $PhI(OAc)_2$ in a one-pot procedure to give 4-iodoisocoumarin **24a** (entry 1). Subjecting $InBr_3$ to the oxidation reaction provided 4-bromoisocumarin **25a** in a high yield (entry 2). Therefore, various types of 2-alkynylbenzoates were surveyed in the sequential oxyindation/halogenation process to give 4-halogenated isocoumarins. Substrates with electron withdrawing groups such as nitro and carbonyl groups gave the target products **24b** and **24c** in high yields (entries 3 and 4). The structure of **24b** was characterized by X-ray crystallographic analysis. Substrates with methyl or aryl groups efficiently afforded the target isocoumarins **24d** and **24e** (entries 5 and 6). Also, 2-alkynylbenzoates, including halogen moieties (Br, Cl and F), were suitable for this reaction system to give the isocoumarins **25f-24h** in moderate yields (entries 7-9). The synthesis of isocoumarins from internal alkynes was also investigated. Optimization of the reaction conditions showed that gallium salts were more suitable than indium salts for the oxymetalation of an internal alkyne (See Table S3 in Experimental Section). Therefore, gallium salts were employed in the reactions of internal alkynes **1i**, **1j** and **1k** to provide the 3,4-disubstituted isocoumarins **24i**, **24j** and **25k** (entries 10-12).

One-pot syntheses of 4-substituted isocoumarins were performed via oxyindation followed by a palladium-catalyzed cross-coupling reaction (Table 3).[30] After the oxymetalation of **1a** using $InBr_3$, the addition of a palladium catalyst, lithium chloride, organic halides **27**, and an additional solvent to the resultant toluene solution afforded the coupling product **28**. Iodobenzene **27a** and the aryl iodides bearing electron donating group **27b** or electron withdrawing group **27c** were applicable to give the 4-arylisocoumarins **28aa-28ac** in high yields (entry 1). Palladium-catalyzed cross coupling with acid chlorides also proceeded efficiently. Reactions using the benzoyl chloride derivatives **27d** and **27e**, as well as the alkanoyl chloride **27f**, afforded the isocoumarins **28ad-28af** with ketone moieties in good yields (entries 2 and 3). The structure of **28ae** was characterized by X-ray crystallographic analysis. In this reaction system, alkyl halides such as the benzyl bromide **27g** and the allyl bromide **27h** were also suitable to give the 4-alkylisocoumarins **28ag** and **28ah**, respectively (entries 4 and 5). Various types of 4-substituted isocoumarins were obtained from an isocoumarin that included a carbon-indium bond by utilizing palladium-catalyzed cross coupling.

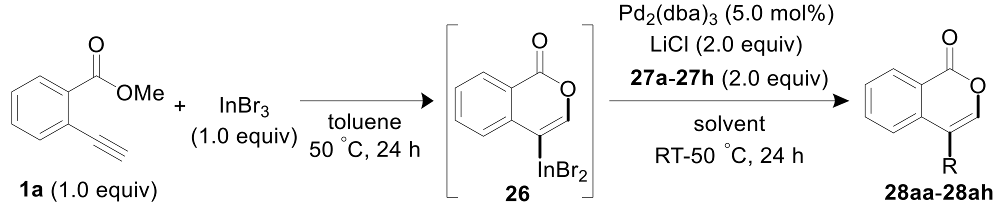
Table 2 Sequential Oxymetalation/Halogenation of Various Types of 2-Alkynylbenzoate **1**.[a]

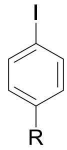
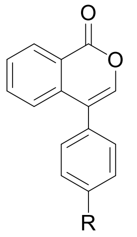
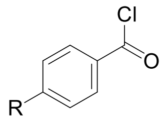
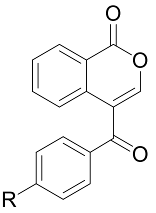
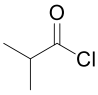
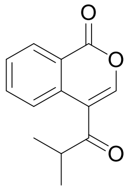
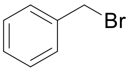
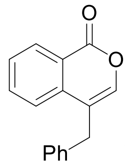
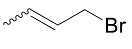
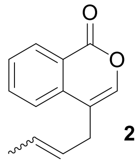


Entry	**1**	MX_3	Target[b]	Entry	**1**	MX_3	Target[b]
1	 **1a**	InI_3	 **24a**: 64%	7	 **1f**	$InBr_3$	 **25f**: 47%
2	 **1a**	$InBr_3$	 **25a**: 73%	8	 **1g**	InI_3	 **24g**: 67%
3	 **1b**	InI_3	 **24b**: 61%	9	 **1h**	InI_3	 **24h**: 61%
4	 **1c**	InI_3	 **24c**: 70%	10	 **1i**	GaI_3	 **24i**: 60%
5	 **1d**	InI_3	 **24d**: 54%	11	 **1j**	GaI_3	 **24j**: 56%
6	 **1e**	InI_3	 **24e**: 54%	12	 **1k**	$GaBr_3$	 **25k**: 60%

[a] First step: **1** (0.5 mmol), MX_3 (0.5 mmol), toluene (1 mL), 50 °C, 24 h. Second step: $PhI(OAc)_2$ (1.0 mmol), Et_2O (1 mL), RT, 12 h. [b] Isolated yields.

Table 3. One-Pot Formation of 4-Substituted Isocoumarins by Palladium-Catalyzed Cross-coupling of Organoindium Species **26** with Organic Halides **27**.[a]

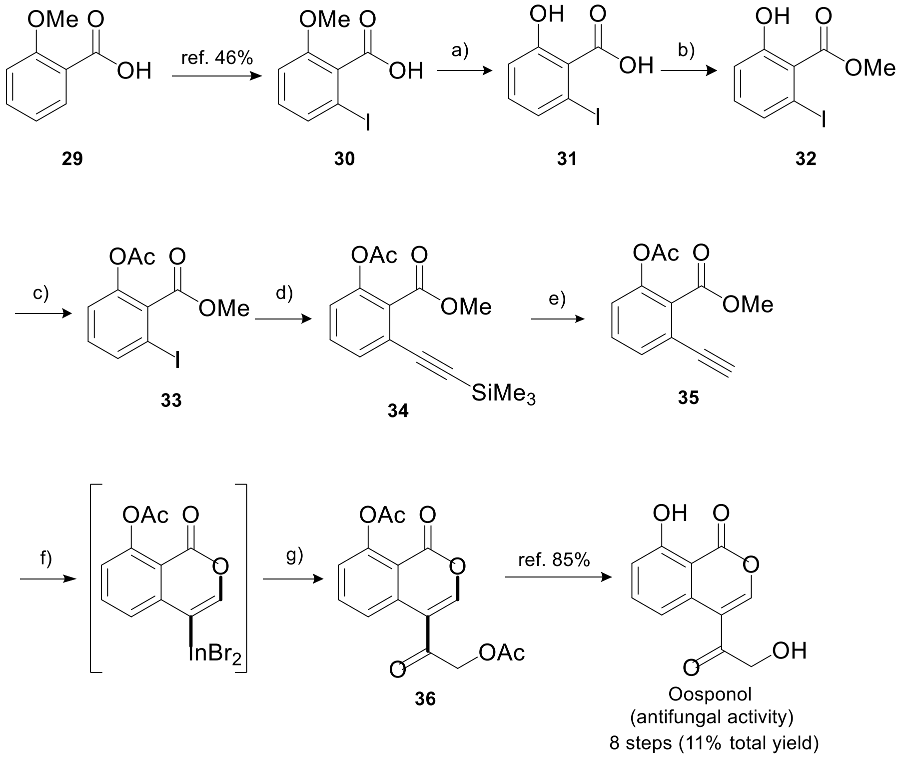


Entry	**27**	Target	Yield (%)[b]
1	 **27a** (R =H) **27b** (R = OMe) **27c** (R = CN)	 **28aa** (R =H) **28ab** (R = OMe) **28ac** (R = CN)	**28aa**: 81 **28ab**: 71 **28ac**: 72
2	 **27d** (R = H) **27e** (R = Cl)	 **28ad** (R = H) **28ae** (R = Cl)	**28ad**: 82 **28ae**: 64
3[c]	 **27f**	 **28af**	61
4[d]	 **27g**	 **28ag**	51
5[d]	 **27h**	 **28ah**	45[e]

[a] Basic reaction conditions of the first step: **1a** (0.5 mmol), $InBr_3$ (0.5 mmol), toluene (1 mL), 50 °C, 24 h. Second step: Pd_2dba_3 (0.025 mmol), LiCl (1.0 mmol), **27** (1.0 mmol), NMP (2.5 mL), 50 °C, 24 h. [b] Isolated yields. [c] HMPA (2.5 mL), RT, 24 h. [d] HMPA (2.5 mL), 50 °C, 24 h. [e] *E*/*Z* = 90:10.

Formal Total Synthesis of Oosponol

Finally, a formal total synthesis of oosponol, which exhibits strong antifungal activity,[15] was conducted (Scheme 8). Firstly, iodination of commercially available compound **29** proceeded via a method found in the literature.[31] During the initial investigation, **30** was transformed into methyl 2-ethynyl-6-methoxybenzoate, and then we attempted the synthesis of the precursor of oosponol via oxyindation and cross-coupling, but the reaction returned a complicated mixture. Therefore, in another synthetic route, the OMe group of **29** was converted to an OAc group with less ability to donate electrons. The OMe moiety of **30** was completely deprotected by BBr$_3$. Acid-catalyzed esterification and acetylation of the phenol moiety gave methyl 6-iodoacetylsalicylate **33** in a high yield. Sonogashira coupling followed by the removal of a silyl moiety afforded the desired 2-alkynylbenzoate derivative **35**. Oxymetalation of **35** using InBr$_3$ and sequential palladium-catalyzed cross coupling with acid chloride **27i** produced the key intermediate **36**, and the hydrolyzation of **36** yielded oosponol.[16b] Our method used a readily available starting material and gave a higher yield than previous works.[16b,32]



Scheme 8. Formal Total Synthesis of Oosponol. Reagents and reaction conditions: a) BBr$_3$ (1 M in CH$_2$Cl$_2$, 2.0 equiv), CH$_2$Cl$_2$, RT, 20 h, 100%. b) H$_2$SO$_4$ (20 mol %), MeOH, Reflux, 20 h, 87%. c) AcCl (1.04 equiv), Pyridine (1.04 equiv), Acetone, RT, 14 h, 97%. d) Ethynyltrimethylsilane (1.1 equiv), PdCl$_2$(PPh$_3$)$_2$ (2.0 mol %), CuI (20 mol %), NEt$_3$, RT, 17 h, 100%. e) 1M KF aq. (1.65 equiv), DMF, RT, 0.5 h, 76%. f) InBr$_3$ (1.0 equiv), Toluene, 50 °C, 24 h. g) Pd$_2$dba$_3$ (5.0 mol %), LiCl (2.0 equiv), 2-(acetyloxy)acetyl chloride **27i** (2.0 equiv), HMPA, RT, 9 h, 44%.

3-3. Conclusion

We achieved the synthesis of isocoumarins bearing a metal-carbon bond at the 4-position via 6-*endo* selective oxymetalation of 2-alkynylbenzoate **1** (Type *endo*-t). Indium and gallium salts showed high activity for the oxymetalation of 2-ethynylbenzoate **1a**. Both the metalated isocoumarin **4b** and the zwitterion intermediate **3** were identified by X-ray crystallographic analysis. This is the first example of the isolation of the product **E** and the benzopyrylium intermediate **F** proposed in the mechanism of oxymetalation (Scheme 2A). The elimination of MeI from zwitterion **3** occurred under heating conditions to give the target product **4a**, which means the rate-determining step was the elimination step. DFT calculation suggested that thermodynamic control led to 6-*endo* selective oxyindation, while kinetic control led to 5-*exo* selective oxyboration. The 6-membered product proved much more stable than the 5-membered product due to a difference in the degree of aromatic stability. The investigation of electrostatic potential of the transition state in the cyclization pathway suggested that a delocalization of negative charge by large atomic radii of In and I atoms stabilizes the zwitterionic transition state. In contrast, small atomic radii of B, Cl, and O atoms causes a localization of negative charge to destabilize the corresponding transition state. The difference in stability between the 6- and 5-membered zwitterions and the elemental character of InI_3 both played important roles in the unique regioselectivity of oxymetalation and in the facile preparation of the **E** species.

These isocoumarins bearing a carbon-metal bond at the 4-position were applied to organic synthesis. Oxymetalation provided isocoumarins on a gram scale. The oxidation of organoindium or gallium species yielded various types of 4-halogenated isocoumarins. Palladium-catalyzed cross coupling with aryl iodide, acid chloride, and alkyl bromide gave a wide range of 4-substituted isocoumarins in a one-pot reaction. Therefore, the unprecedented regioselectivity of the present oxymetalation contributed to the synthesis of new types of isocoumarins. We accomplished a formal total synthesis of oosponol to demonstrate the utility of our reaction system.

3-4. Experimental Section

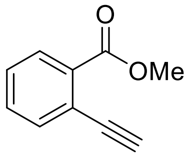
General

New compounds were characterized by ^{1}H and ^{13}C NMR, ^{13}C off-resonance techniques, COSY, HMQC, HMBC, IR, MS, HRMS. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained with TMS as internal standard. IR spectra were recorded as thin films or as solids in KBr pellets. High-resolution mass spectra were obtained by magnetic sector type mass spectrometer. Column chromatography was performed on silica gel (MERK C60 or Fuji Silysia FL100DX). All reactions were carried out under nitrogen. Yields were determined by ^{1}H NMR using internal standards (bromoform). All calculations (Fig. 3-6) were performed with Gaussian09 rev.E.01. The wB97XD density functional and a mixed basis set of DGDZVP for In and I and 6-31+G (d,p) for other atoms were used. All molecular geometries were fully optimized and Gibbs free energies including contribution of vibrational entropy at an appropriate temperature were described in energy profiles. Solvation effect was introduced using the IEFPCM model and toluene was used as a solvent. Aromaticity of 6- and 5-membered zwitterions (**3** and **6**) was calculated by the B3LYP density functional and a mixed basis set of 6-31G (d,p) for C, H, O and DGDZVP for In, I for their optimized structures. Electrostatic potential maps were calculated on the 0.001 au isosurface of electron density for optimized structures of transition states of oxyindation and oxyboration. The potential is depicted with a color gradient from the most negative (red) to the most positive (blue) value (kcal/mol).

Materials

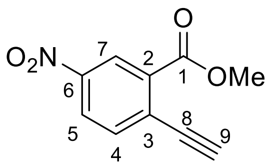
Dehydrated toluene was purchased and used without further purification. 2-Alkynylbenzoate derivatives **1a**, **1c**, **1f**, **1g**, **1i, 1k, 1l, 1m** were synthesized by literature procedures and spectral data of these compounds are shown below. Methyl 2-alkynylbenzoate derivatives **1b**, **1d**, **1e**, **1h**, **1j** are new compounds, and synthetic method and spectral data of these compounds are shown below. All metal salt, organohalides **27a-i** and the starting material of oosponol **29** are commercially available.

(**1a**) Methyl 2-ethynylbenzoate



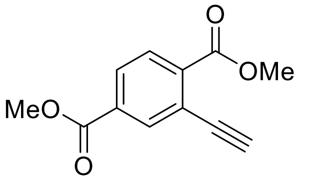
This compound was synthesized by a reported method[33] and the NMR data was agreement with the literature[33].

(**1b**) methyl 2-ethynyl-5-nitrobenzoate



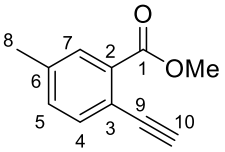
To a three necked flask, methyl 5-nitro-2-((trimethylsilyl)ethynyl)benzoate (2.83 g, 10.2 mmol), MeOH (20 mL) and K_2CO_3 (0.198 g, 1.43 mmol) were added. After stirring for 3 h at RT, the solvent was evaporated and the residue was diluted by CH_2Cl_2 (20 mL). The solution was washed by water (20 mL) and sat. NaCl aq. (20 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (1.56 g, 74%). IR: (KBr) 1701 (C=O) cm^{-1}, 1523 (NO_2) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 8.80 (d, *J* = 2.3 Hz, 1H, 7-H), 8.33 (dd, *J* = 8.6, 2.3 Hz, 1H, 5-H), 7.80 (d, *J* = 8.6 Hz, 1H, 4-H), 4.00 (s, 3H, OMe), 3.73 (s, 1H, 9-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 164.2 (s, C-1), 146.9 (s, C-6), 136.0 (d, C-4), 133.7 (s, C-2), 128.9 (s, C-3), 126.0 (d, C-5), 125.5 (d, C-7), 87.9 (d, C-9), 80.3 (s, C-8), 52.8 (q, OMe); MS: (EI, 70 eV) m/z 205 (M, 100), 174 (81), 147 (51), 128 (72), 100 (49), 74 (41); HRMS: (CI, 70 eV) Calculated ($C_{10}H_8NO_4$) 206.0453 $[M+H]^+$ Found: 206.0451.

(**1c**) dimethyl 2-ethynylterephthalate



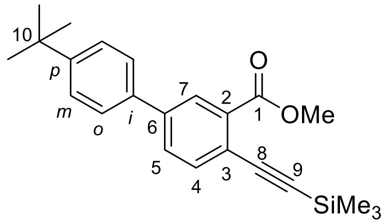
This compound was synthesized by a reported method[33] and the NMR data was agreement with the literature[34].

(**1d**) methyl 2-ethynyl-5-methylbenzoate



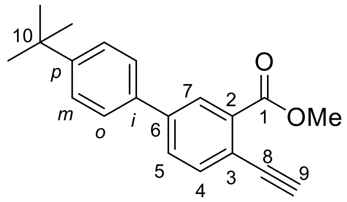
To a three necked flask, methyl 5-methyl-2-((trimethylsilyl)ethynyl)benzoate (7.96 g, 32.3 mmol), MeOH (30 mL) and K_2CO_3 (0.41 g, 3.0 mmol) were added. After stirring for 15 h at RT, the solvent was evaporated and the residue was diluted by CH_2Cl_2 (20 mL). The solution was washed by water (20 mL) and sat. NaCl aq. (20 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (2.33 g, 40%). IR: (KBr) 1720 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.74 (d, *J* = 1.4 Hz, 1H, 7-H), 7.50 (d, *J* = 7.7 Hz, 1H, 4-H), 7.26 (dd, *J* = 7.7, 1.4 Hz, 1H, 5-H), 3.91 (s, 3H, OMe), 3.36 (s, 1H, 10-H), 2.37 (s, 3H, 8-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 166.4 (s, C-1), 138.6 (s, C-6), 134.6 (d, C-4), 132.4 (d, C-5), 132.1 (s, C-2), 130.7 (d, C-7), 119.5 (s, C-3), 82.0 (s, C-9), 81.2 (d, C-10), 51.9 (q, OMe), 21.1 (q, C-8); MS: (EI, 70 eV) m/z 174 (M, 94), 143 (92), 115 (100); HRMS: (CI, 70 eV) Calculated ($C_{11}H_{11}O_2$) 175.0759 $[M+H]^+$ Found: 175.0762.

(Precursor of **1e**) 4'-(*tert*-butyl)-4-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-3-carboxylate



To a three necked flask, methyl 4'-(*tert*-butyl)-4-iodo-[1,1'-biphenyl]-3-carboxylate (1.20 g, 3.04 mmol), THF (4.5 mL), CuI (0.0128 g, 0.127 mmol), PPh$_3$ (0.0202 g, 0.0770 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.101 g, 0.144 mmol), NEt$_3$ (0.475 g, 4.69 mmol) and trimethylsilylacetylene (0.45 g. 4.58 mmol) was added. After stirring for 57 h at RT, the reaction mixture was filtered through a celite pad. The filtrate was evaporated and the residue was purified by column chromatography (hexane, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.984 g, 90%). IR: (KBr) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 8.16 (d, J = 1.9 Hz, 1H, 7-H), 7.66 (dd, J = 8.1, 1.9 Hz, 1H, 5-H), 7.62 (d, J = 8.1 Hz, 1H, 4-H), 7.55 (d, J = 8.7 Hz, 2H, *o*), 7.46 (d, J = 8.7 Hz, 2H, *m*), 3.94 (s, 3H, OMe). 1.35 (s, 9H, 10-Me$_3$), 0.289 (s, 9H, SiMe$_3$); ^{13}C NMR: (100 MHz, CDCl$_3$) 166.9 (s, C-1), 151.2 (s, *p*), 140.8 (s, C-6), 136.2 (s, *i*), 134.9 (d, C-4), 132.9 (s, C-2), 129.6 (d, C-5), 128.6 (d, C-7), 126.6 (d, *o*), 125.9 (d, *m*), 121.6 (s, C-3), 103.4 (s, C-8), 100.0 (s, C-9), 52.0 (q, OMe), 34.6 (s, C-10), 31.3 (q, 10-Me$_3$), -0.091 (q, SiMe$_3$); MS: (EI, 70 eV) m/z 364 (M, 89), 349 (93), 319 (100); HRMS: (EI, 70 eV) Calculated ($C_{23}H_{28}O_2Si$) 364.1859 [M]$^+$ Found: 364.1855.

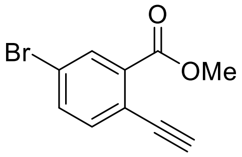
(**1e**) methyl 4'-(*tert*-butyl)-4-ethynyl-[1,1'-biphenyl]-3-carboxylate



To a three necked flask, methyl 4'-(*tert*-butyl)-4-((trimethylsilyl)ethynyl)-[1,1'-biphenyl]-3-carboxylate (0.73 g, 2.00 mmol), MeOH (2.0 mL) and K$_2$CO$_3$ (0.028 g, 0.203 mmol) were added. After stirring for 18 h at RT, the solvent was evaporated and the residue was diluted by CH$_2$Cl$_2$ (5 mL). The solution was washed by water (5 mL) and sat. NaCl aq. (5 mL). The organic layer was dried (MgSO$_4$) and the solvent was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.385 g, 65%). IR: (KBr) 1724 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, CDCl$_3$) 8.18 (d, J = 1.9 Hz, 1H, 7-H), 7.70 (dd, J = 8.2, 1.9 Hz, 1H, 5-H), 7.67 (d, J = 8.2 Hz, 1H, 4-H), 7.56 (d, J = 8.7 Hz, 2H, *o*), 7.49 (d, J = 8.7 Hz, 2H, *m*), 3.96 (s, 3H, OMe). 3.43 (s, 1H, 9-H), 1.36 (s, 9H, 10-Me$_3$); ^{13}C NMR: (100 MHz, CDCl$_3$) 166.5 (s, C-

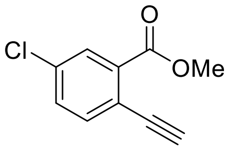
1), 151.4 (s, *p*), 141.2 (s, C-6), 136.2 (s, *i*), 135.4 (d, C-4), 132.9 (s, C-2), 129.9 (d, C-5), 128.7 (d, C-7), 126.7 (d, *o*), 125.9 (d, *m*), 121.0 (s, C-3), 82.5 (d, C-9), 82.1 (s, C-8), 52.2 (q, OMe), 34.6 (s, C-10), 31.3 (q, 10-Me$_3$); MS: (EI, 70 eV) m/z 292 (M, 61), 277 (100); HRMS: (EI, 70 eV) Calculated ($C_{20}H_{20}O_2$) 292.1463 $[M]^+$ Found: 292.1463.

(**1f**) methyl 5-bromo-2-ethynylbenzoate



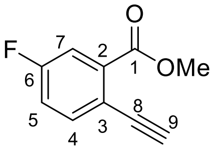
This compound was synthesized by a reported method[33] and the NMR data was agreement with the literature[35].

(**1g**) methyl 5-chloro-2-ethynylbenzoate



This compound was synthesized by a reported method[33] and the NMR data was agreement with the literature[36].

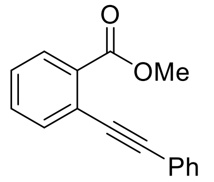
(**1h**) methyl 2-ethynyl-5-fluorobenzoate



To a three necked flask, methyl 5-fluoro-2-((trimethylsilyl)ethynyl)benzoate (1.05 g, 4.20 mmol), MeOH (4.2 mL) and K_2CO_3 (0.063 g, 0.457 mmol) were added. After stirring for 5 h at RT, the solvent was evaporated and the residue was diluted by CH_2Cl_2 (10 mL). The solution was washed by water (10 mL) and sat. NaCl aq. (10 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.502 g, 67%). IR: (KBr) 1724 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.67-7.56 (m, 2H, 4-H and 7-H), 7.19 (td, $J^3_{HH} = 8.2$ Hz, $J^3_{HF} = 8.2$ Hz, $J^4_{HH} = 2.9$ Hz 1H, 5-H), 3.93 (s, 3H, OMe), 3.40 (s, 1H, 9-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 165.0 (s, C-1), 161.7 (d, $J = 250.7$ Hz, C-6), 136.7 (d, $J = 8.2$ Hz, C-4), 134.3 (d, $J = 8.2$ Hz, C-2), 119.1 (d, $J = 22.1$, C-5), 118.6 (d, $J = 4.1$ Hz, C-3), 117.2 (d, $J = 23.8$ Hz, C-7), 82.0 (d, C-9), 80.8 (s, C-8), 52.3

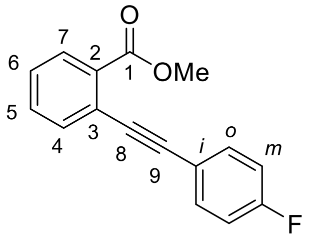
(q, OMe); MS: (EI, 70 eV) m/z 178 (M, 84), 147 (100), 119 (95); HRMS: (CI, 70 eV) Calculated ($C_{10}H_8O_2F$) 179.0508 $[M + H]^+$ Found: 179.0511.

(**1i**) methyl 2-(phenylethynyl)benzoate



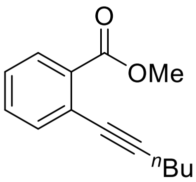
This compound was synthesized by a reported method[33] and the NMR data was agreement with the literature[37].

(**1j**) methyl 2-((4-fluorophenyl)ethynyl)benzoate



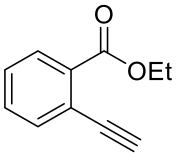
To a three necked flask, methyl 2-iodebenzoate (1.30 g, 4.96 mmol), NEt_3 (5 mL), $PdCl_2(PPh_3)_2$ (0.04 g, 0.057 mmol), CuI (0.050 g, 0.50 mmol) was added and 1-ethynyl-4-fluorobenzene (0.70 g. 5.83 mmol) was dropwised at 0 °C. After stirring for 24 h at RT, the reaction mixture was filtered through a celite pad. The filtrate was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.70 g, 55%). IR: (neat) 1732 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.97 (dd, $J = 8.2$, 1.4 Hz, 1H, 7-H), 7.62 (dd, $J = 7.7$, 1.4 Hz, 1H, 4-H), 7.56 (dd, $J = 9.1$, 5.4 Hz, 2H, *o*), 7.48 (td, $J = 7.7$, 1.4 Hz, 1H, 5-H), 7.37 (td, $J = 7.7$, 1.4 Hz, 1H, 6-H), 7.05 (dd, $J = 9.1$, 8.6 Hz, 2H, *m*). 3.95 (s, 3H, OMe); ^{13}C NMR: (100 MHz, $CDCl_3$) 166.5 (s, C-1), 162.6 (s, d, $^1J_{CF} = 250$ Hz, *p*), 133.8 (d), 133.6 (d), 133.5 (d), 131.7 (d, C-5), 131.6 (s, C-2), 130.4 (d, C-7), 127.9 (d, C-6), 123.5 (s, C-3), 119.3 (s, d, $^4J_{CF} = 2.9$ Hz, *i*), 115.6 (d, d, $^2J_{CF} = 21.9$ Hz, *m*), 93.2 (s, C-8), 87.9 (s, C-9), 52.1 (q, OMe); MS: (EI, 70 eV) m/z 254 (M, 100), 239 (87), 211 (42), 183 (40); HRMS: (EI, 70 eV)
Calculated ($C_{20}H_{20}O_2$) 254.0743 $[M]^+$ Found: 254.0743.

(**1k**) methyl 2-(hex-1-yn-1-yl)benzoate



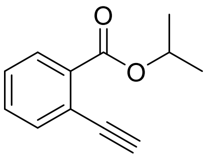
This compound was synthesized by a reported method[33] and the NMR data was agreement with the literature[38].

(**1l**) ethyl 2-ethynylbenzoate



This compound was synthesized by a reported method[34] and the NMR data was agreement with the literature[39].

(**1m**) isopropyl 2-ethynylbenzoate



This compound was synthesized by a reported method[33] and the NMR data was agreement with the literature[40].

Experimental Procedure for the oxymetalation of methyl 2-alkynylbenzoate followed by protonolysis (Table 1 and Scheme 7)

In glove box filled for nitrogen, to a sealed vial, InI_3 (0.5 mmol), toluene (1 mL) and methyl 2-ethynylbenzoate **1a** (0.5 mmol) were added. The solution was stirred at 50 °C and the reaction mixture was quenched by deuterated acetic acid (1 mL) or water. After addition of water (10 mL), the solution was extracted with CH_2Cl_2 (5 mL x 3). The collected organic layer was dried ($MgSO_4$). In the investigation shown in Table 1, the solvent was evaporated and the yield of deuterated isocoumarin **2** was determined by ^1H NMR (400 MHz, in $CDCl_3$). In Scheme 7, the solvent was evaporated and the residue was purified by column chromatography.

Experimental Procedure for the oxymetalation of 2-alkynylbenzoate and quantitation of alkyl halide (Table S1)

In glove box filled for nitrogen, to a sealed vial, InI_3 (0.5 mmol), toluene-d_8 (1 mL) and 2-ethynylbenzoate **1** (0.5 mmol) were added. After stirring at 50 °C for 1 h or 3 h, internal standard ($CHBr_3$) was added to the reaction mixture in glove box filled for nitrogen and then the yield of alkyl halide and the conversion of 2-ethynylbenzoate was determined by ^{1}H-NMR.

Experimental Procedure for the oxymetalation of 2-alkynylbenzoate followed by halogenation (Table 2)

In glove box filled for nitrogen, to a sealed vial, InI_3 (0.5 mmol), toluene (1 mL) and methyl 2-alkynylbenzoate **1** (0.5 mmol) were added. After stirring at 50 °C for 24 h, the slurry was diluted by Et_2O (2 mL) and $PhI(OAc)_2$ (1.0 mmol) was added to the solution in glove box filled for nitrogen. The reaction mixture was stirred at RT for 12 h and then quenched by 1 N HCl aq. (5 mL) and CH_2Cl_2 (2 mL). The solution was extracted with CH_2Cl_2 (2 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography.

Experimental Procedure for the oxymetalation of 2-alkynylbenzoate followed by palladium catalyzed cross coupling (Table 3)

In glove box filled for nitrogen, to a sealed vial, $InBr_3$ (0.5 mmol), toluene (1 mL) and methyl 2-ethynylbenzoate **1a** (0.5 mmol) were added. After stirring at 50 °C for 24 h, Pd_2dba_3 (0.025 mmol), LiCl (1.0 mmol), organohalide **27** (1.0 mmol) and solvent (NMP or HMPA, 2.5 mL) was added to the slurry in glove box filled for nitrogen. The mixture was stirred at RT or 50 °C for 24 h and then quenched by water (10 mL) and Et_2O (5 mL). The solution was extracted with Et_2O (10 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography.

Monitoring of Oxyindation by ^{1}H NMR Spectroscopy

(1) at - 30 °C

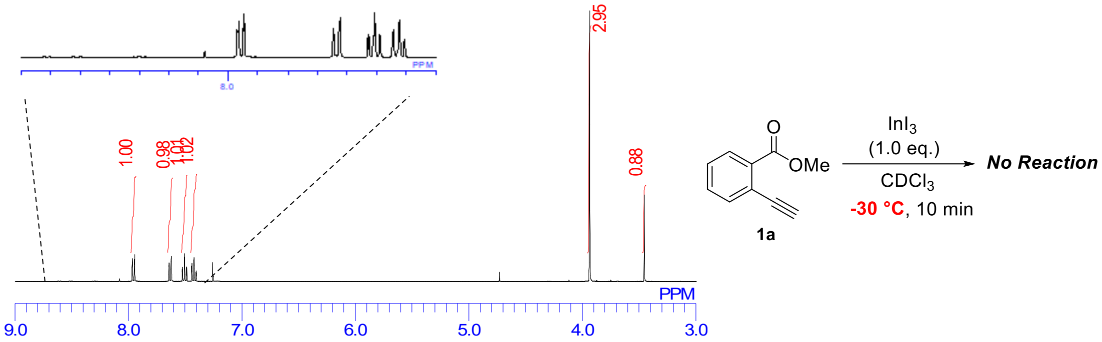


Fig. S1 Monitoring of oxyindation at - 30 °C using ^{1}H NMR (400 MHz, in $CDCl_3$) spectroscopy.

When methyl 2-alkynylbenzoate **1a** was mixed with InI_3 in $CDCl_3$ at - 30 °C, no reaction occurred.

(2) at - 5 °C

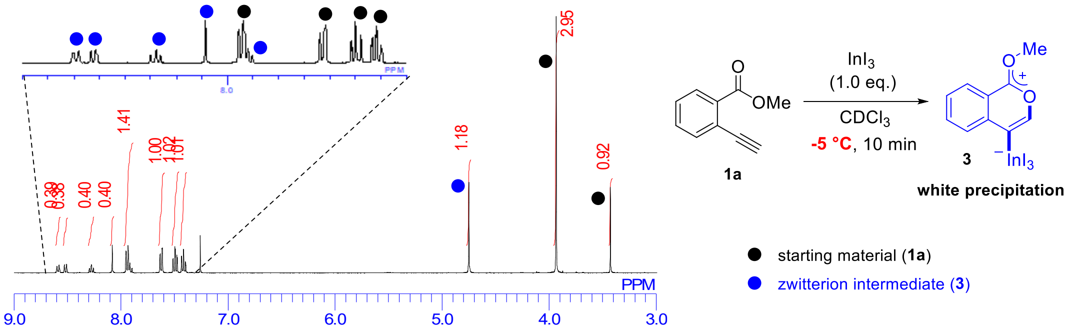


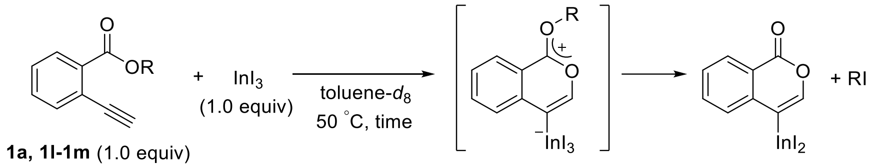
Fig. S2 Monitoring of oxyindation at - 5 °C using ^{1}H NMR (400 MHz, in $CDCl_3$) spectroscopy.

A small amount of zwitterion intermediate **3** was observed.

The Effect of *O*-alkyl Groups on the Elimination of Alkyl Halide

As shown in Eq. 2, elimination of alkyl halide would be rate determining step. Accordingly, the reactivity of *O*-alkyl esters toward the elimination step was compared. Oxyindation of three types of alkyl esters was conducted in a short reaction time and the yields of alkyl halides and conversions of 2-alkynylbenzoate **1** were investigated by ^{1}H NMR (Table S1). The yield of zwitterion intermediate cannot be determined due to its insolubility to toluene. In all cases, fast conversion of **1** and formation of zwitterion species were observed. Methyl ester **1a** and ethyl ester **1l** gave MeI and EtI in 40% and 10% yields, respectively (entries 1 and 2). No alkyl halide was obtained in the case of isopropyl ester **1m** in spite of long reaction time (entry 3). These results indicated that the steric hindrance of *O*-alkyl group inhibited the elimination of alkyl halide.

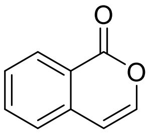
Table S1 The effect of *O*-alkyl groups on the elimination of alkyl halide[a]



entry	R	time	NMR Yield (%) of RI	Conversion (%) of **1**
1	Me (**1a**)	1 h	40	94
2	Et (**1l**)	1 h	10	83
3	^{i}Pr (**1m**)	3 h	0	100

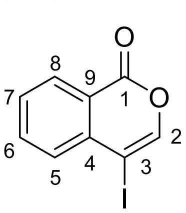
[a] **1** (0.5 mmol), InI_3 (0.5 mmol), toluene-d_8 (1 mL), 50 °C.

Product



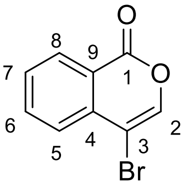
A two necked flask was dried over and filled with nitrogen. To this flask, the InI_3 (4.98 g, 10.0 mmol), toluene (20 mL) and methyl 2-ethynylbenzoate **1a** (1.60 g, 10.0 mmol) were added. The solution was stirred at 50 °C for 21 h and the reaction mixture was quenched by water (30 mL). This solution was extracted with CH_2Cl_2 (30 mL x 3) and the collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (1.14 g, 78%). The NMR data was agreement with the literature[41].

(**24a**) 4-iodo-1*H*-isochromen-1-one



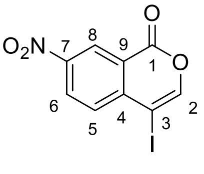
To a solution of InI_3 (0.255 g, 0.515 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.0824 g, 0.514 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.32 g, 0.993 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.090 g, 64%). IR: (KBr) 1718 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 8.26 (d, *J* = 7.7 Hz, 1H, 8-H), 7.82 (t, *J* = 7.6 Hz, 1H, 6-H), 7.59 (m, 3H, 2-H, 5-H, 7-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 161.0 (s, C-1), 147.4 (d, C-2), 136.3 (s, C-4), 135.6 (d, C-8), 130.1 (d), 130.0 (d), 129.7 (d), 121.9 (s, C-9), 75.9 (s, C-3); MS: (EI, 70 eV) *m/z* 272 (M$^+$, 100), 244 (89), 89 (97), 63 (26); HRMS: (CI, 70 eV) Calculated ($C_9H_6IO_2$) 272.9412 [M + H]$^+$ Found 272.9415.

(**25a**) 4-bromo-1*H*-isochromen-1-one



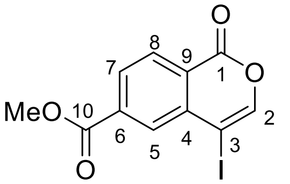
To a solution of InI_3 (0.255 g, 0.515 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.0820 g, 0.512 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.335 g, 1.04 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.0845 g, 73%). IR : (KBr) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 8.31 (d, *J* = 7.5 Hz, 1H, 8-H), 7.85 (t, *J* = 7.5 Hz, 1H, 6-H), 7.74 (d, *J* = 7.5 Hz, 1H, 5-H), 7.62 (t, *J* = 7.5 Hz, 1H, 7-H), 7.51 (s, 1H, 2-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 160.8 (s, C-1), 143.0 (d, C-2), 135.4 (d, C-6), 135.0 (s, C-4), 130.1 (d) 130.0 (d) 125.8 (d, C-5), 121.6 (s, C-9) 103.6 (s, C-3); MS: (EI, 70 eV) *m/z* 224 (M$^+$, 55), 226 (M$^+$ + 2, 54), 196 (59), 89 (100), 63 (22); HRMS: (CI, 70 eV) Calculated ($C_9H_6BrO_2$) 224.9551 [M + H]$^+$ Found 224.9548.

(**24b**) 4-iodo-7-nitro-1*H*-isochromen-1-one



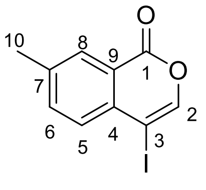
To a solution of InI_3 (0.248 g, 0.500 mmol) in toluene (1 mL), methyl 2-ethynyl-5-nitrobenzoate (0.105 g, 0.512 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.350 g, 1.09 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.0978 g, 61%). This product was recrystallized from CH_2Cl_2 and hexane to give a single crystal and the structure was determined by X-ray crystallographic analysis (CCDC 1576343). IR: (KBr) 1720 (C=O) cm^{-1}, 1342 (NO_2) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 9.10 (d, *J* = 2.7 Hz, 1H, 8-H), 8.61 (dd, *J* = 9.2, 2.7 Hz, 1H, 6-H), 7.84 (d, *J* = 9.2 Hz, 1H, 5-H), 7.76 (s, 1H, 2-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 159.1 (s, C-1), 150.4 (d, C-2), 147.8 (s, C-7), 141.3 (s, C-4), 132.0 (d, C-5), 129.5 (d, C-6), 125.7 (d, C-8), 122.5 (s, C-9), 73.6 (s, C-3); MS: (EI, 70 eV) m/z 317 (M, 100), 289 (68); HRMS: (CI, 70 eV) Calculated ($C_9H_5NO_4I$) 317.9263 $[M + H]^+$ Found: 317.9263.

(**24c**) methyl 4-iodo-1-oxo-1*H*-isochromene-6-carboxylate



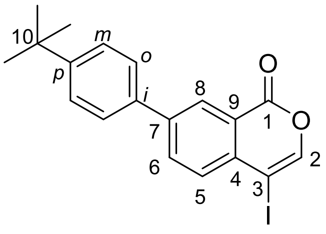
To a solution of InI_3 (0.255 g, 0.515 mmol) in toluene (1 mL), dimethyl 2-ethynylterephthalate (0.11 g, 0.504 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.330 g, 1.02 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and water (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.1171 g, 70%). IR: (KBr) 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 8.35 (d, *J* = 8.0 Hz, 1H, 8-H), 8.27 (d, *J* = 1.2 Hz, 1H, 5-H), 8.20 (dd, *J* = 8.0, 1.2 Hz, 1H, 7-H), 7.64 (s, 1H, 2-H), 4.02 (s, 3H, OMe); ^{13}C NMR: (100 MHz, $CDCl_3$) 165.3 (s, C-10), 160.3 (s, C-1), 148.1 (d, C-2), 136.7 (s), 136.4 (s), 131.6 (d, C-5), 130.5 (d, C-8), 130.0 (d, C-7), 125.0 (s), 75.2 (s, C-3), 52.9 (q, OMe); MS: (EI, 70 eV) m/z 330 (M, 100), 302 (71), 147 (82); HRMS: (CI, 70 eV) Calculated ($C_{11}H_8O_4I$) 330.9467 $[M + H]^+$ Found: 330.9469.

(**24d**) 4-iodo-7-methyl-1*H*-isochromen-1-one



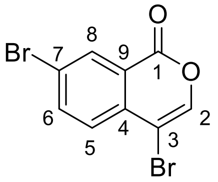
To a solution of InI_3 (0.260 g, 0.525 mmol) in toluene (1 mL), methyl 2-ethynyl-5-methylbenzoate (0.087 g, 0.500 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.335 g, 1.04 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.0774 g, 54%). IR: (KBr) 1751 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 8.07 (s, 1H, 8-H), 7.61 (d, J = 8.2 Hz, 1H, 6-H), 7.54 (s, 1H, 2-H), 7.48 (d, J = 8.2 Hz, 1H, 5-H), 2.50 (s, 3H, 10-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 161.3 (s, C-1), 146.6 (d, C-2), 140.3 (s, C-7), 136.7 (d, C-6), 134.0 (s, C-4), 130.0 (d), 129.8 (d), 121.8 (s, C-9), 75.9 (s, C-3), 21.2 (q, C-10); MS: (EI, 70 eV) m/z 286 (M, 100), 258 (66), 103 (88); HRMS: (CI, 70 eV) Calculated ($C_{10}H_8O_2I$) 286.9569 $[M + H]^+$ Found: 286.9567.

(**24e**) 7-(4-(*tert*-butyl)phenyl)-4-iodo-1*H*-isochromen-1-one



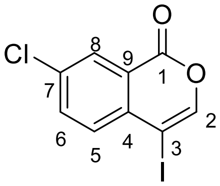
To a solution of InI_3 (0.259 g, 0.523 mmol) in toluene (1 mL), methyl 4'-(*tert*-butyl)-4-ethynyl-[1,1'-biphenyl]-3-carboxylate (0.1453 g, 0.497 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.335 g, 1.04 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.109 g, 54%). IR: (KBr) 1728 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 8.51 (d, J = 1.9 Hz, 1H, 8-H), 8.05 (dd, J = 8.5, 1.9 Hz, 1H, 6-H), 7.67 (d, J = 8.5 Hz, 1H, 5-H), 7.64 (d, J = 8.7 Hz, 2H, *o*), 7.60 (s, 1H, 2-H), 7.53 (d, J = 8.7 Hz, 2H, *m*); ^{13}C NMR: (100 MHz, $CDCl_3$) 161.3 (s, C-1), 151.7 (s, *p*), 147.1 (d, C-2), 142.5 (s, C-7), 135.6 (s, *i*), 135.0 (s, C-4), 134.0 (d, C-6), 130.7 (d, C-5), 127.7 (d, C-8), 126.8 (d, *o*), 126.1 (d, *m*), 122.3 (s, C-9), 75.7 (s, C-3), 34.6 (s, C-10), 31.3 (q, 10-Me x 3); MS: (EI, 70 eV) m/z 404 (M, 56), 389 (100); HRMS: (CI, 70 eV) Calculated ($C_{19}H_{18}O_2I$) 405.0351 $[M + H]^+$ Found: 405.0352.

(**25f**) 4,7-dibromo-1*H*-isochromen-1-one



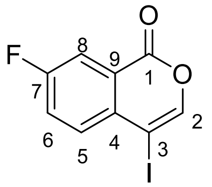
To a solution of $InBr_3$ (0.190 g, 0.536 mmol) in toluene (1 mL), methyl 5-bromo-2-ethynylbenzoate (0.120 g, 0.502 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.322 g, 1.00 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.071 g, 47%). IR: (KBr) 1732 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 8.43 (d, J = 1.8 Hz, 1H, 8-H), 7.94 (dd, J = 8.6, 1.8 Hz, 1H, 6-H), 7.62 (d, J = 8.6 Hz, 1H, 5-H), 7.53 (s, 1H, 2-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 159.5 (s, C-1), 143.3 (d, C-2), 138.5 (d, C-6), 133.9 (s, C-4), 132.6 (d, C-8), 127.6 (d, C-5), 123.5 (s, C-7), 122.8 (s, C-9), 102.8 (s, C-3); MS: (EI, 70 eV) m/z 306 (M + 4, 39), 304 (M + 2, 100), 302 (M, 40), 169 (65), 167 (70); HRMS: (CI, 70 eV) Calculated ($C_9H_5Br_2O_2$) 302.8656 $[M + H]^+$ Found: 302.8654.

(**24g**) 7-chloro-4-iodo-1*H*-isochromen-1-one



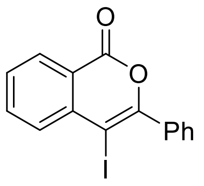
To a solution of InI_3 (0.256 g, 0.516 mmol) in toluene (1 mL), methyl 5-chloro-2-ethynylbenzoate (0.098 g, 0.505 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.321 g, 0.997 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.1036 g, 67%). IR: (KBr) 1724 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 8.24 (d, J = 2.3 Hz, 1H, 8-H), 7.75 (dd, J = 8.7, 2.3 Hz, 1H, 6-H), 7.59 (s, 1H, 2-H), 7.57 (d, J = 8.7 Hz, 1H, 5-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 159.9 (s, C-1), 147.6 (d, C-2), 135.78 (d, C-6), 135.76 (s, C-7), 134.9 (s, C-4), 131.8 (d, C-5), 129.4 (d, C-8), 122.9 (s, C-9), 74.6 (s, C-3); MS: (EI, 70 eV) m/z 308 (M + 2, 35), 306 (M, 100), 278 (64), 123 (84); HRMS: (CI, 70 eV) Calculated ($C_9H_5ClO_2I$) 306.9023 $[M + H]^+$ Found: 306.9022.

(**24h**) 7-fluoro-4-iodo-1*H*-isochromen-1-one



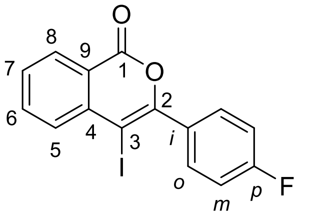
To a solution of InI_3 (0.255 g, 0.515 mmol) in toluene (1 mL), methyl 5-fluoro-2-ethynylbenzoate (0.0913 g, 0.512 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (1 mL) and $PhI(OAc)_2$ (0.330 g, 1.02 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.091 g, 61%). IR: (KBr) 1728 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.93 (d, $^{3}J_{HF}$ = 8.2 Hz, 1H, 8-H), 7.64 (dd, J = 8.9 Hz, $^{4}J_{HF}$ = 5.1 Hz, 1H, 5-H), 7.56 (s, 1H, 2-H), 7.52 (dd, J = 8.9 Hz, $^{3}J_{HF}$ = 8.2 Hz, 1H, 6-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 162.6 (s, d, $^{1}J_{CF}$ = 252 Hz, C-7), 160.1 (s, C-1), 146.6 (d, C-2), 132.9 (s, d, $^{4}J_{CF}$ = 2.5 Hz, C-4), 132.7 (d, d, $^{3}J_{CF}$ = 7.4 Hz, C-5), 123.6 (d, d, $^{2}J_{CF}$ = 22.9 Hz, C-6), 123.3 (s, d, $^{3}J_{CF}$ = 8.2 Hz, C-9), 115.5 (d, d, $^{2}J_{CF}$ = 23.8 Hz, C-8), 74.5 (s, C-3); MS: (EI, 70 eV) m/z 290 (M, 96), 262 (55), 107 (100); HRMS: (CI, 70 eV) Calculated ($C_9H_5FO_2I$) 290.9318 $[M + H]^+$ Found: 290.9315.

(**24i**) 4-iodo-3-phenyl-1*H*-isochromen-1-one



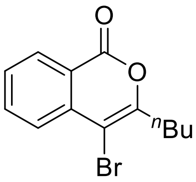
To a solution of GaI_3 (0.230 g, 0.511 mmol) in toluene (1 mL), methyl 2-(phenylethynyl)benzoate (0.116 g, 0.491 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (2 mL) and $PhI(OAc)_2$ (0.322 g, 1.00 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.103 g, 60%). The NMR data was agreement with the literature[38].

(**24j**) 3-(4-fluorophenyl)-4-iodo-1*H*-isochromen-1-one



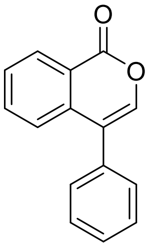
To a solution of GaI_3 (0.231 g, 0.513 mmol) in toluene (1 mL), methyl 2-((4-fluorophenyl)ethynyl)benzoate (0.129 g, 0.507 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (2 mL) and $PhI(OAc)_2$ (0.330 g, 1.02 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.104 g, 56%). IR: (KBr) 1728 (C=O) cm^{-1}; ^1H NMR: (400 MHz, CD_2Cl_2) 8.13 (d, J = 8.2 Hz, 1H, 8-H), 7.77 (d, J = 8.2 Hz, 1H, 5-H), 7.72 (dd, J = 8.2, 7.7 Hz, 1H, 6-H), 7.60 (dd, J = 8.6 Hz, $^4J_{HF}$ = 5.4 Hz, 1H, *o*), 7.48 (dd, J = 8.2, 7.7 Hz, 1H, 7-H), 7.09 (dd, J = 8.6 Hz, $^3J_{HF}$ = 9.1 Hz, 1H, *m*); ^{13}C NMR: (100 MHz, CD_2Cl_2) 163.9 (s, d, $^1J_{CF}$ = 250 Hz, *p*), 161.5 (s, C-1), 154.1 (s, C-2), 138.3 (s, C-4), 136.1 (d, C-6), 132.6 (d, d, $^3J_{CF}$ = 8.6 Hz, *o*), 132.0 (s, d, $^4J_{CF}$ = 3.8 Hz, *i*), 131.9 (d, C-5), 129.9 (d, C-8), 129.8 (d, C-7), 120.6 (s. C-9), 115.6 (d, d, $^2J_{CF}$ = 11.4 Hz, *m*), 77.0 (s, C-3); MS: (EI, 70 eV) m/z 366 (M, 100), 338 (57), 211 (60), 183 (65), 123 (50), 95 (48); HRMS: (CI, 70 eV) Calculated ($C_{15}H_9FIO_2$) 366.9631 $[M+H]^+$ Found: 366.9630.

(**25k**) 4-bromo-3-butyl-1*H*-isochromen-1-one



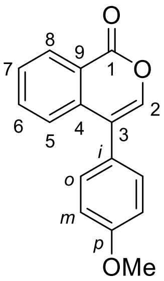
To a solution of $GaBr_3$ (0.169 g, 0.546 mmol) in toluene (1 mL), methyl 2-(hex-1-yn-1-yl)benzoate (0.110 g, 0.509 mmol) was added. The mixture was stirred at 50 °C for 24 h. Et_2O (2 mL) and $PhI(OAc)_2$ (0.322 g, 1.00 mmol) was added to the reaction mixture at RT. After stirring at RT for 12 h, the mixture was quenched by CH_2Cl_2 (2 mL) and 1 N HCl aq. (5 mL), and then extracted with CH_2Cl_2 (2 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.0852 g, 60%). The NMR data was agreement with the literature[42].

(**28aa**) 4-phenyl-1*H*-isochromen-1-one



To a solution of $InBr_3$ (0.185 g, 0.522 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.082 g, 0.512 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.026 g, 0.0284 mmol), LiCl (0.044 g, 1.04 mmol), iodebenzene (0.255 g, 1.25 mmol) and NMP (2.5 mL) was added to the reaction mixture at RT. After stirring at 50 °C for 24 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.0922 g, 81%). The NMR data was agreement with the literature[43].

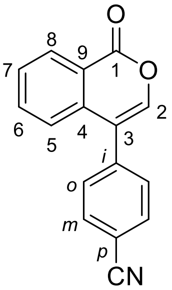
(**28ab**) 4-(4-methoxyphenyl)-1*H*-isochromen-1-one



To a solution of $InBr_3$ (0.179 g, 0.505 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.083 g, 0.518 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.03 g, 0.033 mmol), LiCl (0.059 g, 1.39 mmol), 1-iodo-4-methoxybenzene (0.234 g, 1.0 mmol) and NMP (2.5 mL) was added to the reaction mixture at RT. After stirring at 50 °C for 24 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.0931 g, 71%). IR: (KBr) 1728 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 8.39 (d, *J* = 8.0 Hz, 1H, 8-H), 7.70 (t, *J* = 8.0 Hz, 1H, 6-H), 7.55 (t, *J* = 8.0 Hz, 1H, 7-H), 7.41 (d, *J* = 8.0 Hz, 1H, 5-H), 7.32 (d, *J* = 8.7 Hz, 2H, *o*), 7.23 (s, 1H, 2-H), 7.02 (d, *J* = 8.7 Hz, 2H, *m*); ^{13}C NMR: (100 MHz, $CDCl_3$)

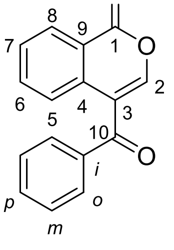
162.1 (s, C-1), 159.7 (s, *p*), 142.0 (d, C-2), 137.1 (s, C-4), 134.6 (d, C-6), 130.9 (d, *o*), 130.0 (d, C-8), 128.4 (d, C-7), 125.1 (s, *i*), 124.6 (d, C-5), 121.3 (s, C-9), 120.2 (s, C-3), 114.2 (d, *m*), 55.3 (q, OMe); MS: (EI, 70 eV) m/z 252 (M, 100), 224 (36), 181 (31), 152 (33); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{13}O_3$) 253.0865 $[M + H]^+$ Found: 253.0861.

(**28ac**) 4-(1-oxo-1*H*-isochromen-4-yl)benzonitrile



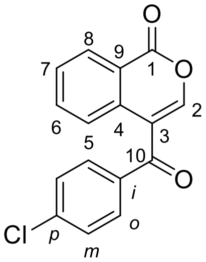
To a solution of $InBr_3$ (0.188 g, 0.530 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.081 g, 0.506 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.026 g, 0.0284 mmol), LiCl (0.0511 g, 1.21 mmol), 1-iodo-4-cyanobenzene (0.250 g, 1.09 mmol) and NMP (2.5 mL) was added to the reaction mixture at RT. After stirring at 50 °C for 24 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.090 g, 72%). IR: (KBr) 2225 (CN) cm^{-1}, 1720 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 8.42 (d, $J = 7.8$ Hz, 1H, 8-H), 7.81 (d, $J = 7.3$ Hz, 2H, *o*), 7.74 (t, $J = 7.8$ Hz, 1H, 6-H), 7.61 (t, $J = 7.8$ Hz, 1H, 7-H), 7.56 (d, $J = 7.3$ Hz, 2H, *m*), 7.33 (d, $J = 7.8$ Hz, 1H, 5-H), 7.30 (s, 1H, 2-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 161.4 (s, C-1), 142.8 (d, C-2), 138.1 (s, C-3), 135.6 (s, C-4), 135.0 (d, C-6), 132.7 (d, *o*), 130.5 (d, *m*), 130.4 (d, C-8), 129.1 (d, C-7), 124.0 (d, C-5), 121.3 (s, C-9), 119.3 (s, *i*), 118.3 (s, *p*), 112.5 (s, CN); MS: (EI, 70 eV) m/z 247 (M, 63), 219 (100), 190 (66); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{10}NO_2$) 248.0712 $[M + H]^+$ Found: 248.0710.

(**28ad**) 4-benzoyl-1*H*-isochromen-1-one



To a solution of $InBr_3$ (0.180 g, 0.508 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.0824 g, 0.514 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.027 g, 0.0295 mmol), LiCl (0.052 g, 1.23 mmol), benzoyl chloride (0.142 g, 1.01 mmol) and NMP (2.5 mL) was added to the reaction mixture at RT. After stirring at 50 °C for 24 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.1058 g, 82%). IR: (KBr) 1735 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 8.39 (d, *J* = 8.0 Hz, 1H, 8-H), 8.16 (d, *J* = 8.2 Hz, 1H, 5-H), 7.88 (d, *J* = 8.5 Hz, 2H, *o*), 7.82 (t, *J* = 8.2 Hz, 1H, 6-H), 7.67 (s, 1H, 2-H), 7.69-7.60 (m, 2H, *p* and 7-H), 7.53 (t, *J* = 8.0 Hz, 2H, *m*); ^{13}C NMR: (100 MHz, $CDCl_3$) 192.4 (s, C-10), 160.5 (s, C-1), 151.7 (d, C-2), 137.6 (s, *i*), 135.3 (d, C-6), 133.9 (s, C-4), 133.5 (d), 129.9 (d, C-8), 129.8 (d, *o*), 129.3 (d), 128.7 (d, *m*), 125.2 (d, C-5), 120.7 (s, C-9), 117.7 (s, C-3); MS: (EI, 70 eV) m/z 250 (M, 97), 249 (100), 105 (78), 77 (52); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{11}O_3$) 251.0708 [M + H]$^+$ Found: 251.0709.

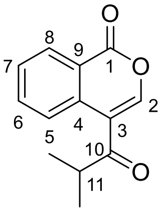
(**28ae**) 4-(4-chlorobenzoyl)-1*H*-isochromen-1-one



To a solution of $InBr_3$ (0.179 g, 0.505 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.080 g, 0.499 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.026 g, 0.0284 mmol), LiCl (0.049 g, 1.16 mmol), 4-chlorobenzoyl chloride (0.180 g, 1.03 mmol) and NMP (2.5 mL) was added to the reaction mixture at RT. After stirring at 50 °C for 24 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.091 g, 64%). This product was recrystallized from CH_2Cl_2 to give a single crystal and the structure was determined by X-ray crystallographic analysis (CCDC 1576344). IR: (KBr) 1763 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 8.37 (d, *J* = 8.0 Hz, 1H, 8-H), 8.10 (d, *J* = 8.0 Hz, 1H, 5-H), 7.86-7.77 (m, 3H, *o* and 6-H), 7.65 (s, 1H, 2-H), 7.63 (t, *J* = 8.0 Hz, 1H, 7-H), 7.50 (d, *J* = 8.7 Hz, 2H, *m*); ^{13}C NMR: (100 MHz, $CDCl_3$) 191.2 (s, C-10), 160.3 (s, C-1), 151.5 (d, C-2), 140.1 (s), 136.0 (s), 135.4

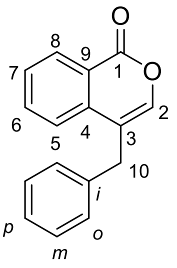
(d, C-6), 133.7 (s, C-4), 131.2 (d, *o*), 130.0 (d, C-8), 129.5 (d, C-7), 129.1 (d, *m*), 125.2 (d, C-5), 120.8 (s, C-9), 117.6 (s, C-3); MS: (EI, 70 eV) m/z 286 (M +2, 32), 284 (M, 93), 283 (49), 249 (40), 139 (100), 111 (55); HRMS: (CI, 70 eV) Calculated ($C_{16}H_{10}ClO_3$) 285.0318 $[M + H]^+$ Found: 285.0318.

(**28af**) 4-isobutyryl-1*H*-isochromen-1-one



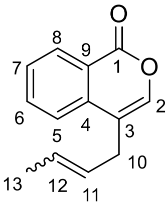
To a solution of $InBr_3$ (0.185 g, 0.522 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.0857 g, 0.535 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.030 g, 0.0328 mmol), LiCl (0.043 g, 1.01 mmol), isobutyryl chloride (0.115 g, 1.08 mmol) and HMPA (2.5 mL) was added to the reaction mixture at RT. After stirring at RT for 24 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.070 g, 61%). IR: (KBr) 1739 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 8.47 (d, *J* = 8.2 Hz, 1H, 5-H), 8.34 (dd, *J* = 7.8, 1.4 Hz, 1H, 8-H), 8.03 (s, 1H, 2-H), 7.81 (ddd, *J* = 8.2, 7.8, 1.4 Hz, 1H, 6-H), 7.60 (t, *J* = 7.8 Hz, 1H, 7-H), 3.29-3.17 (m, 1H, 11-H), 1.25 (d, *J* = 6.9 Hz, 6H, 11-Me_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 160.6 (s, C-10), 150.5 (d, C-2), 135.4 (d, C-7), 133.7 (s, C-4), 129.9 (d, C-5), 129.2 (d, C-6), 125.8 (d, C-8), 120.9 (s, C-9), 117.1 (s, C-3), 37.8 (d, C-11), 19.0 (q, 11-Me_2); MS: (EI, 70 eV) m/z 216 (M, 49), 173 (100), 89 (52); HRMS: (CI, 70 eV) Calculated ($C_{13}H_{13}O_3$) 217.0865 $[M + H]^+$ Found: 217.0863.

(**28ag**) 4-benzyl-1*H*-isochromen-1-one



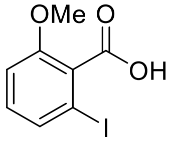
To a solution of $InBr_3$ (0.188 g, 0.530 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.0824 g, 0.514 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.0223 g, 0.0242 mmol), LiCl (0.043 g, 1.01 mmol), benzyl bromide (0.176 g, 1.03 mmol) and HMPA (2.5 mL) was added to the reaction mixture at RT. After stirring at 50 °C for 24 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.062 g, 51%). IR: (KBr) 1720 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 8.34 (d, *J* = 8.2 Hz, 1H, 8-H), 7.67 (dd, *J* = 8.2, 7.8 Hz, 1H, 6-H), 7.51 (dd, *J* = 8.2, 7.8 Hz, 1H, 7-H), 7.44 (d, *J* = 8.2 Hz, 1H, 5-H), 7.35-7.28 (m, 2H, *m*), 7.28-7.21 (m, 3H, *o* and *p*), 7.11 (s, 1H, 2-H), 3.93 (s, 2H, 10-H_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 162.4 (s, C-1), 142.9 (d, C-2), 137.7 (s, *i*), 136.7 (s, C-4), 134.6 (d, C-6), 130.1 (d, C-8), 128.8 (d), 128.4 (d), 128.3 (d, C-7), 126.8 (d, *p*), 123.4 (d, C-5), 121.6 (s, C-9), 115.7 (s, C-3), 33.6 (t, C-10); MS: (EI, 70 eV) m/z 236 (M, 100), 208 (63), 178 (40); HRMS: (CI, 70 eV) Calculated ($C_{13}H_{13}O_3$) 237.0916 $[M + H]^+$ Found: 237.0916.

(**28ah**) 4-(but-2-en-1-yl)-1*H*-isochromen-1-one



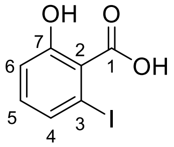
To a solution of $InBr_3$ (0.185 g, 0.522 mmol) in toluene (1 mL), methyl 2-ethynylbenzoate (0.078 g, 0.487 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.026 g, 0.0284 mmol), LiCl (0.057 g, 1.34 mmol), 1-bromobut-2-ene (0.149 g, 1.10 mmol) and HMPA (2.5 mL) was added to the reaction mixture at RT. After stirring at 50 °C for 24 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.0441 g, 45%, *E*/*Z* = 90:10). IR: (KBr) 1728 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 8.34 (d, *J* = 7.8 Hz, 1H, 8-H), 7.76 (t, *J* = 7.8 Hz, 1H, 6-H), 7.59-7.50 (m, 2H, 5-H and 7-H), 7.21 (s 1H, 2-H), 5.73-5.50 (m, 2H, 11-H and 12-H), 3.26 (d, *J* = 4.6 Hz, 2H, 10-H_2), 1.70 (d, *J* = 5.0 Hz, 3H, 13-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 162.6 (s, C-1), 141.8 (d, C-2), 136.9 (s, C-4), 134.5 (s, C-6), 130.0 (d, C-8), 128.4 (d), 128.2 (d), 126.9 (d), 123.1 (d, C-5), 121.5 (s, C-9), 115.9 (s, C-3), 30.3 (t, C-10), 17.9 (q, C-13); MS: (EI, 70 eV) m/z 200 (M, 100), 171 (33), 157 (39), 128 (46), 115 (30); HRMS: (CI, 70 eV) Calculated ($C_{13}H_{13}O_3$) 201.0916 $[M + H]^+$ Found: 201.0913.

(**30**) 2-iodo-6-methoxybenzoic acid



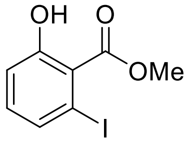
This compound was synthesized by a reported method[44] and the NMR data was agreement with the literature[44].

(**31**) 2-hydroxy-6-iodobenzoic acid



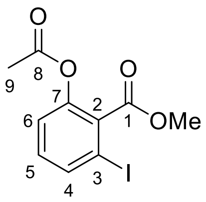
To a three necked flask, 2-iodo-6-methoxybenzoic acid (0.141 g, 0.507 mmol), CH_2Cl_2 (4 mL) and BBr_3 (1 M in CH_2Cl_2, 1.0 mL, 1.0 mmol) were added. After stirring for 20 h at RT, the reaction mixture was evaporated and the residue was diluted with CH_2Cl_2 (10 mL). The solution was washed with 0.5 N HCl aq. (10 mL) and the water layer was extracted by CH_2Cl_2 (10 mL x 3). The corrected organic layer was dried ($MgSO_4$) and the solvent was evaporated to give the product (100% NMR yield). The product was used in next step without further purification. IR: (neat) 3568 (OH) cm^{-1}, 1635 (C=O) cm^{-1}; ^1H NMR: (400 MHz, acetone-d_6) 7.62 (dd, J = 7.7, 0.97 Hz, 1H), 7.19 (t, J = 7.7 Hz, 1H, 5-H), 7.10 (dd, J = 7.7, 0.97 Hz, 1H); ^{13}C NMR: (100 MHz, acetone-d_6) 168.9 (s, C-1), 158.5 (s, C-7), 133.5 (d, C-5), 132.0 (d), 123.5 (s, C-2), 116.8 (d), 93.1 (s, C-3); HRMS: (CI, 70 eV) Calculated ($C_7H_6O_3I$) 264.9362 $[M + H]^+$ Found: 264.9364.

(**32**) methyl 2-hydroxy-6-iodobenzoate



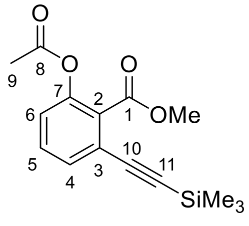
This compound was synthesized by a reported method[45] and the NMR data was agreement with the literature[46].

(**33**) methyl 2-acetoxy-6-iodobenzoate



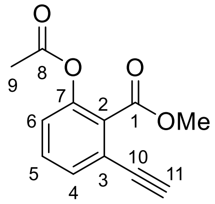
To a three necked flask, methyl 2-hydroxy-6-iodobenzoate (0.136 g, 0.491 mmol), acetone (0.7 mL) and pyridine (0.042 mL, 0.52 mmol) were added. The mixture was cooled to -5 °C and acetyl chloride (37 μL. 0.52 mmol) was added. After stirring for 14 h at RT, the reaction mixture was quenched by H_2O (2 mL). The solution was extracted by CH_2Cl_2 (2 mL x 2). The corrected organic layer was dried ($MgSO_4$) and the solvent was evaporated to give the product (97% NMR yield). The product was used in next step without further purification. IR: (KBr) 1766 (C=O) cm^{-1}, 1732 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.72 (dd, $J = 6.8, 1.9$ Hz, 1H), 7.16 (dd, $J = 8.2, 1.9$ Hz, 1H), 7.13 (dd, $J = 8.2, 6.8$ Hz, 1H, 5-H), 3.93 (s, 3H, OMe), 2.26 (s, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.4 (s, 8), 166.2 (s,1), 147.7 (s, C-7), 136.7 (d), 132.9 (s, C-2), 131.6 (d, C-5), 122.8 (d), 92.2 (s, C-3), 52.7 (q, OMe), 20.6 (q, C-9); MS: (EI, 70 eV) m/z 320 (M, 19), 278 (100), 246 (100); HRMS: (CI, 70 eV) Calculated ($C_{10}H_{10}O_4I$) 320.9624 $[M + H]^+$ Found: 320.9620.

(**34**) methyl 2-acetoxy-6-((trimethylsilyl)ethynyl)benzoate



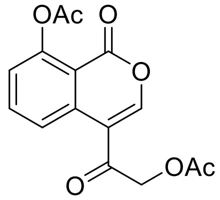
To a three necked flask, methyl 2-acetoxy-6-iodobenzoate (0.156 g, 0.487 mmol), NEt_3 (0.5 mL), $PdCl_2(PPh_3)_2$ (0.0072 g, 0.0103 mmol) and CuI (0.0096 g, 0.0956 mmol) were added. The mixture was cooled to 0 °C and trimethylsilylacetylene (0.0538 g. 0.548 mmol) was added. After stirring for 17 h at RT, the reaction mixture was filtered through a celite pad. The filtrate was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.1581 g, 100%). IR: (neat) 1778 (C=O) cm^{-1}, 1736 (C=O) cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) 7.41 (dd, $J = 7.8, 1.8$ Hz, 1H, 4-H), 7.38 (t, $J = 7.8$ Hz, 1H, 5-H), 7.11 (dd, $J = 7.8, 1.8$ Hz, 1H, 6-H), 3.90 (s, 3H, OMe), 2.29 (s, 3H, 9-H_3), 0.236 (s, 9H, $SiMe_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.9 (s, C-8), 165.5 (s, C-1), 148.2 (s, C-7), 130.7 (d), 130.6 (d), 128.9 (s, C-2), 123.3 (d, C-6), 123.2 (s, C-3), 101.3 (s, C-10), 99.5 (s, C-11), 52.3 (q, OMe), 20.8 (q, C-9), -0.241 (q, $SiMe_3$); MS: (EI, 70 eV) m/z 290 (M, 8), 248 (79), 233 (32), 216 (100), 203 (85); HRMS: (CI, 70 eV) Calculated ($C_{15}H_{19}O_4Si$) 291.1053 $[M + H]^+$ Found: 291.1054.

(**35**) methyl 2-acetoxy-6-ethynylbenzoate



To a three necked flask, methyl 2-acetoxy-6-((trimethylsilyl)ethynyl)benzoate (0.0488 g, 0.168 mmol), DMF (1.7 mL) and 1 M KF aq. (0.28 mL, 0.28 mmol) were added. After stirring for 0.5 h at RT, the reaction mixture was extracted by $CHCl_3$ (5 mL). The organic layer was washed by 10% NH_4Cl aq. (5 mL) and then was dried ($MgSO_4$). The solvent was evaporated to give the product (0.0279 g, 76%). The product was used in next step without further purification. IR: (neat) 1774 (C=O) cm^{-1}, 1732 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.46 (dd, *J* = 8.0, 1.4 Hz, 1H, 4-H), 7.42 (t, *J* = 8.0 Hz, 1H, 5-H), 7.15 (dd, *J* = 8.0, 1.4 Hz, 1H, 6-H), 3.92 (s, 3H, OMe), 3.28 (s, 1H, 11-H), 2.29 (s, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.8 (s, C-8), 165.3 (s, C-1), 148.2 (s, C-7), 131.1 (d), 130.9 (d), 128.9 (s, C-2), 123.8 (d, C-6), 122.3 (s, C-3), 81.8 (s, C-11), 80.2 (d, C-11), 52.5 (q, OMe), 20.7 (q, C-9); MS: (EI, 70 eV) m/z 218 (M, 7), 176 (98), 144 (100), 116 (36); HRMS: (CI, 70 eV) Calculated ($C_{12}H_{11}O_4$) 219.0657 $[M + H]^+$ Found: 219.0654.

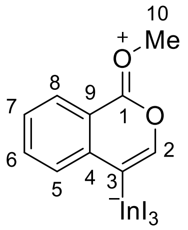
(**36**) 2-(8-acetoxy-1-oxo-1*H*-isochromen-4-yl)-2-oxoethyl acetate



To a solution of $InBr_3$ (0.114 g, 0.322 mmol) in toluene (0.6 mL), methyl 2-acetoxy-6-ethynylbenzoate (0.069 g, 0.316 mmol) was added. The mixture was stirred at 50 °C for 24 h. Pd_2dba_3 (0.0171 g, 0.0187 mmol), LiCl (0.0284 g, 0.670 mmol), 2-chloro-2-oxoethyl acetate (0.087 g, 0.637 mmol) and HMPA (1.5 mL) was added to the reaction mixture at RT. After stirring at RT for 9 h, the mixture was quenched by Et_2O (5 mL) and water (10 mL), and then extracted with Et_2O (10 mL x 3). The collected organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 60:40, column length 11 cm, diameter 26 mm, spherical silica gel) to give the product (0.0420 g, 44%). The NMR data was agreement with the literature[47].

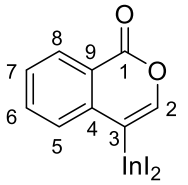
Isolation of Organoindium Compounds

(**3**) zwitterion intermediate



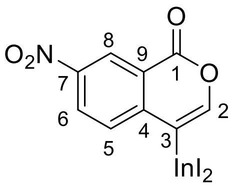
To a sealed vial, InI_3 (0.152 g, 0.307 mmol) in toluene (0.6 mL) and methyl 2-ethynylbenzoate (0.048 g, 0.30 mmol) were added. The mixture was stirred at RT for 24 h. The solvent was removed by decantation to obtain a white solid and the solid was washed by $CHCl_3$ (3 mL x 6). The residue was dried under vacuum to give the product as a white solid including a small amount of a stating ester (0.150 g, 98wt%, 73% yield). This compound was recrystallized from CH_2Cl_2 and hexane to give a single crystal. The structure was determined by X-ray crystallographic analysis (CCDC 1579824). Characterization by NMR study was also carried out and the spectra is shown below. ^{1}H NMR: (400 MHz, CD_2Cl_2) 8.68 (d, J = 8.2 Hz, 1H, 8-H), 8.55 (d, J = 8.2 Hz, 1H, 5-H), 8.35 (t, J = 8.2 Hz, 1H, 6-H), 8.10 (s, 1H, 2-H), 7.97 (t, J = 8.2 Hz, 1H, 7-H), 4.68 (s, 3H, 10-H_3); ^{13}C NMR: (100 MHz, CD_2Cl_2) 171.8 (s, C-1), 146.7 (d, C-2), 144.0 (s, C-4), 141.8 (d, C-6), 132.3 (d, C-7), 130.5 (d, C-5), 129.8 (d, C-8), 127.6 (s, C-3), 115.8 (s, C-9), 62.1 (q, C-10).

(**4a**) (1-oxo-1*H*-isochromen-4-yl)indium(III) iodide



To a sealed vial, zwitterion intermediate **3** (0.190 g, 98wt%, 0.284 mmol) in toluene (0.6 mL) was added. The mixture was stirred at 50 °C for 10 h. The solvent was removed by decantation to obtain a white solid and the solid was washed by $CHCl_3$ (3 mL x 2). The residue was dried under vacuum to give the product as a white solid (0.150 g, 100%). This compound was characterization by NMR study and the spectra is shown below. ^{1}H NMR: (400 MHz, THF-d_8) 8.26 (d, J = 7.7 Hz, 1H, 8-H), 8.09 (d, J = 7.7 Hz, 1H, 5-H), 7.75 (t, J = 7.7 Hz, 1H, 6-H), 7.53 (t, J = 7.7 Hz, 1H, 7-H), 7.17 (s, 1H, 2-H); ^{13}C NMR: (100 MHz, THF-d_8) 161.9 (s, C-1), 149.8 (d, C-2), 141.3 (s, C-4), 135.2 (d, C-6), 130.4 (d, C-8), 129.1 (d, C-7), 128.7 (d, C-5), 124.3 (s, C-9), 120.2 (s, C-3).

(**4b**) (7-nitro-1-oxo-1*H*-isochromen-4-yl)indium(III) iodide



To a sealed vial, InI_3 (0.250 g, 0.505 mmol) in toluene (1.0 mL) and methyl 2-ethynyl-5-nitrobenzoate (0.089 g, 0.434 mmol) were added. The mixture was stirred at 50 °C for 12 h. The solvent was removed by decantation to obtain a white solid and the solid was washed by CH_2Cl_2 (3 mL x 2). The residue was dried under vacuum to give the product as a white solid (0.218 g, 90%). This compound was recrystallized from THF and hexane to give a single crystal. The structure was determined by X-ray crystallographic analysis (CCDC 1576342). Characterization by NMR study was also carried out and the spectra is shown below. ^{1}H NMR: (400 MHz, THF-d_8) 8.99 (s, 1H, 8-H), 8.61 (d, J = 7.2 Hz, 1H, 6-H), 8.25 (d, J = 7.2 Hz, 1H, 5-H), 7.35 (s, 1H, 2-H); ^{13}C NMR: (100 MHz, THF-d_8) 160.8 (s, C-1), 152.7 (d, C-2), 148.1 (s, C-7), 146.5 (s, C-4), 130.2 (d), 129.4 (d), 125.7 (d, C-8), 124.8 (s, C-9), 119.3 (s, C-3).

The energy profile of dissociation of In_2I_6 and In_2Cl_6

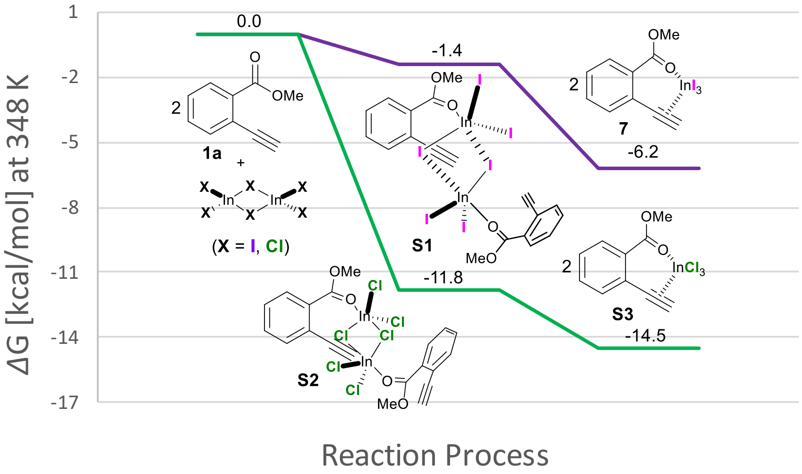


Fig. S3 The energy profile of dissociation of In_2I_6 and In_2Cl_6.

Coordination of two molecules of **1a** to In_2X_6 gives **S1** or **S2**. The aggregation of In_2X_6 was dissociated to generate **7** or **S3**. The all steps are exergonic to afford the complex **7** or **S3** initiatively.

The energy profile of intramolecular elimination of MeI

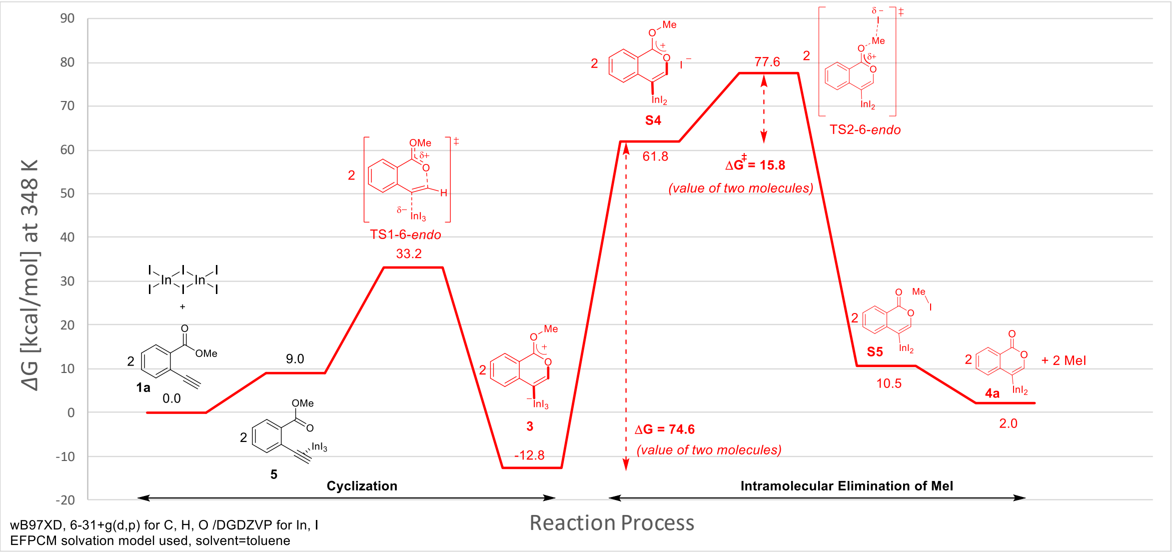


Fig. S4 The energy profile of intramolecular elimination of MeI.

In this pathway, oxyindation proceeds in a concerted mechanism, and then dissociation of iodide from zwitterion **3** gives complex **S4**. Elimination of MeI takes places to give **S5**. The activation energy of dealkylation step (**S4** to **S5**) is only 7.9 kcal/mol. However, the intermediate **S4** is too unstable to be generated.

The energy profile of oxyindation using $InCl_3$

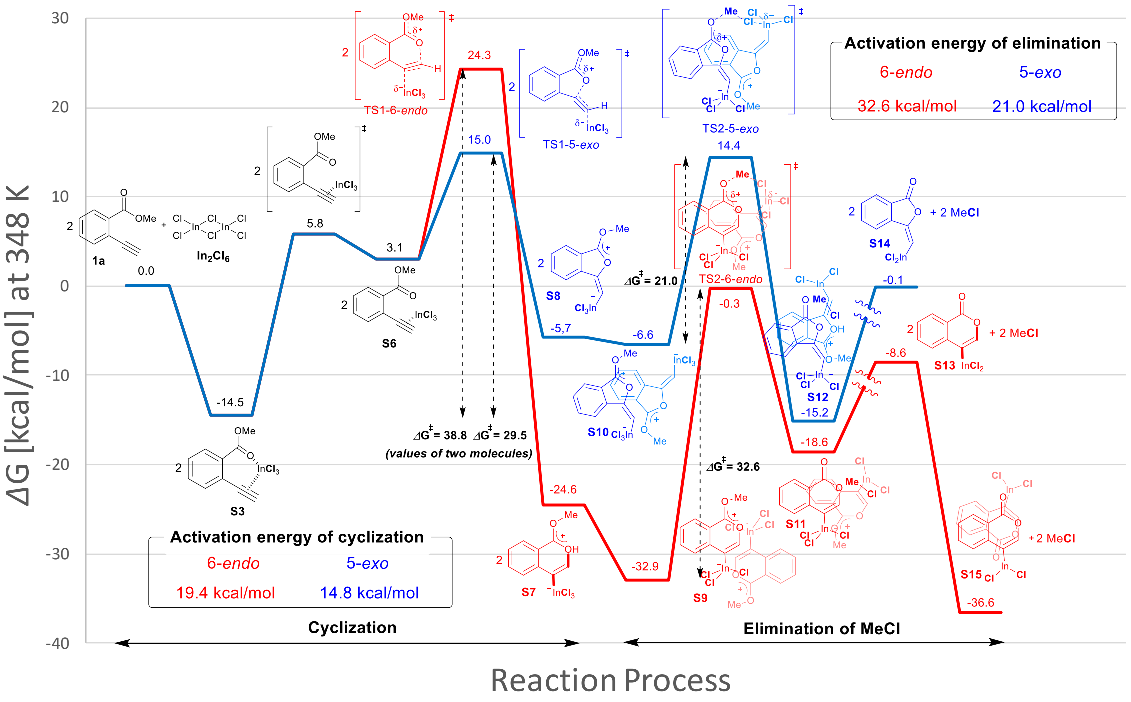


Fig. S5 The energy profile of oxyindation using $InCl_3$.

We found that oxyindation using InCl$_3$ proceeds through the same fashion with InI$_3$. In the case of InCl$_3$, the energy level of all structures became lower than that of the case with InI$_3$. The remarkable difference between the cases of InCl$_3$ and InI$_3$ was the activation energy of elimination step. The elimination of MeCl (**S9** to TS2-6-*endo*) showed higher activation energy (32.7 kcal/mol) than that of the elimination of MeI (**8** to TS2-6-*endo*, 28.7 kcal/mol). This inhibition of elimination step, which is a rate determining step, was rationalized by the low nucleophilicity of Cl$^-$, and it caused much less reactivity of InCl$_3$.

The comparison of elimination steps in oxyboration

(i) The energy profile of elimination of MeCl by chloride on the zwitterion intermediate

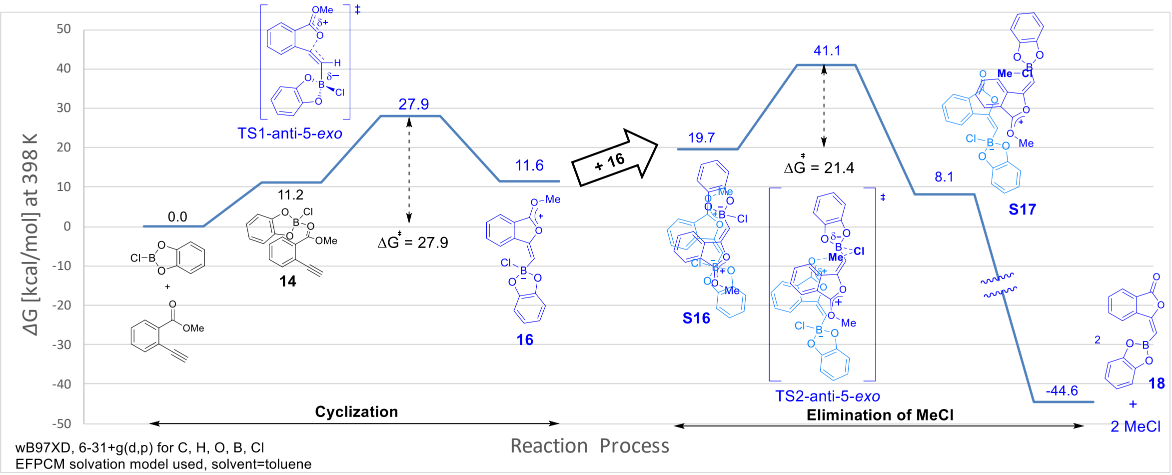


Fig. S6 The energy profile of elimination of MeCl by another zwitterion intermediate.

After 5-*exo* cyclization, two zwitterions aggregate in head to tail fashion to give the complex **S16**. The elimination step starts from **S16**. Intermolecular nucleophilic substitution of methyl group by chloride proceeds in S$_N$2 manner to give complex **S17** and MeCl, and then further elimination of MeCl affords target product.

(ii) The energy profile of elimination of MeCl by free chloride

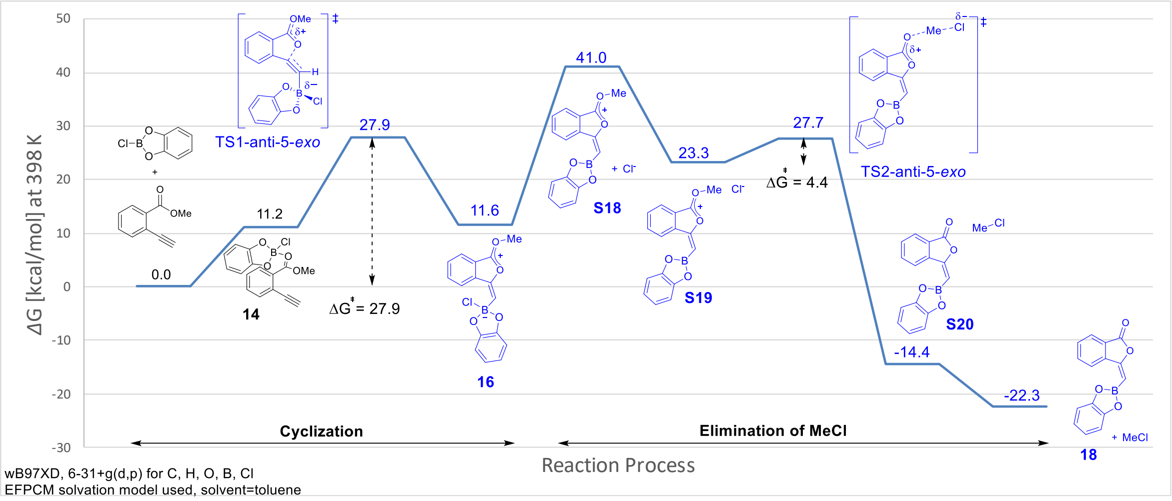


Fig. S7 The energy profile of elimination of MeCl by free chloride.

After 5-*exo* cyclization, dissociation of chloride from zwitterion **16** provides free chloride **S18**. After the chloride move toward the methyl moiety (**S19**), elimination of MeCl proceeds to give **S20**.

(iii) The energy profile of elimination of MeCl by $[Cl_2Bcat]^-$ (the most probable path)

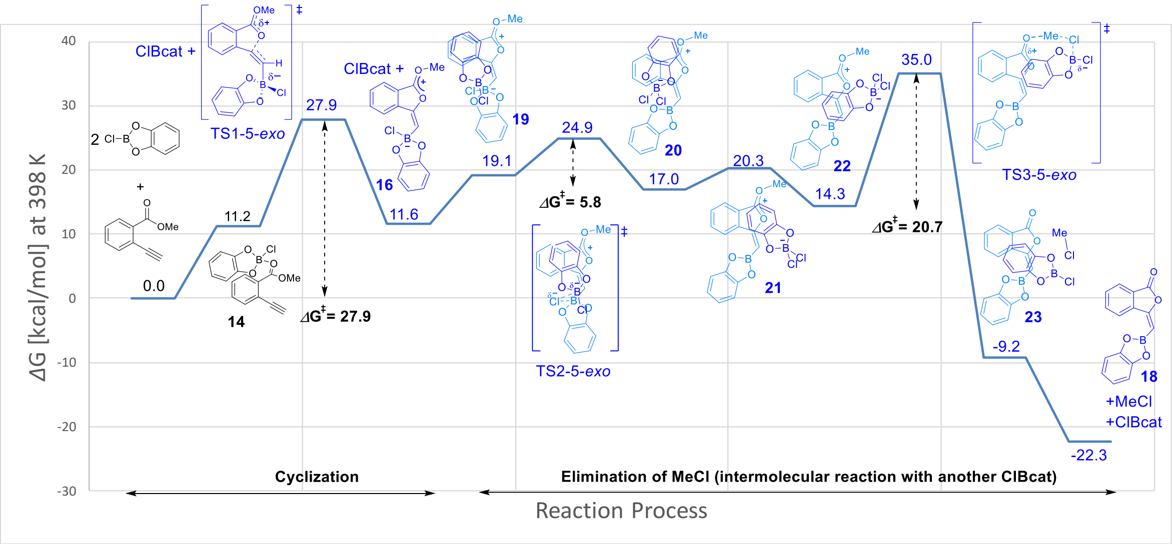


Fig. S8 The energy profile of elimination of MeCl by $[Cl_2Bcat]^-$.

In the case of path i, the activation energy of elimination step (**S16** to **S17**, 21.4 kcal/mol) is higher than that of elimination in the path iii (**22** to **23**, 20.7 kcal/mol). In the path ii, the activation energy of dealkylation step (**S19** to **S20**) is only 4.4 kcal/mol. However, the intermediate **S18**, which has naked Cl-, is too unstable to be generated. Therefore, path iii is the most probable reaction process of oxyboration.

The value of electrostatic potential

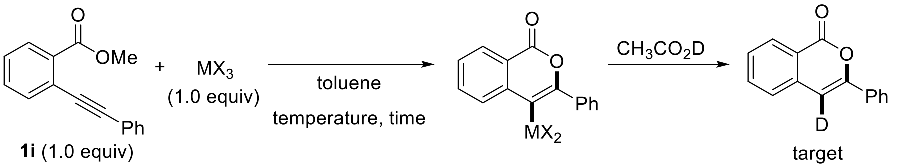
The value of V_{max}, V_{min} and the difference ΔV was summarized in Table S2. The value of V_{max} was higher in transition state of oxyindation than that of oxyboration. However, the transition state of oxyboration showed much more negative value of V_{min} than that of oxyindation, and thus the value of difference ΔV was small in the case of oxyindation compared with oxyboration. As the total result, the transition state of oxyindation delocalized the increasing charge more efficiently than that of oxyboration.

Table S2 The value of V_{max}, V_{min} and the difference ΔV for the electrostatic potential of transition state of cyclization step

	Oxyindation	*Oxyboration*
	TS1-6-*endo*	TS1-5-*exo*
V_{max} (kcal/mol)	43.0	33.2
V_{min} (kcal/mol)	-21.3	-43.8
ΔV (kcal/mol)	64.3	77.0

Optimization of Reaction Conditions for Oxymetalation of Internal Alkyne

Table S3 The effect of Lewis acids on the oxymetalation of internal alkyne **1i**.[a]



entry	MX_3	temperature	time (h)	NMR yield of target (%)
1	InI_3	50 °C	46	19
2	$InBr_3$	80 °C	25	17
3	**GaI_3**	**50 °C**	**23**	**73**
4	$GaBr_3$	50 °C	23	60

[a]Reaction conditions: **1i** (0.5 mmol), MX_3 (0.5 mmol), Toluene (1 mL).

The internal alkyne **1i** was subjected to the oxyindation/protonation process to afford a target product in low yield (entries 1 and 2), but the cases using gallium salts gave high yields (entries 3 and 4).

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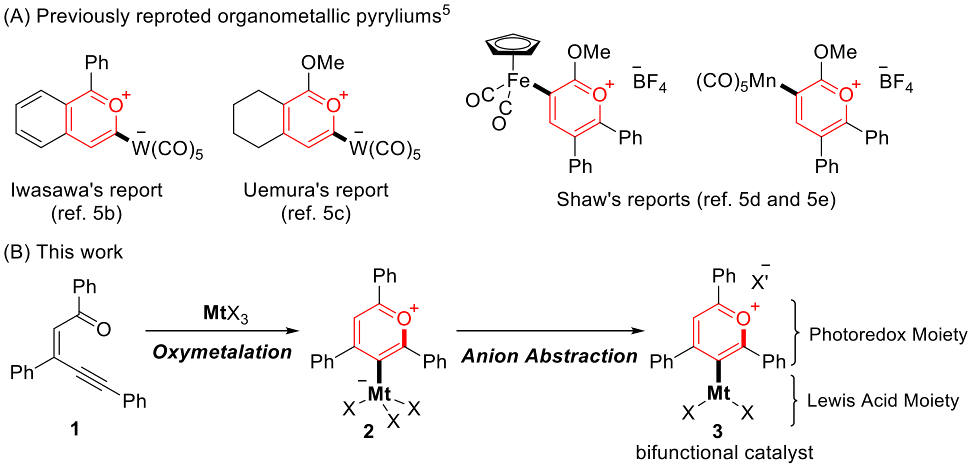
Chapter 4

Synthesis of 2,4,6-Triarylpyryliums Bearing a Carbon-Metal Bond and their Application to Bifunctional Photocatalyst

4-1. Introduction

Pyrylium is an important class of oxygen-containing heteroaromatic compounds in photochemistry and organic synthetic chemistry. Plant pigments such as anthocyanidin include a pyrylium framework.[1] The application of 2,4,6-triarylpyryliums to a photoredox catalyst is well-established[2] because 2,4,6-triarylpyryliums absorb visible light and the corresponding excited state works as a strong oxidant due to its cationic character. Pyryliums also work as a synthetic building block to give various heterocycles.[3] Especially, pyryliums bearing a carbon-metal bond have been utilized as an useful intermediate to synthesize oxacycles and polycyclic compounds.[4] The organometallic pyryliums are usually unstable, thus, isolation of them has been seldom reported (Scheme 1A).[5] Iwasawa and Uemura synthesized pyryliums bearing a carbon-tungsten bond and applied it in Dield-Alder reaction.[5b,5c] Shaw investigated redox properties of pyryliums including a carbon-manganese or carbon-iron bond.[5d,5e] However, the structure and physicochemical properties of organometallic pyryliums have been much less investigated than that of no-metalated pyryliums, and there have been no reports for the application to a photocatalsyt. Herein, the synthesis of two types of 2,4,6-triphenylpyryliums bearing a carbon-metal bond (**2** and **3**) by intramolecular oxymetalation of carbonyl-ene-yne **1** and anion abstraction is described (Scheme 1B). Determination of their structures and evaluation of physicochemical properties were conducted, and their application as a photocatalyst possessing a Lewis acidic metal moiety[6] was also investigated.

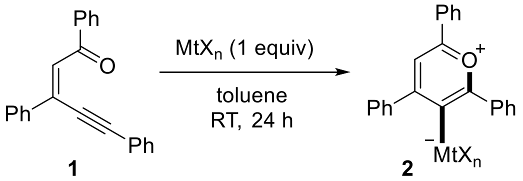


Scheme 1. (A) Previously developed organometallic pyryliums. (B) This work: synthesis and evaluation of physicochemical properties of 2,4,6-triphenylpyryliums bearing a caebon-metal bond and thier application to a bifunctional catalyst.

4-2. Results and Discussion

Investigation of suitable metal salts for synthesis of 2,4,6-triphenylpyryliums bearing a carbon-metal bond was carried out (Table 1). In chapter 3, it was revealed that the intramolecular oxymetalation of 2-alkynylbenzoate with indium or gallium trihalides afforded zwitterionic benzopyryliums bearing a carbon-metal bond.[7] Therefore, the oxymetalation of the carbonyl-ene-yne **1** using indium or gallium salts was conducted to access triphenylpyryliums. Oxyindation of **1** with InI_3 provided 2,4,6-triphenylpyrylium **2a** in high yield (entry 1). GaI_3 and $GaBr_3$ also gave organometallic pyrylium **2b** and **2c**, respectively, in moderate yields (entries 2 and 3). Subjecting $AgSbF_6$ and $AuSbF_6$, which work as an excellent π-electrophilic Lewis acid,[8] into the oxymetalation of **1** also gave metalated triphenylpyryliums (entries 4 and 5). Other Lewis acids such as boron and aluminum salts were not effective (entries 6-8).

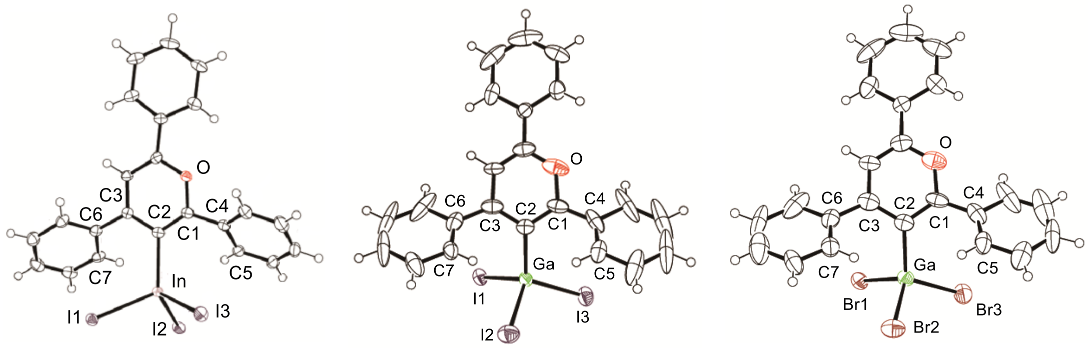
Table 1. Investigation of suitable metal salts for oxymetalation of the carbonyl-ene-yne **1**.[a]



Entry	MtX_n	Yield of **2** (%)[b]
1	InI_3	**2a**: 83
2	GaI_3	**2b**: 66
3	$GaBr_3$	**2c**: 54
4	$AgSbF_6$	**2d**: 81
5	$AuSbF_6$	**2e**: 67
6	AlI_3	**2f**: 0
7	$AlBr_3$	**2g**: 12
8	BBr_3	**2h**: 0

[a] Reaction conditions: **1** (1 equiv), MtX_n (1 equiv), toluene, RT, 24 h. [b] Isolated yield.

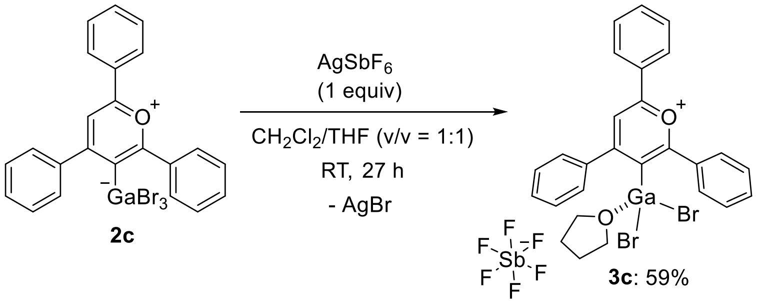
As shown in Figure 1, X-ray crystallographic analysis of **2a**-**2c** revealed that the formation of zwitteionic 2,4,6-triphenylpyryliums including a carbon-metal bond at the 3-position. Torsion angles of C2-C1-C4-C5 and C2-C3-C6-C7 for **2a**-**2c** (average 38.58°) are much larger than that of a pyrylium without a carbon-metal bond (average 15.44°, see Figure S1 in Experimental Section for X-ray structure of the pyrylium without a carbon-metal bond). This result suggested that the two phenyl groups at the 2 and 4-positions rotated to decrease a steric repulsion between the phenyl groups and MtX_3 moiety.



2a **2b** **2c**

Figure 1. The X-ray crystallographic structure of the zwitterionic metalated pyryliums **2a**-**2c** with the thermal ellipsoids shown at 50% probability. Selected bond lengths (Å) and torsion angles (deg) for **2a**: C2-In = 2.223(4), In-I1 = 2.7324(3), In-I2 = 2.7296(3), In-I3 = 2.7236(3), C2-C1-C4-C5 = 43.97, C2-C3-C6-C7 = 44.91. **2b**: C2-Ga = 2.037(7), Ga-I1 = 2.6108(11), Ga-I2 = 2.5267(11), Ga-I3 = 2.5498(9), C2-C1-C4-C5 = 34.92, C2-C3-C6-C7 = 38.34. **2c**: C2-Ga = 2.016(3), Ga-Br1 = 2.4062(6), Ga-Br2 = 2.3259(6), Ga-Br3 = 2.3541(5), C2-C1-C4-C5 = 34.48, C2-C3-C6-C7 = 34.85.

The complex **2**, in which the metal center has a formal negative charge, was treated with $AgSbF_6$ to abstract a halide anion on the metal. This anion abstraction efficiently occurred only in the case of **2c** (Eq. 1), and the cases using **2a** or **2b** resulted in complicated mixture. Recrystallization of **3c** from $CHCl_3$ provided a single crystal to be suitable for X-ray diffraction analysis (Figure 2). Two phenyl groups at 2- and 4-positions in **3c** rotated in the same manner as **2c**. The gallium atom was coordinated with two bromide atoms and THF, and its geometry has a distorted tetrahedral. The coordination of THF to gallium center shows that **3c** works as a Lewis acid.



(1)

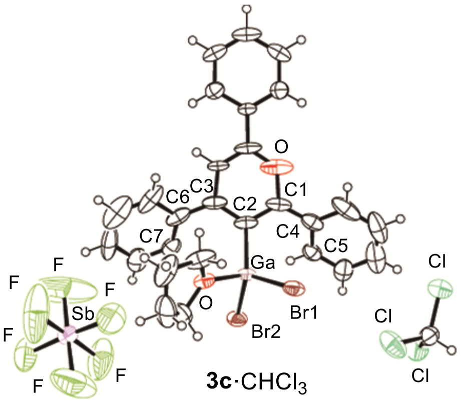


Figure 2. The X-ray crystallographic structure of the metalated pyrylium **3c** with the thermal ellipsoids shown at 50% probability. Selected bond lengths (Å) and dihedral angles (deg): C2-Ga = 2.004(5), Ga-O = 1.949(5), Ga-Br1 = 2.3155(9), Ga-Br2 = 2.3055(9), C2-C1-C4-C5 = 34.65, C2-C3-C6-C7 = 37.20.

Electronic absorption and fluorescence spectra of the organometallic pyryliums are shown in Figure 3. The metalated triphenylpyryliums **2a**, **2c** and **3c** exhibited broad absorption bands at the almost same wavelengths (389, 383, 398 nm, respectively). On the other hand, two sharp absorption bands (370, 417 nm) were observed for no-metalated triphenylpyrylium **4**. Thus, the longest absorption wavelength of organomettalic pyryliums became a little bit shorter than that of **4**. Fluorescence wavelengths are the almost same whether the triphenylpyryliums have a metal moiety or not. To compare the characteristics between metalated and no-metalated triphenylpyryliums, density functional theory (DFT) calculation was performed for **2c** and **4**. Time-dependent (TD)-DFT calculation showed that the lowest-energy transition for **2c** and **4** is assigned to the HOMO-6- LUMO and HOMO-LUMO transition, respectively (See Table S1 and S2 in Experimental Section for TD-DFT calculation). The energy level of HOMO-6 for **2c** is close to HOMO of **4**, but **2c** has the higher LUMO level than **6** to induce blue shift of the longest absorption wavelength (See Figure S2 in Experimental Section for energy level diagrams and molecular orbitals). The higher LUMO level for **2c** would be ascribed to less π-conjugation between phenyl groups and the pyrylium framework caused by the rotation of two phenyl groups at the 2- and 4-positions (Figure 1 and 2).

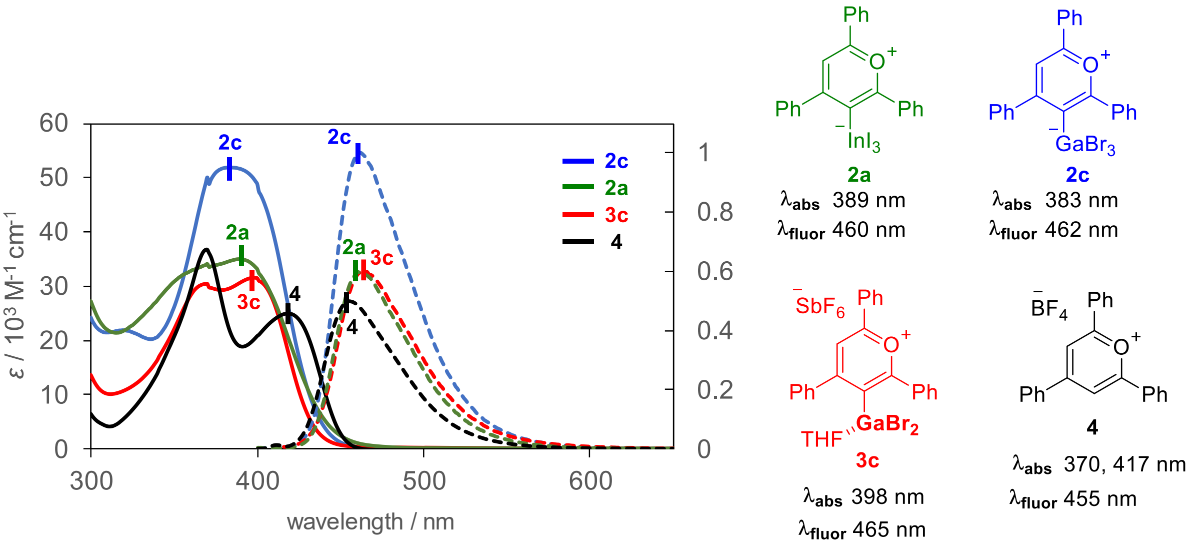


Figure 3. Electronic absorption (solid lines) and normalized fluorescence spectra (dotted lines) for **2a**, **2c**, **3c** and **4** in CH_2Cl_2.

Reduction potential of the triphenylpyryliums including a carbon-metal bond is determined by cyclic voltammetry (Figure 4). The organometallic triphenylpyryliums **2a**, **2c** and **3c** have the almost same reduction peak at -1.02, 1.04, and -1.03 V, respectively. On the other hand, reduction potential of the no-metalated pyrylium **4** is -0.79 V. Therefore, the metalated triphenylpyryliums show more negative reduction potential than **4**, which agrees with the higher LUMO level of **2c**.

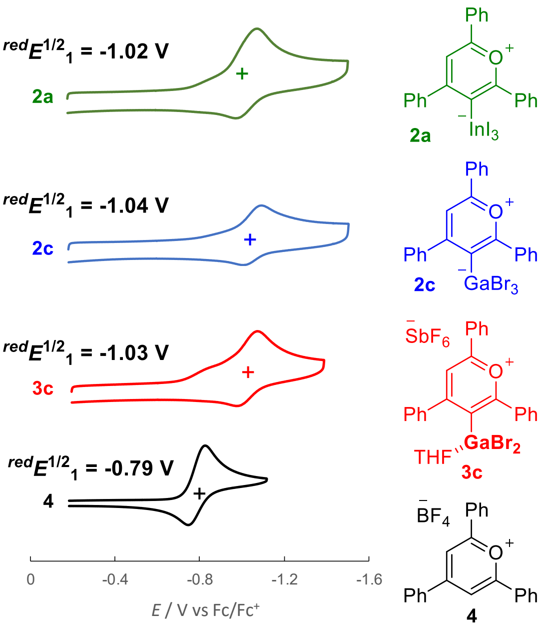


Figure 4. Cyclic voltammogram of **2a**, **2c**, **3c** and **4** (V vs. Fc/Fc+, in 0.1M $^{n}Bu_4NClO_4/CH_2Cl_2$, scan rate =100 mVs^{-1} for **4**, 800 mVs^{-1} for **2a**, **2c** and **3c**, room temperature).

Reduction potential of excited state of the organometallic pyryliums **2a**, **2c** and **3c** is estimated using fluorescence wavelength and reduction potential of their groud state (Figure 5).[2b] The organometallic triphenylpyryliums show highly positive reduction potential although the potentials are less positive than the reference compound **4**. Therefore, the excited triphenylpyryliums including a carbon-metal bond work as a strong oxidant.

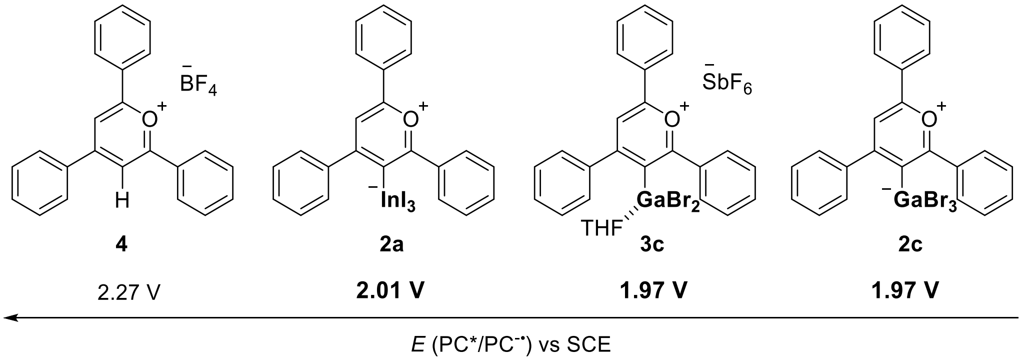
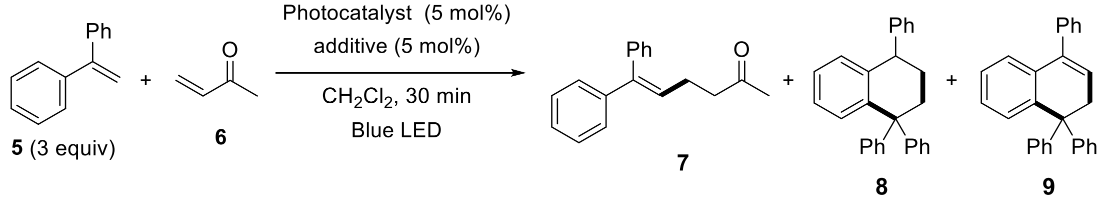
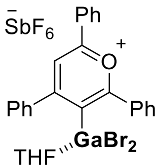
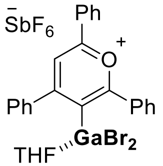
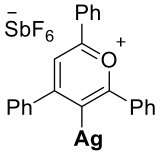
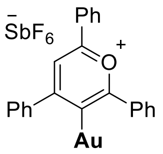
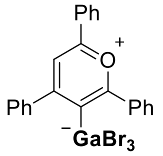
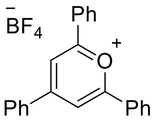
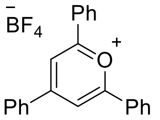


Figure 5. Reductive potential of excited state of the organometallic triphenylpyryliums **2a**, **2c**, **3c** and the triphenylpyrylium tetrafluoroborate **4**.

The organometallic triphenylpyryliums was applied as a photocatalyst including a Lewis acid moiety. Mattay reported that the triphenylpyrylium **4** worked as a photocatalyst in dimerization of 1,1-diphenylethyrene **5**, in which one electron oxidation of **5** followed by addition of the radical cation to another **5** led to the homo-coupling products.[9] In the case that the Lewis acid moiety of the triphenylpyrylium catches a radical acceptor, the radical cation generated from **5** reacts with the caught acceptor in prior to **5** to accomplish the desired cross-coupling. Thus, a conjugate addition of 1,1-diphenylethyrene **5** with α,β-unsaturated ketone **6**[10] was carried out under blue LED light irradiation in the presence of synthesized triphenylpyryliums (Table 2). Gratifyingly, the triphenylpyrylium **3c** including a Lewis acidic gallium moiety gave target product **7** in high yield (entry 1). Irradiation conditions accelerated the cujugated addition because the yield was decreased in dark condtions (entry 2). On the other hand, the triphenylpyryliums bearing carbon-silver or carbon-gold bonds (**2d** and **2e)** were less effective for the cross-coupling than **3c** (entries 3 and 4). The zwitterionic organogallium pyrylium **2c** and the triphenylpyrylium **4**, which have no Lewis acidic moiety, afforded **7** in low yields (entries 5 and 6). Interestingly, the combination of **4** with $GaBr_3$ showed a lower yield than **3c** (entry 7). This result suggested that **3c** which has a Lewis acidic moiety promoted the conjugate addition.

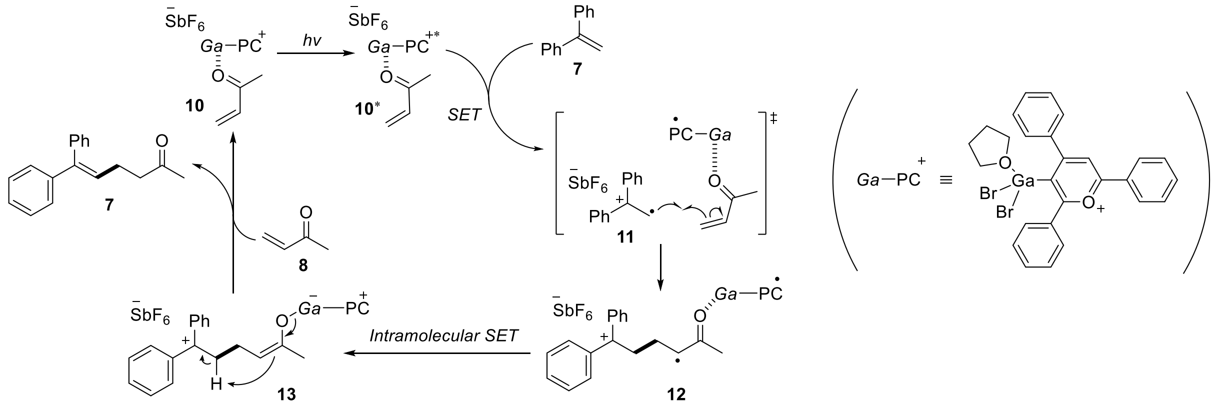
Table 2. Effect of photocatalysts on direct conjugate addition of the alkene **5** to the ketone **6**.[a]



Entry	Photocatalyst	additive	Yield (%)[b]		
			7	**8**	**9**
1	 **3c**	none	88	5	23
2[c]	 **3c**	none	51	0	0
3	 **2d**	none	42	7	12
4	 **2e**	none	31	6	14
5	 **2c**	none	32	4	7
6	 **4**	none	30	8	17
7	 **4**	GaBr3	46	4	9

[a] Reaction conditions: **5** (3 equiv), **6** (1 equiv), photocatalyst (5 mol%), additive (5 mol%), CH_2Cl_2, RT, 30 min, 40W Blue LED. [b] NMR yield. [c] In dark.

Proposed mechanism of the conjugate addition is described in Scheme 1. Firstly, the enone **6** coordinates to the gallium moiety of the organometallic triphenylpyrylium **3c**. Triphenylpyrylium **10** coordinated by **6** absorbs visible light and exicited pyrylium **10*** oxidizes diphenylethyrene **5** to generate radical cation **11** (See Figure S3 in Experimental Section for **S**tern-Volmer fluorescence quenching studies of **3c**). The conjugate addition of radical species **11** with **6** coordinating to the gallium proceeds smoothly because these reactants are adjacent to each other in the case that a photocatalyst possesses a Lewis acid moiety. Intramolecular single electron transfer (SET) from the pyrylium moiety of **12** to the α-carbonyl radical occurs to give gallium enolate **13**. Finally, proton transfer and ligand exchange afford the target product **7** and regenerate the photocatalyst **10**.



Scheme 1. Proposed mechanism of the cross-coupling between 1,1-diphenylethyrene **5** and methyl vinyl ketone **6**.

4-3. Conclusion

Intramolecualr oxymetalation of the carbonyl-ene-yne **1** proceeded efficiently by using π-electrophilic Lewis acids such as indium, gallium, silver and gold salts to construct the triphenylpyryliums framework. X-ray crystallographic analysis revealed that formation of the triphenylpyryliums bearing a carbon-metal bond at the 3-positon and the steric hindrance of metal moiety induced the rotation of phenyl groups in the 2-and 4-positions. Anion abstraction enhanced the Lewis acidity of the zwitterionic gallium complex **2c**. Evaluation of optical and electrochemical properties of the organometallic triphenylpyryliums suggested the increase of their LUMO level compared with the no-metalated triphenylpyrylium **4,** which is supported by the DFT calculations. However, exicited states of the metalated triphenylpyryliums have high reduction potential enough to oxidize simple alkenes. The triphenylpyrylium **3c** possessing a Lewis acidic gallium moiety worked well in the photo-induced direct conjugate addition of alkenes to enones. The pyrylium moiety generates the active radical species and the intramolecular gallium moiety not only activates the enone but also positions the radical acceptor close to the alkyl radical to accelerate the cross-coupling. Therefore, the triphenylpyryliums including a Lewis acidic moiety acts as a bifunctional catalyst in the reaction system.

4-4. Experimental Section

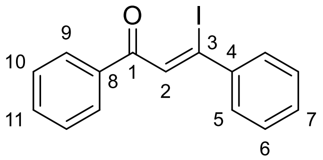
General

New compounds were characterized by ^{1}H and ^{13}C NMR, ^{13}C off-resonance techniques, COSY, HMQC, HMBC, IR, MS, HRMS. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained with TMS as internal standard. High-resolution mass spectra were obtained by magnetic sector type mass spectrometer. UV-vis-NIR spectra were recorded in in a quartz cell (optical path length: 1 cm) using a JASCO V-630 spectrophotometer. Fluorescence spectra were recorded using a HITACHI F-4500 fluorescence spectrophotometer. Blue LED light irradiation was performed using a Kessil A160WE Tuna Blue. Cyclic voltammetric measurements were performed with an ALS-600C electrochemical analyzer using a glassy carbon working electrode, a Pt counter electrode, and an Ag/AgNO$_3$ reference electrode at room temperature in CH$_2$Cl$_2$ containing 0.1 M Bu$_4$NClO$_4$ as the supporting electrolyte. All calculations were performed with Gaussian09 rev.E.01. The RB3LYP density functional and a mixed basis set of DGDZVP for Ga and Br and 6-31+G(d,p) for other atoms were used to optimize all molecular geometries. Excitation energies were calculated at the TD-B3LYP density functional and the same basis set as above. Column chromatography was performed on silica gel (MERK C60 or Fuji Silysia FL100DX). All reactions were carried out under nitrogen. Yields were determined by ^{1}H NMR using internal standards (1,1,2,2-tetrachloroethane).

Materials

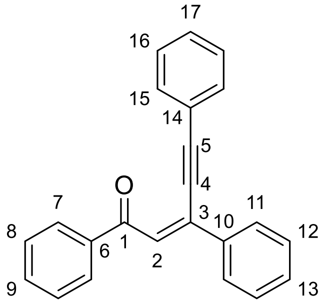
Dehydrated toluene, THF were purchased and used without further purification. Anhydrous CH$_2$Cl$_2$ was purchased and degassed by a repeated freeze-pump-thaw method (3 times). The carbonyl-ene-yne **1** is new compounds, and synthetic method and spectral data of **1** are shown below. AuSbF$_6$ was prepared from AgSbF$_6$ and AuCl and used without purification.[11] The other metal salts, 1,1-diphenylethyrene **5**, methyl vinyl ketone **6** and triphenylpyrylium tetrafluoroborate **4** are commercially available.

(starting material for synthesis of **1**) (*Z*)-3-iodo-1,3-diphenylprop-2-en-1-one[12]



To a three necked flask, 1,3-diphenylprop-2-yn-1-one (8.25 g, 40 mmol), acetic acid (30 mL) and NaI (19.2 g, 128 mmol) was added. The mixture was stirred at 110 °C for 6 h and cooled to rt, The solution was poured into CH_2Cl_2 (50 mL) and H_2O (50 mL) and the resultant mixture was extracted with CH_2Cl_2 (50 mL x 2). The collected organic layer was washed with 5% Na_2CO_3 aq. and sat. $Na_2S_2O_3$ aq., and the organic layer was dried ($MgSO_4$). The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 24 cm, diameter 26 mm, spherical silica gel) to give the product (7.0 g, 52%). ^{1}H NMR: (400 MHz, $CDCl_3$) 8.00 (d, J = 7.2 Hz, 2H, 9-H), 7.63-7.55 (m, 3H, 5-H and 11-H), 7.53 (s, 1H, 2-H), 7.48 (t, J = 7.2 Hz, 2H, 10-H), 7.41-7.35 (m, 3H, 6-H and 7-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 190.3 (s, C-1), 143.1 (s, C-4), 136.9 (s, C-8), 133.4 (d), 131.4 (d, C-2), 129.9 (d), 128.7 (d), 128.6 (d), 128.4 (d), 113.2 (s, C-3); MS: (EI, 70 eV) *m/z* 334 (M^+, 28), 207 (29), 105 (100), 77 (57); HRMS: (CI, 70 eV) Calculated ($C_{15}H_{12}IO$) 334.9933 (M + 1) Found 334.9931.

(**1**) (*Z*)-1,3,5-triphenylpent-2-en-4-yn-1-one[13]



To a three necked flask, (*Z*)-3-iodo-1,3-diphenylprop-2-en-1-one (3.33 g, 9.96 mmol), NEt_3 (40 mL), $PdCl_2(PPh_3)_2$ (0.072 g, 0.103 mmol) and CuI (0.024 g, 0.126 mmol) was added. After cooling the mixture to 0 °C, ethynylbenzene (1.40 g, 13.7 mmol) was added slowly. The mixture was stirred at rt for 11 h. The resultant solution was filtered through Celite pad and the solvent was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate = 90:10, column length 24 cm, diameter 26 mm, spherical silica gel) to give the product (1.90 g, 62%). ^{1}H NMR: (400 MHz, $CDCl_3$) 8.05 (d, J = 7.2 Hz, 2H, 7-H), 7.92-7.85 (m, 2H, 11-H), 7.61-7.56 (m, 1H), 7.56-7.42 (m, 8H), 7.41-7.30 (m, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) 190.1 (s, C-1), 138.6 (s), 137.5 (s), 135.1 (s), 132.7 (d), 132.2 (d), 130.0 (d), 129.2 (d), 128.7 (d), 128.5 (d), 128.3 (d), 127.6 (d), 127.3 (d), 122.5 (s), 101.7 (s), 88.0 (s); HRMS: (CI, 70 eV) Calculated ($C_{23}H_{17}O$) 309.1279 (M + 1) Found 309.1274.

Experimental procedure in oxymetalation of 1 (Table 1).

In a glove box filled for nitrogen, to a sealed vial, (*Z*)-1,3,5-triphenylpent-2-en-4-yn-1-one **1** (0.3 mmol), toluene (0.6 mL) and metal salt (0.3 mmol) were added. The solution was stirred at RT for 24 h. The reaction mixture was washed by hexane (3 mL x2) and $CHCl_3$ (3 mL x 6). The residue was dried under vacuum to give the product as a solid.

Experimental procedure in the direct conjugate addition (Table 2).

In a glove box filled for nitrogen, to a sealed vial, 1,1-diphenylethyrene **5** (0.3 mmol), CH_2Cl_2 (1.5 mL), methyl vinyl ketone **6** (0.3 mmol) and photocatalyst (0.015 mmol) were added. The solution was stirred cooling with a fan at RT under 40W blue LED light irradiation. The reaction vessel was positioned at a distance of 7 cm from the blue LED. After stirring for 30 min, the reaction mixture was diluted with CH_2Cl_2 (10 mL). The solvent was evaporated and the yield of products **7**, **8** and **9** was determined by ^{1}H-NMR. The products **7**, **8** and **9** are known compounds and the spctra agreed wirh the literature.[9,10a]

X-ray structure of the pyrylium without a carbon-metal bond

After oxymetalation of carbonyl-ene-yne **1** with $AlBr_3$ (Table 1, entry 7), the product was recrystallized from CH_3CN to give a single crystal. X-ray diffraction analysis showed that the crystal is not the target organometallic triphenylpyrylium **2g** but a protonated triphenylpyrylium as shown below.

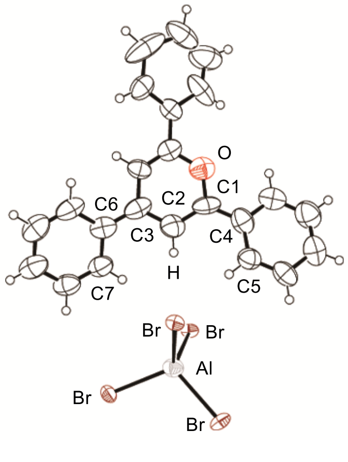


Figure S1. The X-ray crystallographic structure of the triphenylpyrylium without a carbon-metal bond with the thermal ellipsoids shown at 50% probability. Selected dihedral angles (deg): C2-C1-C4-C5 = 11.44, C2-C3-C6-C7 = 19.44.

TD-DFT calculation of 2c and 4

Table S1. Excitation energies of **2c**.

Excited state	Excitation energy /eV (wavelength /nm)	Excitation amplitudes	Oscillator strength	$<S^2>$
7	3.16 (392.9)	0.694 (HOMO-6 - LUMO)	0.2612	0.000
8	3.23 (383.4)	0.612 (HOMO-7 - LUMO) 0.165 (HOMO-9 - LUMO) -0.295 (HOMO-8 - LUMO)	0.0198	0.000
11	3.39 (365.9)	0.465 (HOMO-9 - LUMO) -0.320 (HOMO-7 - LUMO) -0.407 (HOMO-8 - LUMO)	0.2401	0.000

Table S2. Excitation energies of **4**.

Excited state	Excitation energy /eV (wavelength /nm)	Excitation amplitudes	Oscillator strength	$<S^2>$
1	2.85 (435.6)	0.677 (HOMO - LUMO) -0.199 (HOMO-1 - LUMO)	0.3042	0.000
5	3.41 (363.7)	0.687 (HOMO-4 - LUMO) 0.157 (HOMO - LUMO+1)	0.2663	0.000
9	3.94 (315.1)	0.640 (HOMO-7 - LUMO) 0.277 (HOMO - LUMO+1)	0.3765	0.000

Energy level diagrams and molecular orbitals of 2c and 4

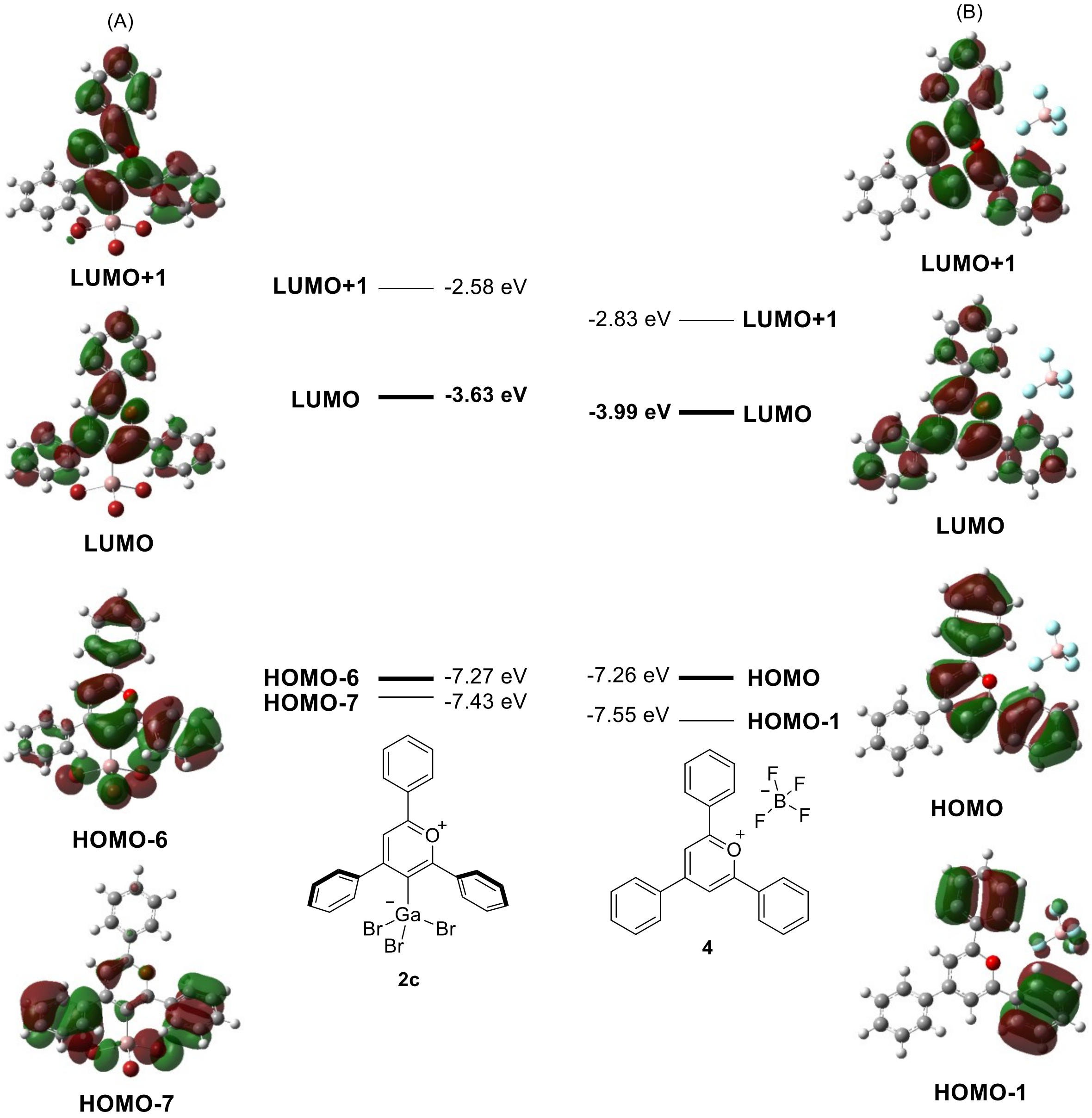


Figure S2. (A) HOMO-6, HOMO–7, LUMO and LUMO+1 of **2c**. (B) HOMO, HOMO–1, LUMO and LUMO+1 of **4**.

Stern-Volmer fluorescence quenching studies

Fluorescence quenching studies were performed using a HITACHI F-4500 fluorescence spectrophotometer. In each experiment, the photocatalyst and various concentrations of the quencher were combined in CH_2Cl_2 in screw-top 1.0 cm quartz cell. The emission quenching of the triphenylpyrylium including a carbon-gallium bond **3c** was achieved using the photocatalyst concentration of 2.0 x 10^{-6} M under excitation at 420 nm. The emission intensity was observed at 465 nm. Plots were constructed according to the Stern–Volmer equation $I_0/I = 1 + k_q\tau_0[Q]$.[14] The exicited state of **3c** was quenched by not the methyl vinyl ketone **6** but the 1,1-diphenylpyrylium **5**.

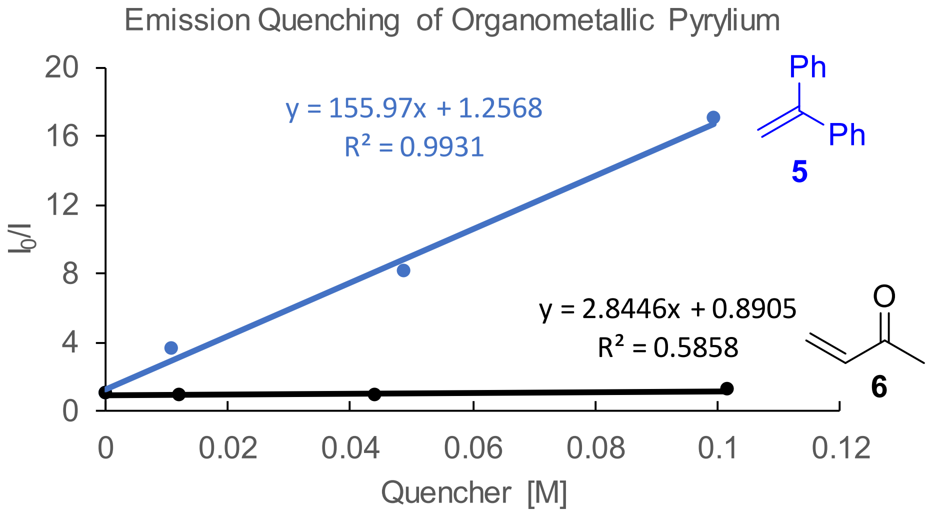
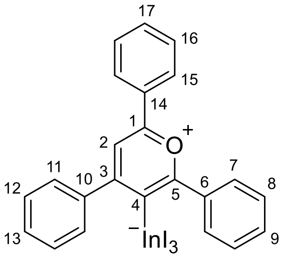


Figure S3. Stern-Volmer fluorescence quenching studies for the oraganogallium triphenylpyrylium **3c**.

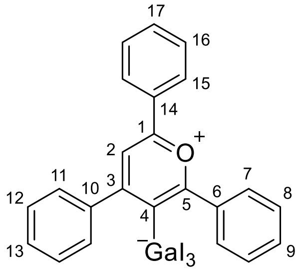
Product

(**2a**) 2,4,6-triphenylpyrylium including InI_3 moiety at 3-position



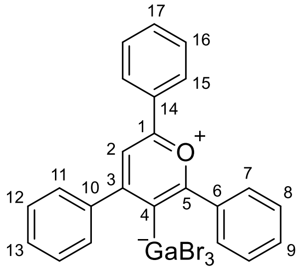
To a sealed vial, InI_3 (0.152 g, 0.307 mmol), toluene (0.6 mL) and (*Z*)-1,3,5-triphenylpent-2-en-4-yn-1-one (0.0924 g, 0.30 mmol) were added. The mixture was stirred at RT for 24 h. The reaction mixture was washed by hexane (3 mL x 2) and $CHCl_3$ (3 mL x 6). The residue was dried under vacuum to give the product as a yellow solid (0.20 g, 83% yield). This compound was recrystallized from CH_3CN to give a single crystal. The structure was determined by X-ray crystallographic analysis. Characterization by NMR study was also carried out and the spectra is shown below. ^{1}H NMR: (400 MHz, $CDCl_3$) 8.28-8.14 (m, 5H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.85-7.69 (m, 9H); ^{13}C NMR: (100 MHz, $CDCl_3$) 178.6 (s), 177.2 (s), 168.8 (s, C-3), 139.8 (s), 135.4 (d), 134.6 (d), 134.1 (d), 133.9 (s), 131.4 (d), 130.44 (d), 130.36 (d), 130.08 (d), 128.6 (s), 128.2 (s), 127.7 (d), 116.4 (d).

(**2b**) 2,4,6-triphenylpyrylium including GaI_3 moiety at 3-position



To a sealed vial, GaI_3 (0.139 g, 0.309 mmol), toluene (0.6 mL) and (*Z*)-1,3,5-triphenylpent-2-en-4-yn-1-one (0.093 g, 0.302 mmol) were added. The mixture was stirred at RT for 24 h. The reaction mixture was washed by hexane (3 mL x 2) and $CHCl_3$ (3 mL x 6). The residue was dried under vacuum to give the product as a yellow solid (0.15 g, 66% yield). This compound was recrystallized from CH_3CN to give a single crystal. The structure was determined by X-ray crystallographic analysis. Characterization by NMR study was also carried out and the spectra is shown below. ^1H NMR: (400 MHz, $CDCl_3$) 8.36 (d, *J* = 7.5 Hz, 2H), 8.18 (d, *J* = 8.0 Hz, 2H, 11-H), 8.16 (s, 1H, 2-H), 8.15 (d, *J* = 8.2 Hz, 2H), 7.84-7.77 (m, 2H), 7.77-7.66 (m, 7H); ^{13}C NMR: (100 MHz, $CDCl_3$) 178.6 (s), 177.8 (s), 168.2 (s, C-3), 139.5 (s), 135.4 (d), 134.6 (d), 133.99 (s), 133.94 (d), 132.6 (s, C-4), 131.8 (d), 130.8 (d), 130.3 (d), 129.8 (d), 129.6 (d), 128.5 (s), 127.7 (d, C-11), 117.1 (d, C-2).

(**2c**) 2,4,6-triphenylpyrylium including $GaBr_3$ moiety at 3-position



To a sealed vial, $GaBr_3$ (0.094 g, 0.304 mmol), toluene (0.6 mL) and (*Z*)-1,3,5-triphenylpent-2-en-4-yn-1-one (0.0928 g, 0.301 mmol) were added. The mixture was stirred at RT for 24 h. The reaction mixture was washed by hexane (3 mL x 2) and $CHCl_3$ (3 mL x 6). The residue was dried under vacuum to give the product as an orange solid (0.10 g, 54% yield). This compound was recrystallized from CH_3CN to give a single crystal. The structure was determined by X-ray crystallographic analysis. Characterization by NMR study was also carried out and the spectra is shown below. ^1H NMR: (400 MHz, $CDCl_3$) 8.29 (d, *J* = 7.3 Hz, 2H), 8.19 (s, 1H, 2-H), 8.18 (d, *J* = 7.3 Hz, 2H, 11-H), 8.06 (d, *J* = 7.1 Hz, 2H), 7.82-7.77 (m, 2H), 7.77-7.65 (m, 7H); ^{13}C NMR: (100 MHz, $CDCl_3$) 178.8 (s), 178.2 (s), 168.5 (s, C-3), 139.5 (s), 137.7 (s, C-4), 135.4 (d), 134.4 (d), 133.73 (d), 133.65 (s), 131.5 (d), 130.4 (d), 129.7 (d), 129.5 (d), 128.5 (s), 127.7 (d, C-11), 117.0 (d, C-2).

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Conclusion

This thesis reported the direct functionalization of alkenes and regioselective formation of oxacycles from alkynes utilizing heavier group 13 metal salts which have moderate Lewis acidity and high π-electron affinity.

Chapter 1 revealed that various enol derivatives such as vinyl ethers, vinyl esters, vinyl silyl ethers and vinyl carbamates were suitable for the $GaBr_3$-catalyzed cross coupling of enol derivatives with silyl ketene acetals. Mechanistic studies revealed that this coupling reaction proceeds through addition-elimination mechanism. The turnover limiting step in the case of a vinyl ether is the elimination step while the addition step determines the reaction rate in the reaction using a vinyl ester.

In Chapter 2, I developed the formal hydrofunctionalization that installed a wide range of functional groups into the styrene derivatives. Various organosilicon nucleophiles were applicable in this hydrofunctionalization. This reaction is composed of two steps: Brønsted acid-catalyzed formation of cyclic ether followed by InI_3-catalyzed C-O bond cleavage.

In Chapter 3, I achieved the facile synthesis of 4-substituted isocoumarins by 6-*endo* selective oxymetalation of 2-ethynylbenzoate. This cyclization proceeds in *anti*-Markovnikov addition manner. Full investigation of the mechanism by experimental data and theoretical calculations suggested that large ionic radius of indium had a great influence on the 6-*endo* selective heterocyclization. The synthesis of 3-nonsubstituted isocoumarins is difficult in spite of an important class of bioactive compounds. However, the isocoumarins bearing a carbon-indium bond enable easy access to 3-nonsubstituted isocoumarins.

Chapter 4 mentioned the synthesis of new types of organometallic pyryliums. I determined the structures by X-ray crystallographic analysis and evaluated their optical and electrochemical properties. The triphenylpyrylium including a gallium moiety worked as not only photocatalyst but also Lewis acid catalyst. This bifunctional catalyst showed high activity for the direct conjugate addition of alkenes to enones.

Chapters 1 and 2 give a knowledge that gallium and indium cleavage not only carbon-carbon multiple bonds but also carbon-oxygen bonds. It is difficult for π-electrophilic Lewis acidic transition metals such as silver and gold to cleavage carbon-oxygen bonds due to the low oxophilicity. On the other hand, heavier group 13 metals have moderate oxophilicity to accomplish such advanced transformations. A knowledge obtained from Chapters 3 and 4 is that gallium and indium provide stable organometallic ate complex because of their capacity of delocalizing anion charge.

The obtained knowledge provides an unprecedent strategy to functionalize carbon-carbon multiple bonds using main group metals and an opportunity to isolate unknown organometallic species that seems to be not isolated due to the unstability.