Studies on Preparation of Functionalized Organozinc Reagents via Zinciomethylation

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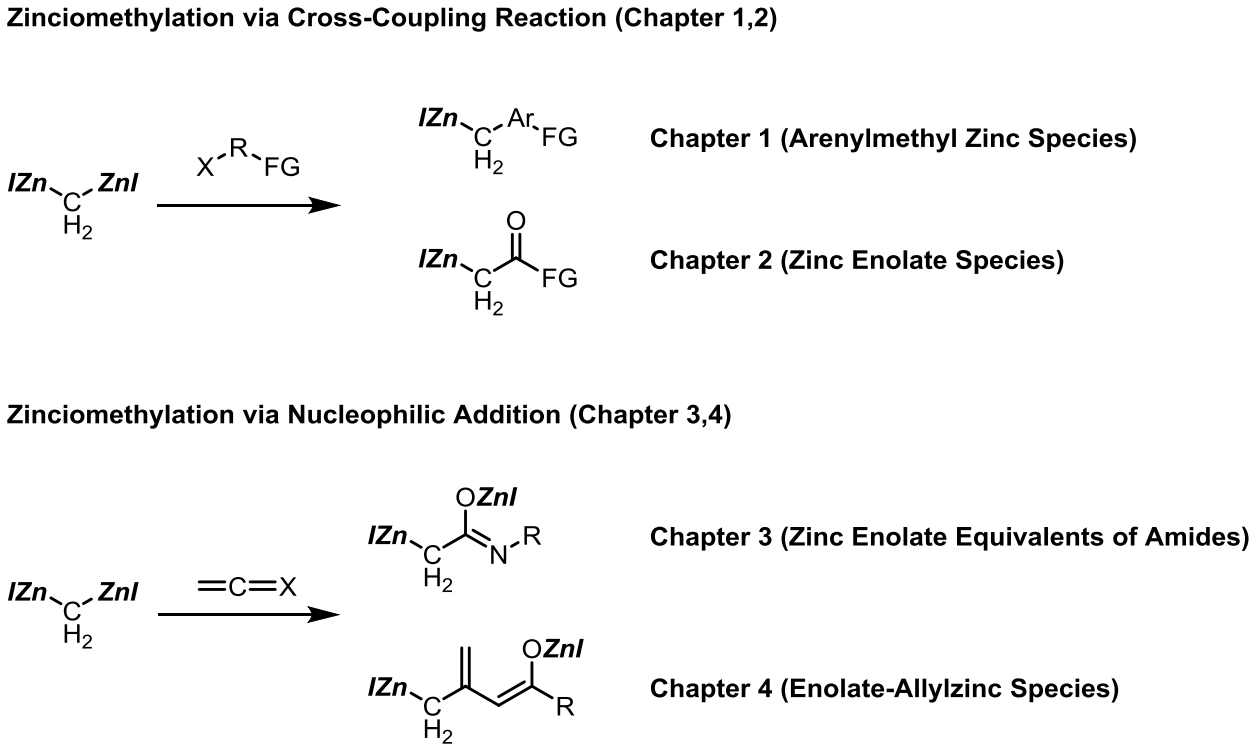
Contents

Abbreviations

Ac acetyl
aq. Aqueous
Ar aryl
Bn benzyl
br broad (spectral)
Bu butyl
°C degrees Celsius
calcd calculated
cat. catalytic
cm centimeter(s)
Co. company
Cy cyclohexyl
δ chemical shift in parts per million
d doublet (spectral)
dba dibenzylideneacetone
dppp 1,3-bis(diphenylphosphino)propane
dppe 1,2-bis(diphenylphosphino)ethane
dr diastereomeric ratio
E *entgegen* (means "opposite")
Ed(s) editor(s)
El electrophile
ee enantiomeric excess
eq equivalent(s)
ESI electrospray ionization
Et ethyl
g gram(s)
h hour(s)
HRMS high-resolution mass spectrum
Hz hertz (s^{-1})
i iso
Inc. incorporated
IR infrared (spectral)
J coupling constant (spectral)
m multiplet (spectral)
m meta
M molar (1 M = 1 mol dm^{-3})
Me methyl
mg milligram(s)
MHz megahertz
min minute(s)
mL milliliter(s)
mm millimeter(s)
mmol millimole(s)
Mp. melting point
Ni nickel
nm nanometer(s)
NMR nuclear magnetic resonance
o ortho
p para
Ph phenyl
Pd palladium
ppm parts per million (spectral)
Pr propyl
q quartet (spectral)
ref reference
R_f retention factor (TLC)
r.t. room temperature (25 ± 3 °C)
s singlet (spectral)
t triplet (spectral)
t (*tert*) tertiary
TBS *tert*-butyldimethylsilyl
Tf trifluoromethanesulfonyl
THF tetrahydrofuran
TLC thin-layer chromatography
TMS trimethylsilyl
Vol. volume(s)
UV ultraviolet
Z *zusammen* (means "together")

General Introduction

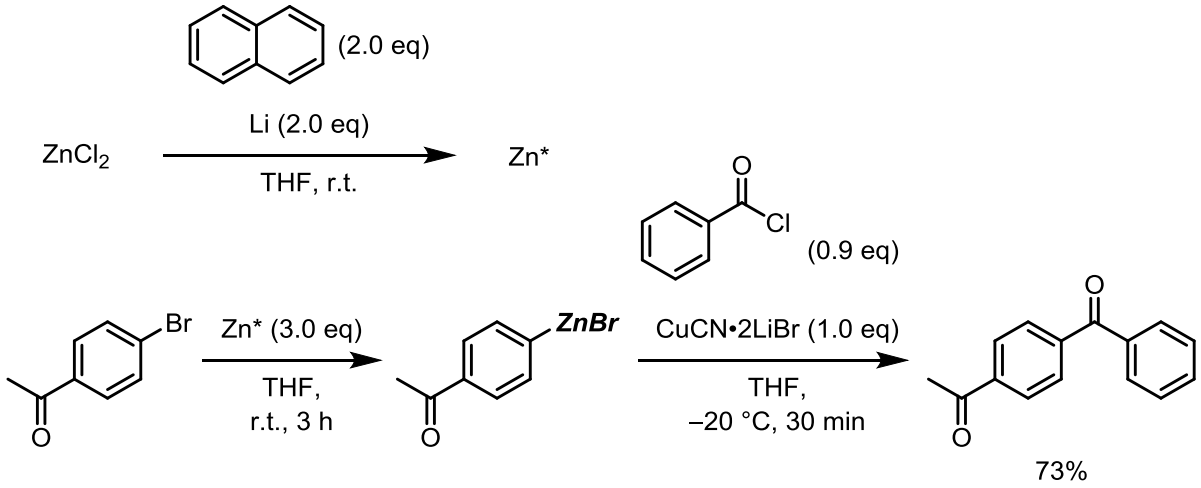
Organo main-group reagents have been utilized as carbanion equivalents in organic synthesis, and they work as efficient *C*-nucleophiles. Among them, organozinc reagents have occupied a unique position in organic synthesis. As organozinc reagents are not equipped with strong basicity and nucleophilicity, they can be used as versatile nucleophiles with high selectivitity. For example, cross-aldol reactions using the Reformatsky reagent[1] and Negishi cross-coupling reactions[2] have been established as highly chemoselective reactions. Besides, the zinc atom has reasonable Lewis acidity, which can be utilized in the design of stereoselective reactions through effective interactions with a Lewis base. For example, asymmetric addition of organozinc reagents to carbonyl groups,[3] such as the Soai reaction[4] proceed with high diastereo- and enantioselectivity. If organozinc reagents carrying a variety of functional groups could be utilized in these transformations, it would be possible to directly assemble highly functionalized molecules from both functionalized nucleophiles and electrophiles. However, the preparation of functionalized organozinc reagents is sometimes hampered by their traditionally reductive or strongly basic preparation conditions. For this reason, significant efforts have been made recently to improve the preparation of organozinc reagents. In contrast, the author attempted to develop a novel method for their preparation, based on a completely different mechanism. He paid attention to bis(iodozincio)methane,[5] which has two C–Zn bonds from the same carbon atom, as a synthetic tool for the introduction of a -CH_2ZnI group (Scheme 1). In this thesis, the author devoted his efforts to designing various types of highly functionalized organozinc reagents based on the zinciomethylation strategy. First, he will introduce the recent progress on the preparation of functionalized organozinc reagents. Next, he will demonstrate the potential of zinciomethylation for the preparation of functionalized organozinc reagents on the basis of previously reported examples.



Scheme 1. Concept of Zinciomethylation Using Bis(iodozincio)methane.

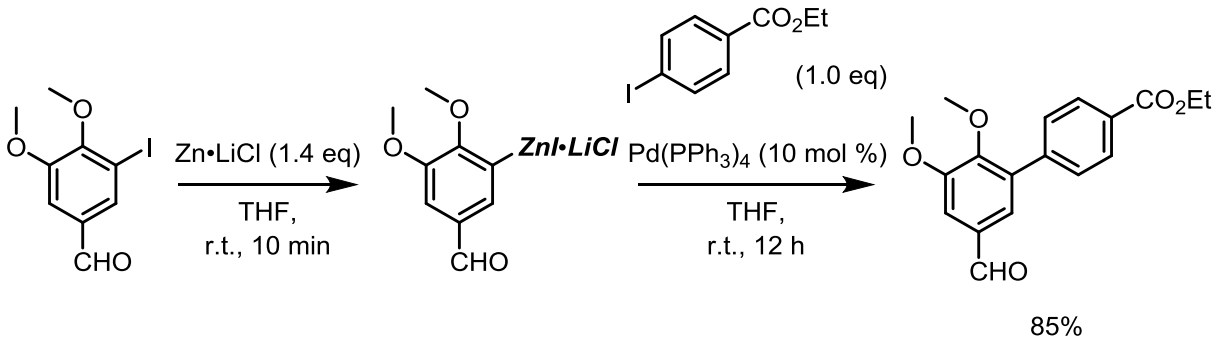
1. Recent Example of Preparation of Functionalized Organozinc Reagents

The primary method for the preparation of organozinc reagents is the direct insertion of zinc metal into organic halides.[6] Although the more reactive halides such as alkyl iodides and α-halo esters could be used, most vinyl and aryl halides proved difficult to utilize. Rieke zinc, which is prepared by the lithium naphthalenide reduction of $ZnCl_2$, is so reactive that it allowed the use of most vinyl and aryl halides for the preparation of corresponding organozinc reagents under mild reaction conditions (Scheme 2).[7]



Scheme 2. Rieke Zinc for the Preparation of Functionalized Arylzinc Reagents.

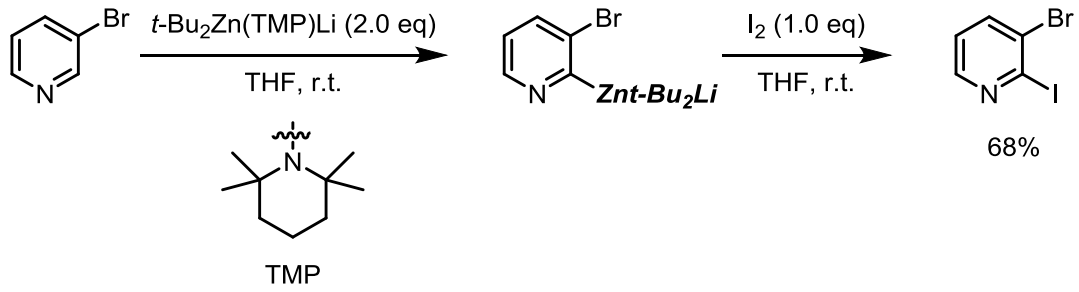
Knochel discovered a more practical method for the preparation of organozinc reagents. According to his strategy, the addition of LiCl facilitated the oxidative addition of zinc metal to various organic halides under mild reaction conditions.[8] This method enabled the preparation of organozinc reagents, including those containing a reactive formyl group, as shown in Scheme 3.



Scheme 3. LiCl- Mediated Oxidative Addition of Zinc Metal into Organic Halides.

Among the preparation methods for arylzinc reagents, the directed ortho deprotonative zincation of aromatic compounds by organo zincates has also attracted great attention, because of the high functional tolerability. As a representative work, Uchiyama developed lithium di-*tert*-butyl(tetramethylpiperidino)zincate (TMP–zincate); it can utilize the alkoxy, cyano,

methyl ester, or pyridyl group on an aromatic ring as a metalation-directing group (Scheme 4).[9]



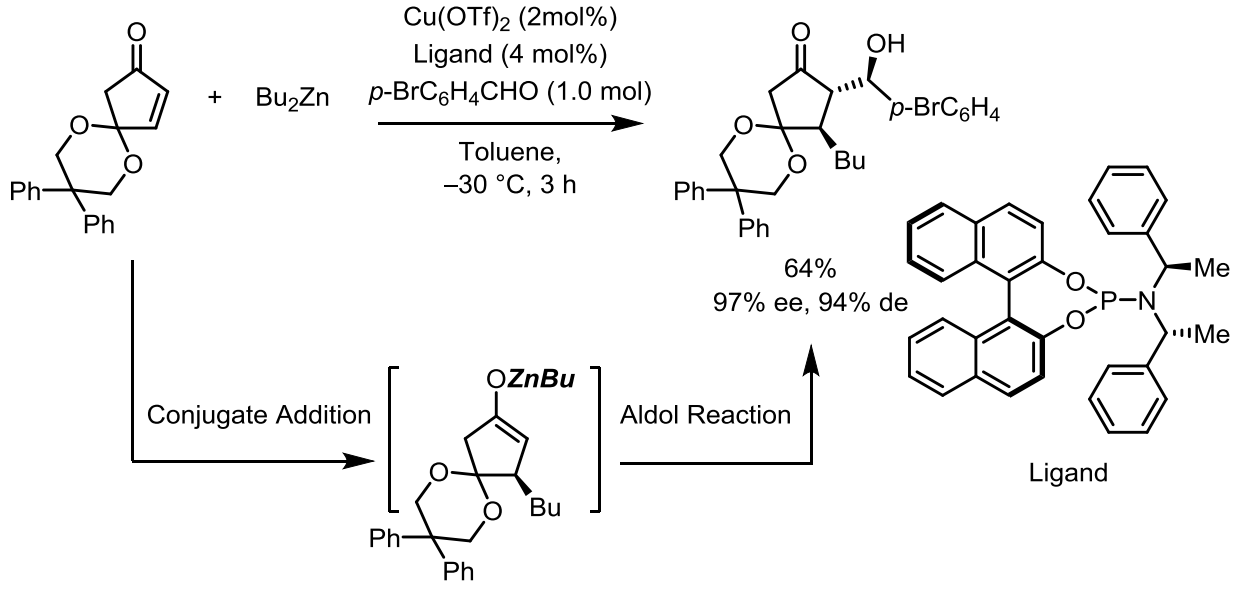
Scheme 4. TMP-zincate- Mediated Directed Ortho Zincation of Pyridine.

These progressions have enabled access to a variety of functionalized organozinc reagents, which can be utilized for the synthesis of complex molecules.[10] On the other hand, the development of completely different methods is also desirable, since they can afford the organozinc reagents that are difficult to prepare by the method described above.

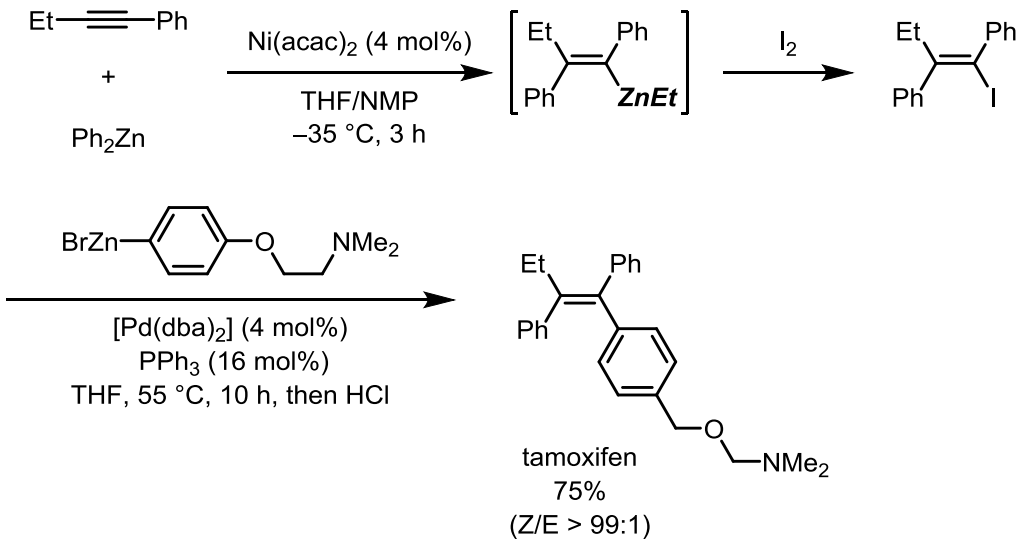
2. Carbozincation of Alkene or Alkyne for Preparation of Functionalized Organozinc Reagents

Carbozincation involves the addition of organozinc reagents to C–C multiple bonds to afford a new organozinc reagent including C–C bond formation. Considering the high chemoselectivity of organozinc reagents, this method has potential for the preparation of functionalized organozinc reagents. Although more reactive organozinc reagents such as allyl zinc[11] and zinc enolate[12] can react with alkenes and alkynes without any additive, the poorly reactive organozinc reagents such as alkyl or aryl zinc species cannot add to C–C multiple bonds in the absence of an additional additive. Transition metal catalysts enable the addition of such poorly reactive organozinc reagents to various types of carbon–carbon multiple bonds. For example, copper- catalyzed conjugate addition of organozinc reagents to electron deficient alkenes provided zinc enolate species, which were utilized for subsequent C–C bond formation reactions.[13] Moreover, the use of a chiral copper catalyst allowed for the generation of a chiral

zinc enolate species, as shown in Scheme 5.[14]



Scheme 5. Copper- Catalyzed Asymmetric Conjugate Addition of Organozinc Reagents.



Scheme 6. Nickel- Catalyzed Carbozincation of Alkynes.

Transition metal catalysts also enable the use of electronically unbiased C–C multiple bonds in carbozincation. As shown in Scheme 6, the addition of diphenyl zinc to internally

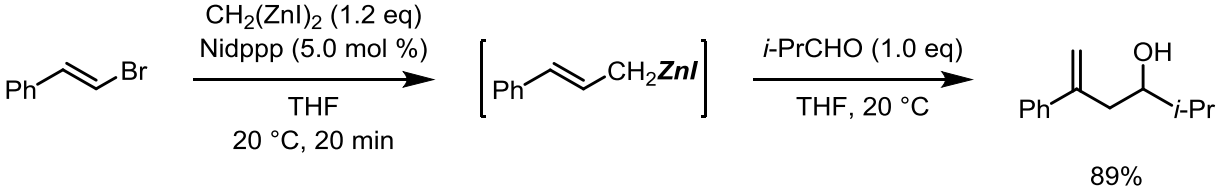
asymmetric alkynes in the presence of nickel catalysis proceeded with perfect regioselectivity to provide the alkenyl zinc reagents.[15] This reaction was applied for the synthesis of (*Z*)-tamoxifen.

These examples of carbozincation suggest that more structurally elaborate organozinc reagents can be prepared from readily available substrates and parent organozinc reagents via C–C and C–Zn bond formation.

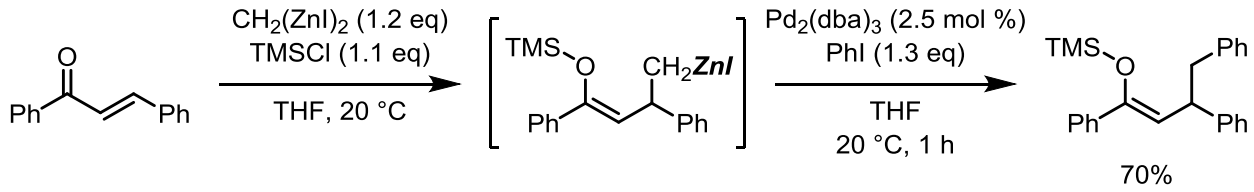
3. Zinciomethylation Strategy for Preparation of Organozinc Reagents

The use of *gem*-dizinc reagents has opened a new route to organozinc reagents. An example is the cross-coupling reaction of *gem*-dizinc reagents with vinyl halides to afford allyl zinc derivatives, which can undergo subsequent C–C bond formation reaction (Scheme 7).[16] Allyl halides and propargyl halides could also be utilized in this cross-coupling reaction to provide the one carbon increased organozinc reagents. Conjugate addition of *gem*-dizinc reagents to electron deficient olefins was also possible (Scheme 8).[17] This transformation was accelerated by the addition of chlorotrimethylsilane to provide the homoallyl zinc bearing silyl enol ether. The formed organozinc species can react with aryl halides in the presence of a palladium catalyst.

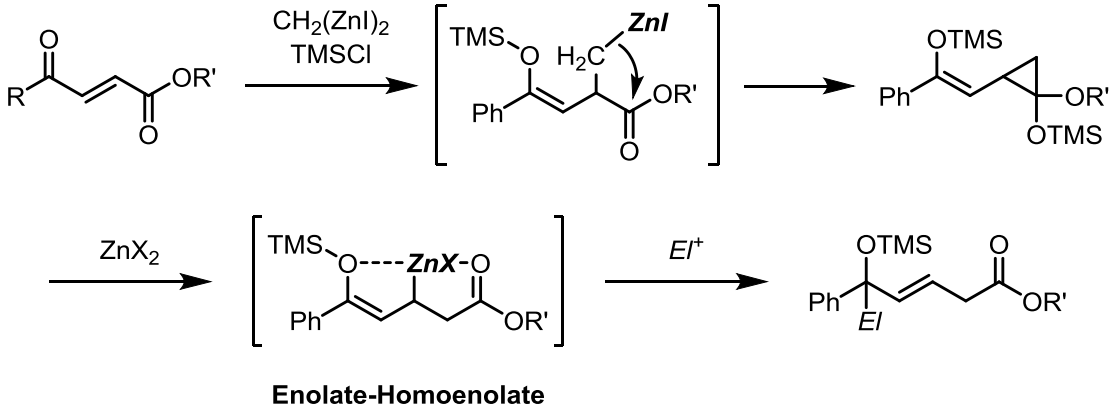
These examples suggest the potential of preparing functionalized organozinc reagents via typical reactions of organomonozinc reagents such as cross-coupling reactions or carbozincation. Moreover, *gem*-dizinc reagents also enabled a unique transformation for the preparation of enolate-homoenolate zinc species (Scheme 9).[18]



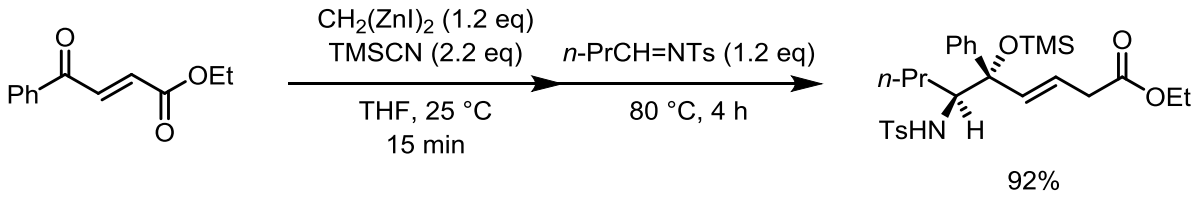
Scheme 7. Cross-Coupling Reaction of Bis(iodozincio)methane with Organic Halides.



Scheme 8. Conjugate Addition of Bis(iodozincio)methane to Electron Deficient Alkenes.



Scheme 9. Sequence of Conjugate Addition, Intramolecular Nucleophilic Addition, and Ring Opening of Cyclopropanol.

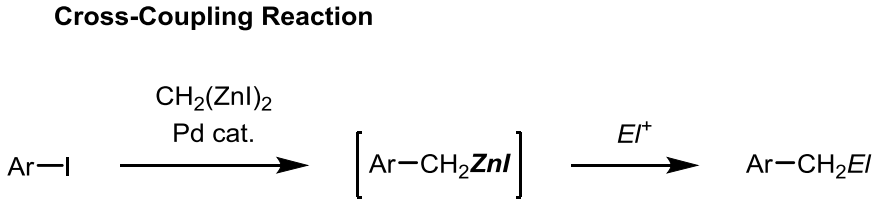


Scheme 10. Addition of Enolate-Homoenolate Species to Imines.

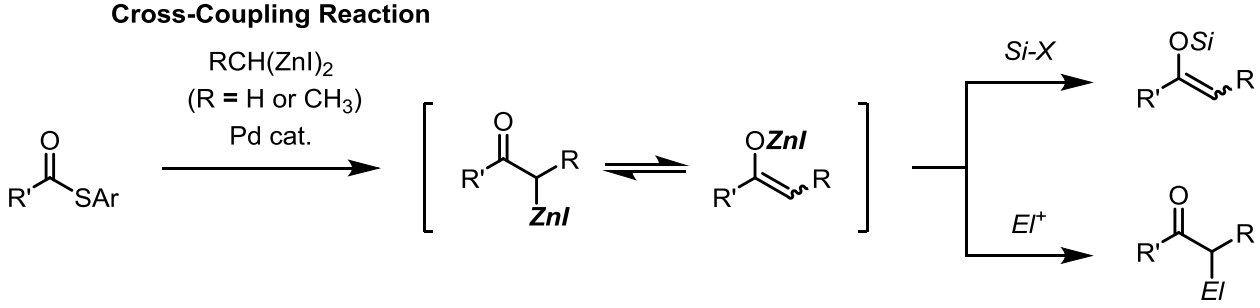
This transformation includes conjugate addition, intramolecular nucleophilic addition, and ring opening of cyclopropanol. The formed organozinc species can react with imines to afford 1,2-aminoalcohol derivatives diastereoselectively (Scheme 10).

4. Overview of this thesis

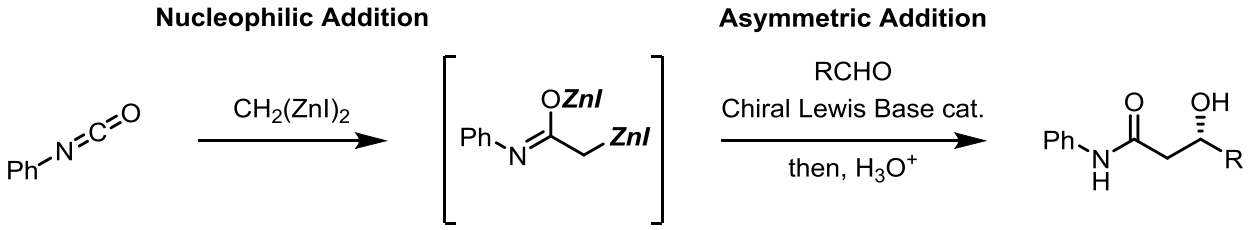
To establish zinciomethylation as a general and versatile approach toward highly functionalized organozinc reagents, the author explored the development of reactions of bis(iodozincio)methane with various electrophiles. In Chapter 1, he described the cross-coupling reaction of iodoarenes with a *gem*-dizinc reagent. This transformation was catalyzed by palladium or nickel complexes to afford functionalized arenylmethylzinc reagents (Scheme 11). In Chapter 2, he described the preparation of zinc enolates bearing functional groups based on the cross-coupling reaction of thioesters with bis(iodozincio)methane (Scheme 12). In Chapter 3, he demonstrated that nucleophilic addition of *gem*-dizinc reagents to heterocumulenes provides zinc enolate equivalents, which contain two zinc atoms in each molecule (Scheme 13). In Chapter 4, he discussed the successful preparation of enolate-allyl zinc species by conjugate addition of *gem*-dizinc reagents to allenone (Scheme 14).



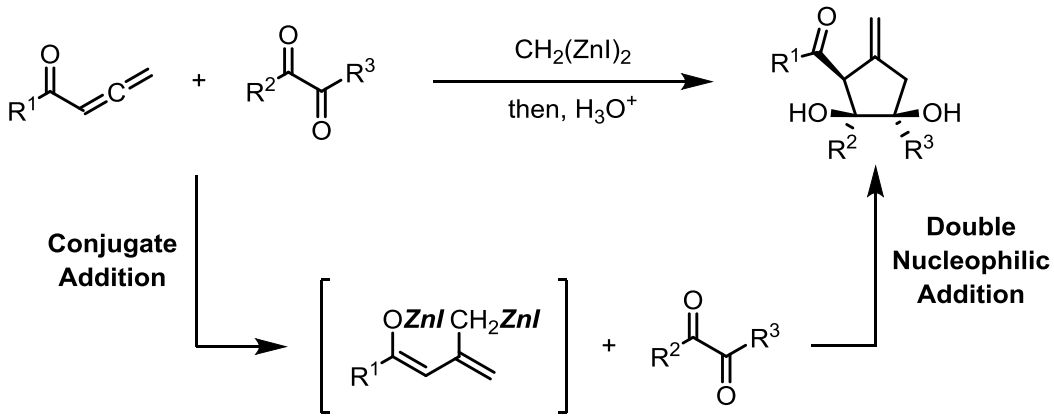
Scheme 11. Preparation of Arenylmethylzincs from Iodoarenes and Bis(iodozincio)methane.



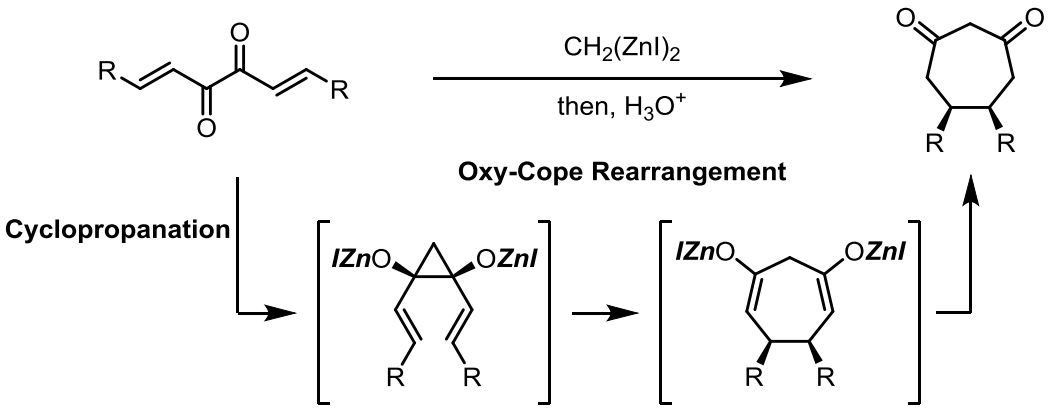
Scheme 12. Preparation of Zinc Enolate Species from Thiol Esters and Bis(iodozincio)methane.



Scheme 13. Preparation of Zinc Enolate Equivalents of Amides from Isocyanates and Bis(iodozincio)methane.



Scheme 14. Preparation of Enolate-Allyl Zinc Species from Allenones and Bis(iodozincio)methane.

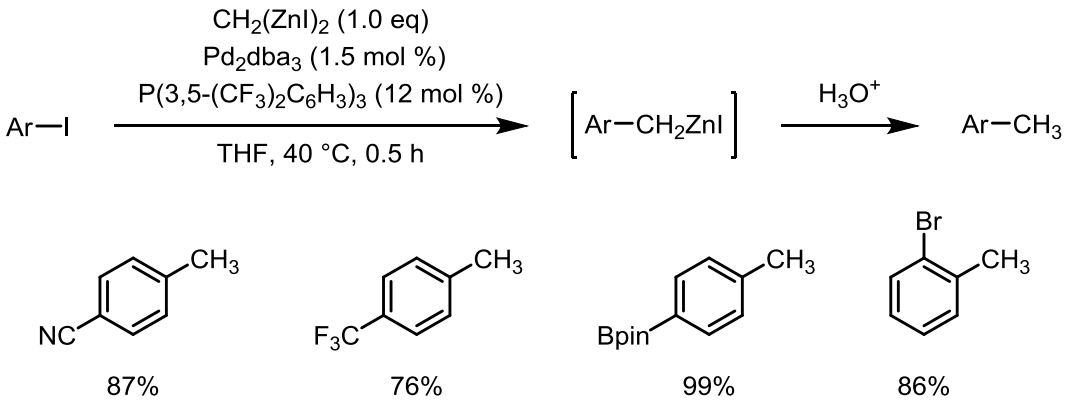


Scheme 15. Preparation of Cycloheptane Ring from 1,2-Diketone and Bis(iodozincio)methane via Oxy-Cope Rearrangement.

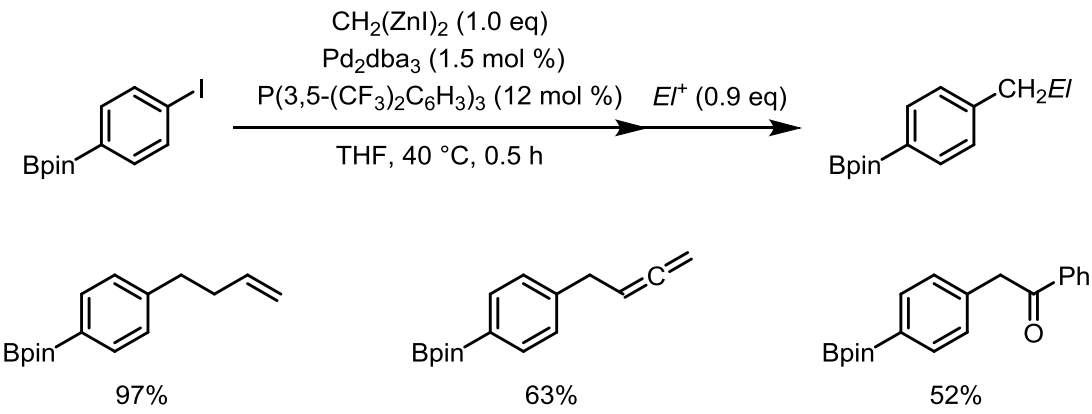
In Chapter 5, he outlined the synthesis of the dizinc enolate of a 7-membered carbocycle using divinyl diketones and bis(iodozincio)methane (Scheme 15). In this reaction, nucleophilic cyclopropanation and oxy-Cope rearrangement sequence took place to provide a dizinc enolate of the cycloheptane-1,3-dione species, which could undergo subsequent aldol reaction.

4.1. Preparation of an Arenylmethylzinc Reagent with Functional Groups by Chemoselective Cross-Coupling Reaction of Bis(iodozincio)methane with Iodoarenes (Chapter 1)

Aromatic components are important structures for pharmaceuticals and materials, and their insertion has been studied intensively in order to synthesize novel functionalized molecules. Arylzinc reagents are recognized as one of the most valuable synthetic tools for the introduction of aromatic moieties, as they have broad functional tolerability and reasonable reactivity. In contrast, the homologous arenylmethylzinc reagents that contain several functional groups have not been well studied, though they can also play a crucial role in the introduction of an aromatic group.



Scheme 16. Preparation of Arenylmethylzincs from Iodoarenes and Bis(iodozincio)methane.



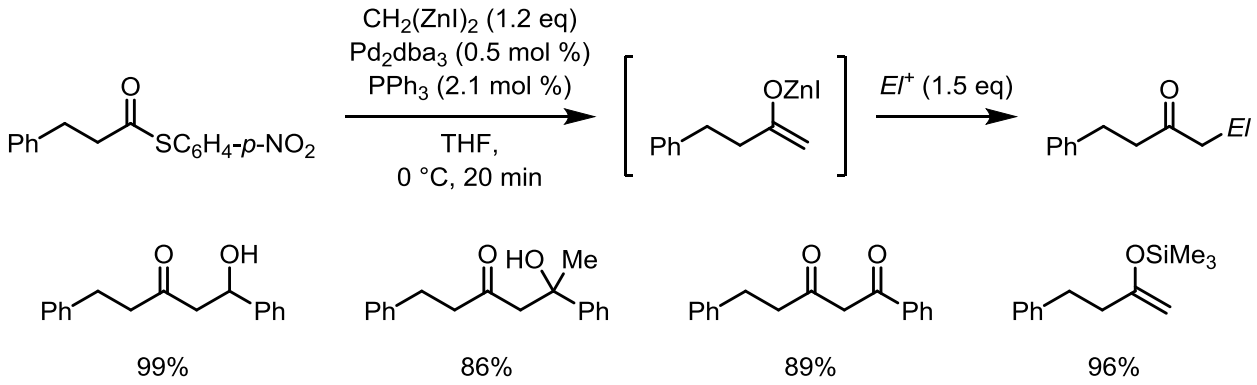
Scheme 17. Products Synthesized from Arenylmethylzinc Compounds with Various Electrophiles.

In Chapter 1, the author illustrated the preparation of arenylmethylzinc compounds by means of a transition metal-catalyzed cross-coupling reaction of bis(iodozincio)methane with iodoarenes.[19] A variety of functional groups can be tolerated in this protocol (Scheme 16). Moreover, the arenylmethylzinc compounds formed could further react with various electrophiles to provide the corresponding products, as shown in Scheme 17.

4.2. Chemo- and Regioselective Preparation of Zinc Enolate from Thiol Esters by Palladium Catalyzed Cross-Coupling Reaction (Chapter 2)

Previously, the Matsubara group reported that the palladium catalyzed cross-coupling reaction of acyl chlorides with a *gem*-dizinc reagent provided zinc enolate species. However, the zinc enolate reacted with acyl chloride to afford 1,3-symmetric diketones even in the presence of other electrophiles.[20] To enhance the value of zinc enolates prepared by zinciomethylation strategy, the use of milder acylating electrophiles is required.

In Chapter 2, the author described the preparation of zinc enolate derivatives by means of the cross-coupling reaction of bis(iodozincio)methane with thioesters.[21] The zinc enolates formed can react with various electrophiles such as aldehydes, ketones, acyl cyanides, and silylating reagents to afford the corresponding products (Scheme 18).



Scheme 18. Preparation of Zinc Enolate Derivatives from Thiol Esters and Bis(iodozincio)methane.

Furthermore, it should be noted that the initially formed enolate did not isomerize to the corresponding thermodynamic enolate under these reaction conditions. Thus, the chemo- and regioselective preparation of the kinetic enolates in the polycarbonyl compounds was achieved, and the corresponding silyl enol ethers were obtained, as shown in Figure 2.

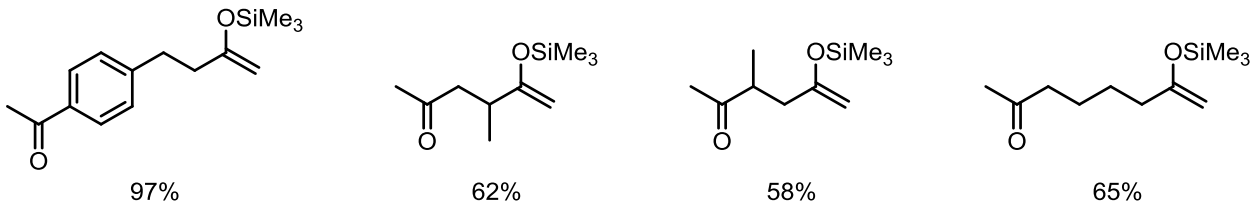
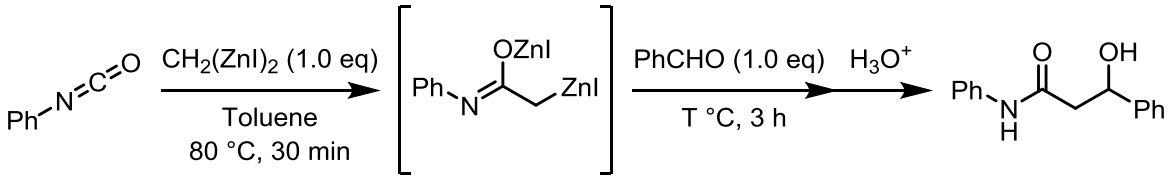


Figure 2. Chemo- and Regioselective Preparation of the Kinetic Silyl Enol Ethers in the Polycarbonyl Compounds.

4.3. Preparation of the Zinc Enolate Equivalent of Amides by Zinciomethylation of Isocyanates: Catalytic Asymmetric Reformatsky-Type Reaction (Chapter 3)

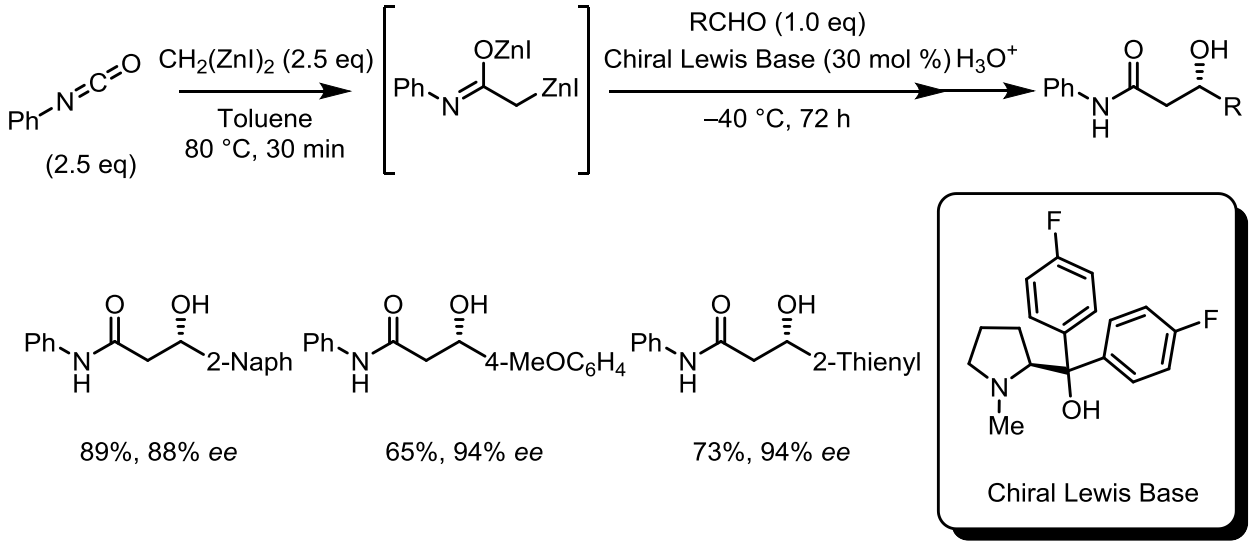
In Chapter 3, the author described the preparation of zinc enolate equivalents of amide, which were generated from bis(iodozincio)methane and isocyanates.[22] These zinc enolate equivalents reacted with benzaldehyde to afford the corresponding product in only 13% yield at room temperature (Scheme 19).



T (°C)	Yield (%)
25	13
60	56
140	85

Scheme 19. Reactivity of Zinc Enolate Equivalents of Amide toward Benzaldehyde.

To take advantage of this low reactivity, the author developed the asymmetric addition of zinc enolate equivalents of amide to aldehydes in the presence of a catalytic amount of an optically active aminoalcohol. Various aldehydes could be applied in this reaction to afford the corresponding products in good yields with high enantioselectivities (Scheme 20).

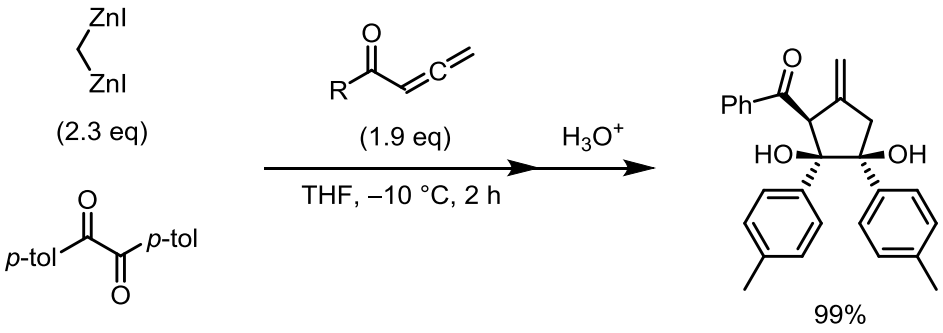


Scheme 20. Chiral Lewis Base-Catalyzed Asymmetric Reformatsky-Type Reaction.

4.4. Preparation of Enolate-Allyl Zinc Species by Means of Conjugate Addition of Bis(iodozincio)methane to Allenones (Chapter 4)

Highly functionalized cyclopentane moieties are widely found in biologically active compounds. Hence, synthesis of five-membered carbocycles with simultaneous introduction of heteroatoms into the carbon skeleton is greatly attractive. In light of this, the double nucleophilic addition of 1,3-dimetallic compounds with vicinal electrophiles would be one of the most ideal methods for the synthesis of highly functionalized five-membered rings.

In Chapter 4, the author confirmed that conjugate addition of *gem*-dizinc reagents to allenones generated the enolate-allyl zinc species, which are expected to be reactive 1,3-dimetallic compounds. In the presence of diketones, these 1,3-dizinc species underwent double nucleophilic addition to give highly functionalized cyclopentanes with perfect diastereoselectivity (Scheme 21).[23]

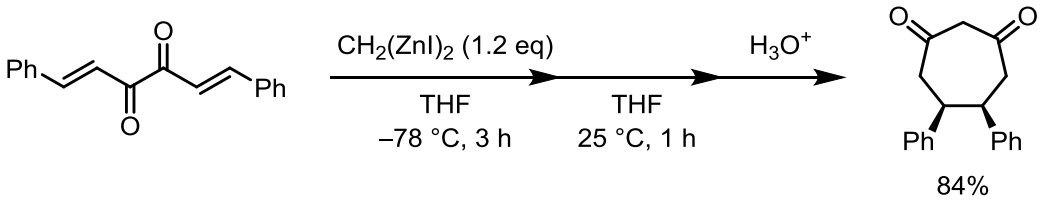


Scheme 21. Highly Functionalized Five-Membered Carbocycle Synthesis.

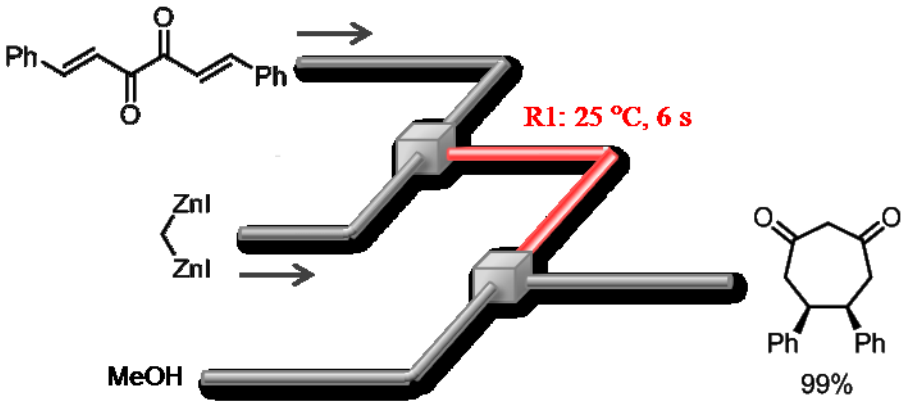
4.5. Preparation of Cycloheptane Ring by Nucleophilic Cyclopropanation of 1,2-Diketones with Bis(iodozincio)methane (Chapters 5)

Cope rearrangement of divinylcyclopropane has been recognized as an efficient route to 7-membered carbocycles because of the thermodynamic advantage by resulting from the strain release of cyclopropane. In this transformation, the stereochemistry of divinyl cyclopropane is very important. When *cis*-divinyl cyclopropane is used, the Cope rearrangement proceeds, even at low temperature. On the other hand, the *trans*-isomer does not readily undergo Cope

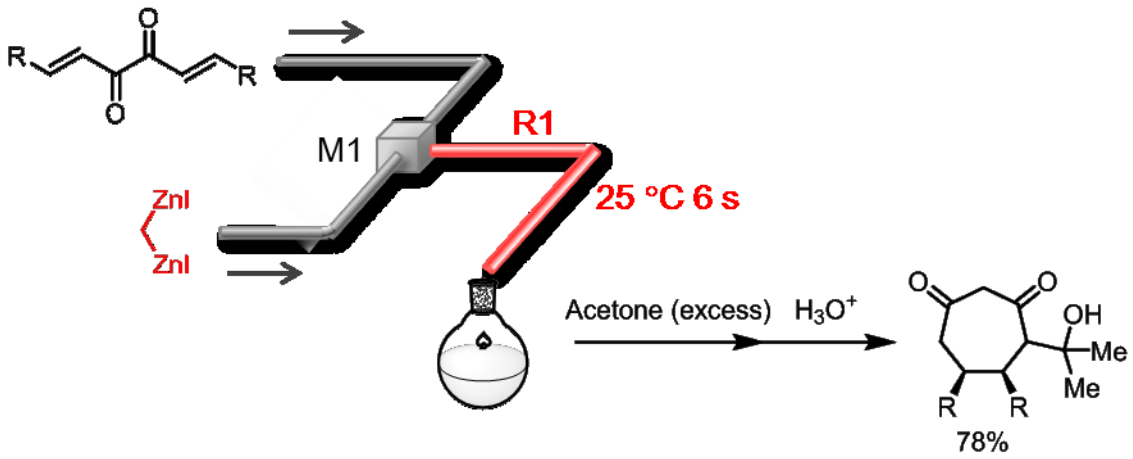
rearrangement due to the slight overlap of orbitals from the two olefin groups. Indeed, when *trans*-divinyl cyclopropane was used, very high temperatures were required for the reaction to proceed via isomerization of the *trans*-isomer to the *cis*-isomer. Thus, the stereoselective preparation of the *cis*-isomer is preferable. In Chapter 5, the author discussed the development of an effective cycloheptane synthesis, which involved the nucleophilic [2+1] cyclopropanation of diketone and subsequent oxy-Cope rearrangement to construct 7-membered carbocycles (Scheme 22).[24] He also found that the microflow system was the convenient for this reaction. In the microflow system, the 7-membered carbocycles were obtained at room temperature within 6 s (Scheme 23). Moreover, he found that the generated zinc enolate species could react with ketones to provide the corresponding aldol products (Scheme 24).



Scheme 22. [6+1] Cycloheptane Synthesis Using Diketones and Bis(iodozincio)methane.



Scheme 23. Microflow System for [6+1] Cycloheptane Synthesis Using Diketones and Bis(iodozincio)methane.



Scheme 24. Tandem Reaction of the Formed Zinc Enolate with Ketones.

References and Notes

1. (a) Ocampo, R.; Dolbier, Jr., W. R. *Tetrahedron* **2004**, *60*, 9325. (b) Choppin, S.; Ferreiro-Medeiros, L.; Barbarotto, M.; Colobert, F. *Chem. Soc. Rev.* **2013**, *42*, 937. (c) Fernández-Ibáñez, M. Á.; Maciá, B.; Alonso, D. A.; Pastor, I. M. *Eur. J. Org. Chem.* **2013**, 7028.
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Instrumental and Materials

^{1}H NMR (500 MHz), ^{13}C NMR (125.7 MHz) and ^{19}F NMR (188 MHz) spectra were taken on Varian UNITY INOVA 500 spectrometer using tetramethylsilane for ^{1}H NMR as an internal standard (δ = 0 ppm), $CDCl_3$ for ^{13}C NMR as an internal standard (δ = 77.0 ppm) and hexafluorobenzene for ^{19}F NMR as an internal standard (δ = 0 ppm). Mass spectra were recorded on a SHIMADZU GCMS-QP2010 Plus (EI) and a Thermo Scientific Exactive (ESI, APCI) spectrometers. High performance liquid chromatography (HPLC) was performed with a SHIMADZU Prominence. Infrared (IR) spectra were determined on a SHIMADZU IR Affinity-1 spectrometer. Melting points were determined using a YANAKO MP-500D. Optical rotations were measured on a HORIBA SEPA-200. X-ray data were taken on a Rigaku XtaLAB mini diffractometer equipped with a CCD detector. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and/or such as an aqueous alkaline $KMnO_4$ solution followed by heating. Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Unless otherwise noted, commercially available reagents were used without purification. THF and Et_2O were purchased from Kanto Chemical Co., stored under argon, and used as they are.

Chapter 1

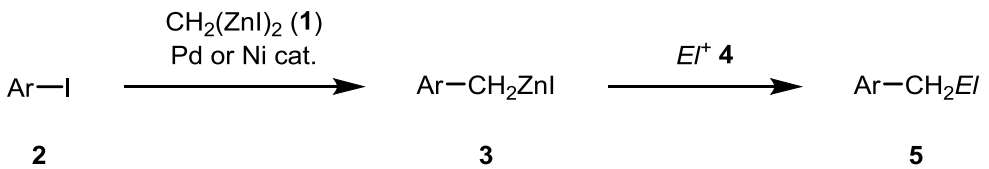
Preparation of an Arenylmethylzinc Reagent with Functional Groups by Chemoselective Cross-Coupling Reaction of Bis(iodozincio)methane with Iodoarenes

Palladium-catalyzed cross-coupling reaction of bis(iodozincio)methane with iodoarenes carrying various functionalities such as ester, boryl, cyano, and halo groups proceeded chemoselectively to give the corresponding arenylmethylzinc species efficiently. The moderate reactivity of the *gem*-dizinc reagent imparted functional group tolerance to the process. The obtained arenylmethylzinc species underwent the copper-mediated coupling reaction with a range of organic halides.

Introduction

Aromatic components are important structures for pharmaceuticals and materials, and their insertion has been studied intensively in order to synthesize many molecules.[1] Nucleophilic introduction of arene moieties is often performed by using the corresponding arenylmetals. Schlosser developed an approach for the preparation of highly functionalized arenyllithium through the oriented deprotonation method.[2] In addition, the formation of a functionalized arenylmagnesium from the magnesium amide is also an efficient route.[3] Compared with the established route for the preparation of highly functionalized arenylmetals, the homologous arenylmethylmetals with several functional groups have not been well studied, although they can also play a crucial role in the introduction of an aromatic skeleton. Recently, Knochel and co-workers reported an efficient route to heteroarenylmethylzinc reagents from iodoheteroarenes through magnesium–iodine exchange, chloromethylation, and reduction with Zn-LiCl.[4,5] Given that highly functional iodoarenes had been established by the oriented deprotonation method, this homologative method was considered to be an easily accessible and reasonable route.

Bis(iodozincio)methane (**1**),[6,7] which have two C–Zn bonds at the same carbon, works as a dianion equivalent. This reagent can be used to introduce the iodozinciomethyl group into substrates directly. Thus, the author tried to develop a shorter route from aryl iodide **2** to arenylmethylzinc reagent. As shown in Scheme 1, the cross-coupling reaction of **1** with **2** was examined in the presence of a transition-metal catalyst.[8]

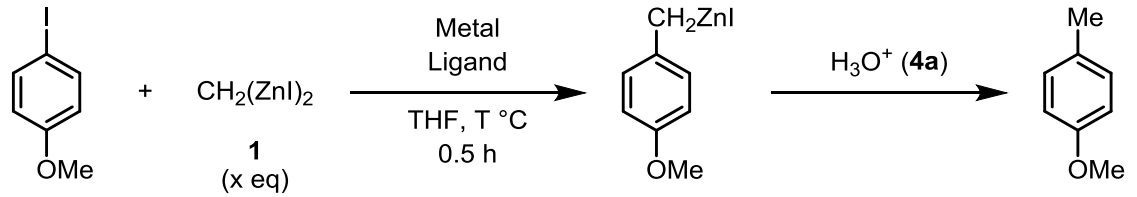


Scheme 1. Zinciomethylation of Iodoarenes.

Results and Discussion

To find an appropriate catalyst for the cross-coupling reaction, treatment of iodoanisole (**2a**) with bis(iodozincio)methane (**1**) was examined in the presence of palladium catalyst (5 mol %) with various ligands (Table 1).

Table 1. Optimization of Zinciomethylation of **2a**.[a]



2a **3a** **5aa**

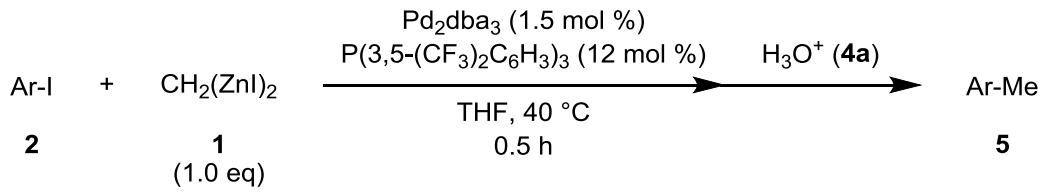
entry	x (eq)	T (° C)	Metal (mol %)	Ligand (mol %)	Yield of **5aa** (%)[b]
1	1.1	25	$PdCl_2$ (5)	PPh_3 (10)	<5
2	1.1	25	$PdCl_2$ (5)	$P(OEt)_3$ (10)	<5
3	1.1	25	$PdCl_2$ (5)	P(2-furyl)$_3$ (10)	<5
4	1.1	25	$PdCl_2$ (5)	P(3-$CF_3C_6H_4$)$_3$ (10)	19
5	1.1	25	$PdCl_2$ (5)	P(3,5-$(CF_3)_2C_6H_3$)$_3$ (10)	45
6	1.1	25	Pd_2dba_3 (2.5)	P(3,5-$(CF_3)_2C_6H_3$)$_3$ (10)	50
7	1.1	40	Pd_2dba_3 (2.5)	P(3,5-$(CF_3)_2C_6H_3$)$_3$ (10)	22
8	1.1	40	Pd_2dba_3 (2.5)	P(3,5-$(CF_3)_2C_6H_3$)$_3$ (20)	91
9	1.0	40	Pd_2dba_3 (2.5)	P(3,5-$(CF_3)_2C_6H_3$)$_3$ (20)	99
10	1.0	40	Pd_2dba_3 (1.5)	P(3,5-$(CF_3)_2C_6H_3$)$_3$ (12)	93

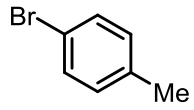
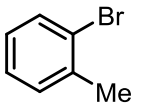
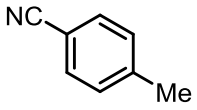
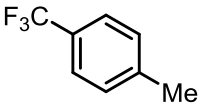
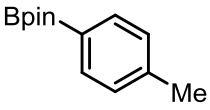
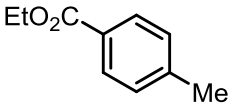
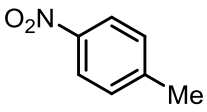
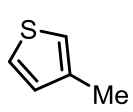
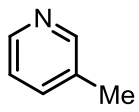
[a] Reactions were carried out using *gem*-dizinc **1** and iodoarene **2a** (1.0 mmol) in THF (6.8 mL). [b] Yields were determined by GC analysis using dodecane as an internal standard.

The obtained arenylmethylzinc species **3a** was quenched with 1 M aqueous HCl and its yield was estimated by the amount of 4-methoxytoluene (**5aa**). A use of the electron-deficient

ligand, tris(3,5-bis(trifluoromethyl)phenyl)phosphine, gave good results. As the migrating iodozinciomethyl group can be regarded as an electron-rich moiety, the electron-withdrawing ligand might be necessary for the transmetalation and the reductive elimination.[9] The use of Pd_2dba_3 as a palladium source resulted in satisfactory yield (entries 5 and 6). Further tuning of the reaction temperature and the ratio of the ligand gave the product in excellent yields (entries 6–10). The further cross-coupling product, bis(4-methoxyphenyl)methane, was not identified in the reaction mixture.[10]

Scheme 2. Zinciomethylation of Iodoarenes Bearing a Functional Group.[a]

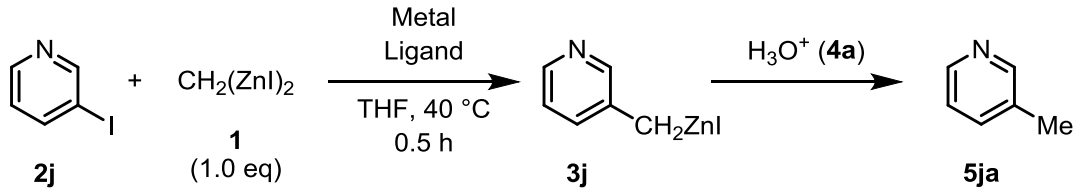


Product.[b]		
		
5ba (92%)	**5ca** (86%)	**5da** (87%)
		
5ea (76%)	**5fa** (99%)	**5ga** (89%)
		
5ha (12%)	**5ia** (73%)	**5ja** (20%)

[a] Reactions were carried out using *gem*-dizinc **1** (1.0 mmol), iodoarene **2** (1.0 mmol), Pd_2dba_3 (0.015 mmol), and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (0.12 mmol) in THF (6.8 mL). [b] Yields were determined by GC analysis using dodecane as an internal standard.

As shown in Scheme 2, the functional group tolerance of this coupling reaction was examined. Halo, cyano, trifluoromethyl, boryl, and ester groups did not disturb the transformation; however, 4-nitro-1-iodobenzene afforded the corresponding zinc reagent in only 12% yield. The zinciomethylation of 3-iodopyridine under the Pd catalyst also gave the corresponding coupling product in low yield. To achieve high yield in the cross-coupling reaction of 3-iodopyridine, the use of nickel catalyst instead of a palladium catalyst was shown to be effective (Table 2). Especially, the catalyst prepared from $NiCl_2$ (5 mol %) and PPh_3 (10 mol %) gave the cross-coupling product in 99% yield (entry 8).

Table 2. Optimization of Zinciomethylation of **2j**.[a]



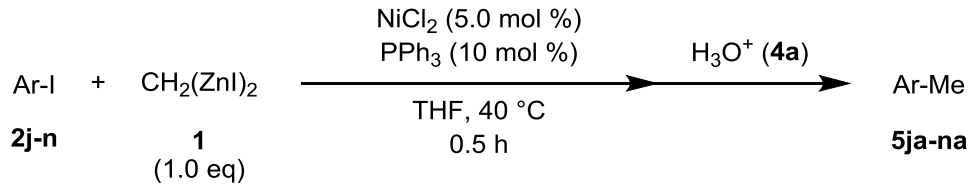
entry	Metal (mol %), Ligand (mol %)	Yield of **5ja** (%)[b]
1	Pd_2dba_3 (2.5), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (20)	20
2	Pd_2dba_3 (2.5), $P(2\text{-furyl})_3$ (20)	10
3	$NiCl_2$dppp (5)	40
4	$NiCl_2$dppe (5)	38
5	$NiCl_2(PPh_3)_2$ (5)	76
6	$NiCl_2$ (5), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (10)	2
7	$NiCl_2$ (5), $P(2\text{-furyl})_3$ (10)	38
8	$NiCl_2$ (5), PPh_3 (10)	99

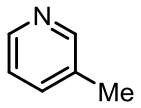
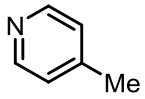
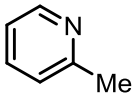
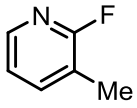
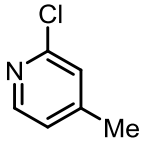
[a] Reactions were carried out using *gem*-dizinc **1** (1.0 mmol) and iodoarene **2j** (1.0 mmol) in THF (6.8 mL). [b] Yields were determined by GC analysis using dodecane as an internal standard.

As shown in Scheme 3, a range of iodopyridines were examined as substrate for the cross-coupling reaction with *gem*-dizinc **1** in the presence of nickel catalyst. Fluoro and chloro

groups did not disturb the reaction (**5ma**, **5na**).

Scheme 3. Zinciomethylation of Iodopyridines **2j-n**.[a]

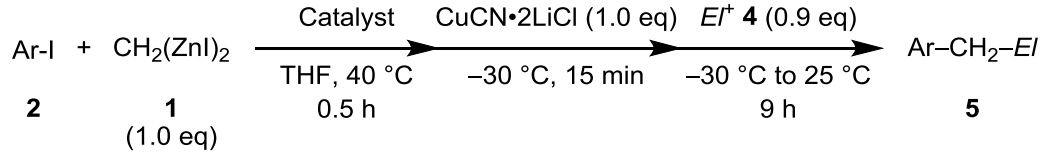


Product.[b]				
				
5ja (99%)	**5ka** (74%)	**5la** (71%)	**5ma** (45%)	**5na** (30%)

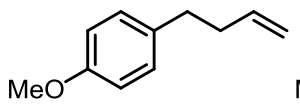
[a] Reactions were carried out using *gem*-dizinc **1** (1.0 mmol), iodopyridines **2j-n (**1.0 mmol), $NiCl_2$ (0.05 mmol), and PPh_3 (0.1 mmol) in THF (6.8 mL). [b] Yields were determined by GC analysis using dodecane as an internal standard.

The copper-mediated reactions of the arenylmethylzinc reagents, which had been prepared from iodoarenes (**2a,j**) and *gem*-dizinc **1**, with various electrophiles are shown in Table 3. Allyl- and propargyl bromide gave the coupling compounds regioselectively. The use of benzoyl cyanide gave arenylmethyl phenyl ketones in good yields. Instead of benzoyl cyanide, the use of benzoyl chloride resulted in the formation of 4-benzoyloxy-1-halobutane, which was formed by a ring-opening of THF.

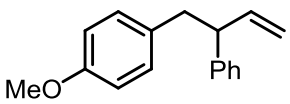
Scheme 4. Sequential Reaction of Arenylmethylzinc with Electrophiles Mediated by Copper Salt.



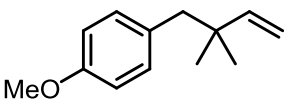
entry	**2**	Catalyst (mol %)	El^+	Yield of **5** (%)[c]
1[a]	**2a**	Pd (3)	allyl bromide (**4b**)	91 (**5ab**)
2[a]	**2a**	Pd (3)	cinnamyl bromide (**4c**)	68 (**5ac**)
3[a]	**2a**	Pd (3)	prenyl bromide (**4d**)	81 (**5ad**)
4[a]	**2a**	Pd (3)	propargyl bromide (**4e**)	91 (**5ae**)
5[a]	**2a**	Pd (3)	benzoyl cyanide (**4f**)	91 (**5af**)
6[b]	**2j**	Ni (5)	allyl bromide (**4b**)	65 (**5jb**)
7[b]	**2j**	Ni (5)	cinnamyl bromide (**4c**)	75 (**5jc**)
8[b]	**2j**	Ni (5)	prenyl bromide (**4d**)	59 (**5jd**)
9[b]	**2j**	Ni (5)	propargyl bromide (**4e**)	61 (**5je**)
10[b]	**2j**	Ni (5)	benzoyl cyanide (**4f**)	55 (**5jf**)



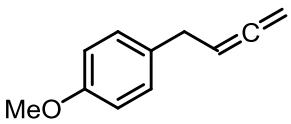
5ab



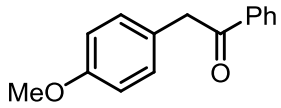
5ac



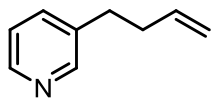
5ad



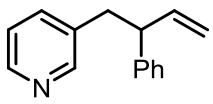
5ae



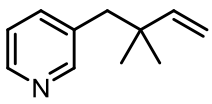
5af



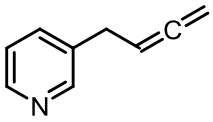
5jb



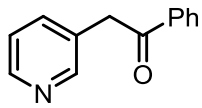
5jc



5jd



5je

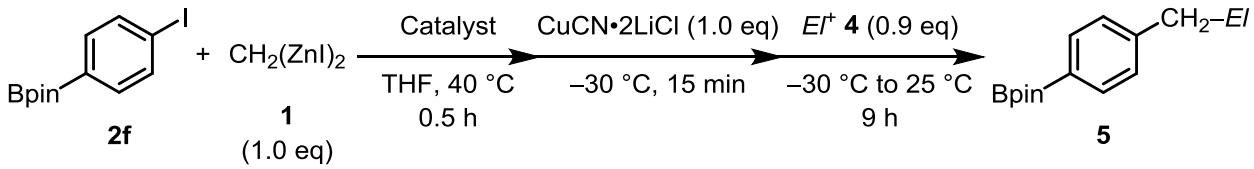


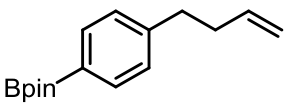
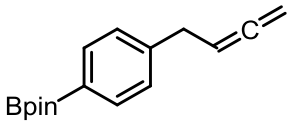
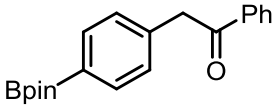
5jf

[a] Reactions were carried out using *gem*-dizinc **1** (1.0 mmol), iodoarene **2a** (1.0 mmol), Pd_2dba_3 (0.015 mmol), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (0.12 mmol), CuCN·2LiCl (1.0 mmol), and El^+ **4** (0.9 mmol) in THF (8.3 mL). [b] Reactions were carried out using *gem*-dizinc **1** (1.0 mmol), iodoarene **2j** (1.0 mmol), $NiCl_2$ (0.05 mmol), PPh_3 (0.1 mmol), CuCN·2LiCl (1.0 mmol), and El^+ **4** (0.9 mmol) in THF (8.3 mL). [c] Isolated yields.

As described above, the merit of the present method is the functional group tolerance. As shown in Scheme 5, the Bpin group remained intact throughout the whole transformation. Starting from the pinacol ester of 4-iodophenylboronic acid **2f**, the iodozinciomethylation and the copper-mediated coupling with a range of halides afforded various organoboronic acid esters. These products can be transformed into various aromatic compounds through the Suzuki–Miyaura coupling reaction.

Scheme 5. Reaction of the Pinacol Ester of 4-Iodophenylboronic Acids (**2f**).[a]



Product.[b]		
		
5fb (97%)	**5fe** (63%)	**5ff** (52%)

[a] Reactions were carried out using *gem*-dizinc **1** (1.0 mmol), iodoanisole (**2a**, 1.0 mmol), Pd_2dba_3 (0.015 mmol), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (0.12 mmol), CuCN·2LiCl (1.0 mmol), and El^+ **4** (0.9 mmol) in THF (8.3 mL). [b] Isolated yields.

Conclusion

In conclusion, the author have shown a novel method that can be used to prepare the arenylmethylzinc reagent bearing functional groups. The introduction of the C–Zn bond was performed by zinciomethylation through transition-metal-catalyzed cross-coupling reaction, so the higher functional tolerance compared with the existing methods was demonstrated.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. Zinc powder was used after washing with 10% HCl according to the reported procedure.[11] All iodoarenes listed in Chapter 1 were commercially available. Tris(dibenzylideneacetone)dipalladium, nickel(II) chloride, triphenylphosphine, and tris(3,5-bis(trifluoromethyl)phenyl)phosphine were commercially available.

Preparation of bis(iodozincio)methane (1)

A mixture of pure zinc dust (150 mmol), diiodomethane (1.0 mmol), and $PbCl_2$ (0.005 mmol) in THF (5.0 mL) was sonicated for 1 h in an ultrasonic cleaner bath under Ar. When pyrometallurgy zinc dust was used instead of pure zinc, it is not necessary to add $PbCl_2$. Both of pure zinc and pyrometallurgy zinc are commercially available. To the mixture, diiodomethane (50 mmol) in THF (45 mL) was added dropwise over 30 min at 0 °C with vigorous stirring. The mixture was stirred for 4 h at 25 °C. After the stirring was stopped, the reaction vessel was allowed to stand undisturbed for several hours. Excess zinc was separated by sedimentation. ^{1}H NMR spectra of the obtained supernatant showed a broad singlet at –1.2 ppm at 0 °C, which corresponded to the methylene proton of **1**. The supernatant was used for the further reaction as a solution of 1 in THF (0.1–0.5 M). Bis(iodozincio)methane in THF can be kept unchanged at least for a month in a sealed reaction vessel.

General procedure for the cross-coupling reaction of bis(iodozincio)methane with iodoarenes

To a mixture of Pd_2dba_3 (0.015 mmol, 13.7 mg) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (0.12 mmol, 74.4 mg) in THF (2 mL), a solution of iodoarenes **2** (1.0 mmol, 330 mg) in THF (2.0 mL) was added.

The mixture was stirred for 5 min at 40 °C, then a solution of bis(iodozincio)methane (**1**, 0.36 M in THF, 1.0 mmol, 2.8 mL) was added. The resulting mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched by aqueous work-up (sat. aq NH_4Cl) and the organic layer was extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the corresponding coupling product **5**.

General procedure for the cross-coupling reaction of bis(iodozincio)methane with iodopyridines

To a mixture of $NiCl_2$ (0.015 mmol, 13.7 mg) and PPh_3 (0.12 mmol, 74.4 mg) in THF (2 mL), a solution of iodopyridines **2** (1.0 mmol, 330 mg) in THF (2.0 mL) was added. The mixture was stirred for 5 min at 40 °C, then a solution of bis(iodozincio)methane (**1**, 0.36 M in THF, 1.0 mmol, 2.8 mL) was added. The resulting mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched by aqueous work-up (sat. aq NH_4Cl) and the organic layer was extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the corresponding coupling product **5**.

General procedure for the sequential reaction of arenylmethylzinc with electrophiles mediated by copper salt

To a mixture of Pd_2dba_3 (0.015 mmol, 13.7 mg) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (0.12 mmol, 74.4 mg) in THF (2 mL) or a mixture of $NiCl_2$ (0.015 mmol, 13.7 mg) and PPh_3 (0.12 mmol, 74.4 mg) in THF (2 mL), iodoarenes **2** (1.0 mmol, 330 mg) in THF (2.0 mL) was added. The mixture was stirred for 5 min at 40 °C, then a solution of bis(iodozincio)methane (**1**, 0.36 M in THF, 1.0 mmol, 2.8 mL) was added. The resulting mixture was stirred for 30 min at the same temperature. The mixture was cooled to –30 °C, then a solution of CuCN·2LiCl (1.0 M in THF, 1.0 mmol, 1.0 mL) was added and the resulting mixture was stirred for 15 min at the same temperature. A

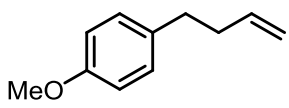
solution of electrophiles (0.9 mmol, 118 mg) in THF (0.5 mL) was added at the same temperature and the mixture was stirred for 10 h at 25 °C. The reaction mixture was quenched by aqueous work-up (sat. aq NH_4Cl) and the organic layer was extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product. Purification on a neutral silica gel column chromatography gave the corresponding product **5**.

General procedure for the sequential reaction of arenylmethylzinc bearing pinacol ester of boronic acid with electrophiles mediated by copper salt

To a mixture of Pd_2dba_3 (0.015 mmol, 13.7 mg) and $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (0.12 mmol, 74.4 mg) in THF (2 mL), a solution of **2** (1.0 mmol, 330 mg) in THF (2.0 mL) was added. The mixture was stirred for 5 min at 40 °C, then a solution of bis(iodozincio)methane (**1**, 0.36 M in THF, 1.0 mmol, 2.8 mL) was added. The resulting mixture was stirred for 30 min at the same temperature. The mixture was cooled to –30 °C, then a solution of CuCN·2LiCl (1.0 M in THF, 1.0 mmol, 1.0 mL) was added and the resulting mixture was stirred for 15 min at the same temperature. A solution of benzoyl cyanide (0.9 mmol, 118 mg) in THF (0.5 mL) was added at the same temperature and the mixture was stirred for 10 h at 25 °C. The reaction mixture was quenched by aqueous work-up (sat. aq NH_4Cl) and the organic layer was extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product. Purification by silica gel column chromatography (5 wt% boric acid) gave the corresponding compound **5**.

Characterization data

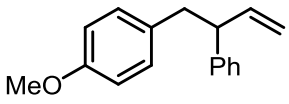
1-(But-3-en-1-yl)-4-methoxybenzene (5ab): CAS RN [20574-98-5].



Yellow oil. ^1H NMR ($CDCl_3$) δ 7.15 (ddd, J = 8.5, 3.0, 2.5 Hz, 2H), 6.87 (ddd, J = 9.0, 3.0, 2.5 Hz, 2H), 5.90 (ddt, J = 17.0, 10.0, 7.0 Hz,

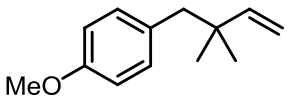
1H), 5.08 (ddt, *J* = 17.0, 2.0, 2.0 Hz, 1H), 5.02 (ddt, *J* = 10.0, 2.0, 1.0 Hz, 1H), 3.82 (s, 3H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.38 (ttd, *J* = 7.5, 7.0, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 157.7, 138.1, 133.9, 129.3, 114.8, 113.6, 55.2, 35.8, 34.4.

1-Methoxy-4-(2-phenylbut-3-en-1-yl)benzene (5ac): CAS RN [1244556-55-5].



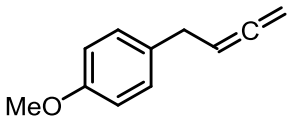
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 7.19 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.15 (m, 2H), 6.97 (dd, *J* = 9.5, 2.5 Hz, 2H), 6.76 (dd, *J* = 9.5, 2.5 Hz, 2H), 6.02 (ddd, *J* = 17.0, 10.5, 7.5 Hz, 1H), 5.02 (ddd, *J* = 10.5, 1.5, 1.0 Hz, 1H), 4.95 (ddd, *J* = 17.0, 1.5, 1.5 Hz, 1H), 3.76 (s, 3H), 3.52 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.46 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 157.7, 143.7, 141.4, 132.1, 130.1, 128.3, 127.8, 126.2, 114.7, 113.4, 55.1, 51.8, 41.3.

1-(2,2-Dimethylbut-3-en-1-yl)-4-methoxybenzene (5ad): CAS RN [140836-84-6].



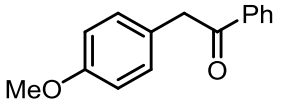
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.03 (ddd, *J* = 9.0, 3.0, 2.5 Hz, 2H), 6.80 (ddd, *J* = 8.5, 3.0, 2.5 Hz, 2H), 5.85 (dd, *J* = 17.5, 11.0 Hz, 1H), 4.91 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.85 (dd, *J* = 17.5, 1.5 Hz, 1H), 3.79 (s, 3H), 2.52 (s, 2H), 0.98 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 157.8, 148.2, 131.4, 130.9, 112.9, 110.4, 55.1, 48.1, 37.7, 26.3.

1-(Buta-2,3-dien-1-yl)-4-methoxybenzene (5ae): CAS RN [343950-65-2].



Yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.19 (ddd, *J* = 9.0, 3.0, 2.5 Hz, 2H), 6.89 (ddd, *J* = 9.0, 3.0, 2.5 Hz, 2H), 5.30 (tt, *J* = 7.0, 6.5 Hz, 1H), 4.76 (dt, *J* = 6.5, 3.0 Hz, 2H), 3.83 (s, 3H), 3.35 (dt, *J* = 7.0, 3.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 208.8, 158.0, 132.2, 129.3, 113.7, 89.9, 75.0, 55.1, 34.2.

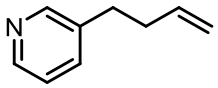
2-(4-Methoxyphenyl)-1-phenylethan-1-one (5af): CAS RN [24845-40-7].



Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.03 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.46 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 2H), 7.21 (ddd, *J* =

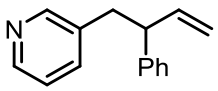
8.5, 3.0, 2.5 Hz, 2H), 6.89 (ddd, *J* = 8.5, 3.0, 2.5 Hz, 2H), 4.24 (s, 2H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.8, 158.4, 136.4, 133.0, 130.4, 128.5, 128.4, 126.3, 114.0, 55.1, 44.4.

3-(But-3-en-1-yl)pyridine (5jb): CAS RN [71532-24-6].



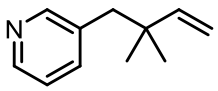
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.44 (m, 2H), 7.49 (ddd, *J* = 7.5, 2.0, 1.5 Hz, 1H), 7.20 (dd, *J* = 7.5, 5.0 Hz, 1H), 5.82 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.01 (m, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.37 (dd, *J* = 7.5, 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 150.0, 147.4, 137.1, 136.9, 135.8, 123.2, 115.6, 35.1, 32.4.

3-(2-Phenylbut-3-en-1-yl)pyridine (5jc).



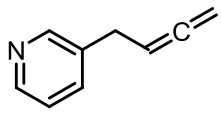
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.46 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.38 (d, *J* = 1.5 Hz, 1H), 7.35 (m, 3H), 7.26 (m, 1H), 7.19 (m, 3H), 6.08 (ddd, *J* = 17.5, 10.0, 7.5 Hz, 1H), 5.12 (ddd, *J* = 10.5, 1.0, 1.0 Hz, 1H), 5.05 (ddd, *J* = 17.5, 1.5, 1.0 Hz, 1H), 3.59 (ddd, *J* = 8.0, 7.5, 7.5 Hz, 1H), 3.11 (dd, *J* = 13.5, 7.5 Hz, 1H), 3.05 (dd, *J* = 13.5, 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 150.5, 147.4, 142.7, 140,6, 136.6, 135.3, 128.5, 127.7, 126.6, 123.0, 115.2, 51.4, 39.2. TLC: R_f 0.26 (hexane/EtOAc = 2:1). IR (neat) 3027.4, 2923.3, 1734.1, 1637.6, 1601.0, 1575.0, 1479.5, 1452.5, 1422.6, 1243.2, 1192.1, 1074.4, 1027.1, 994.4, 917.2, 799.5, 755.2, 714.7, 701.2 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{15}N$: $[M]^+$, 209.1204. Found: *m/z* 209.1201.

3-(2,2-Dimethylbut-3-en-1-yl)pyridine (5jd).



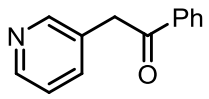
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.41 (m, 2H), 7.45 (m, 1H), 7.22 (m, 1H), 5.81 (dd, *J* = 17.5, 11.0 Hz, 1H), 4.94 (dd, *J* = 11.0, 1.0 Hz, 1H), 4.82 (dd, *J* = 17.5, 1.0 Hz, 1H), 2.57 (s, 2H), 1.00 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 151.1, 147.1, 146.9, 138.0, 134.3, 122.7, 111.5, 46.0, 26.3, 17.6. TLC: R_f 0.32 (hexane/EtOAc = 2:1). IR (neat) 2964.7, 2929.0, 2363.9, 1575.9, 1476.6, 1457.3, 1419.7, 1363.7, 1190.1, 1027.1, 1007.9, 912.4, 798.6, 714.7 cm^{-1}. HRMS (ESI) Calcd for $C_{11}H_{15}N$: $[M]^+$, 161.1204. Found: *m/z* 161.1202.

3-(Buta-2,3-dien-1-yl)pyridine (5je).



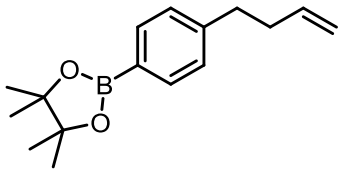
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.45 (m, 2H), 7.53 (m, 1H), 7.21 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 5.25 (tt, *J* = 7.0, 7.0 Hz, 1H), 4.71 (dt, *J* = 7.0, 3.0 Hz, 2H), 3.33 (dt, *J* = 7.0, 3.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 209.0, 149.9, 147.7, 136.0, 135.4, 123.2, 88.7, 75.8, 32.0. TLC: R_f 0.26 (hexane/EtOAc = 2:1). IR (neat) 2964.7, 2933.9, 2889.5, 2878.9, 2363.9, 2340.7, 1955.9, 1718.7, 1576.9, 1476.6, 1423.5, 1270.2, 1118.8, 1103.3, 1027.1, 851.6, 713.7 cm^{-1}. HRMS (EI) Calcd for C_9H_8N: $[M–H]^+$, 130.0657. Found: *m/z* 130.0654.

1-Phenyl-2-(pyridin-3-yl)ethan-1-one (5jf): CAS RN [1081-48-7].



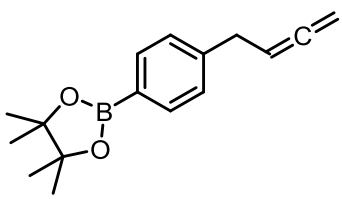
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.54 (br s, 2H), 8.03 (m, 2H), 7.28 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.60 (m, 2H), 7.50 (m, 2H), 4.31 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 196.4, 150.6, 148.3, 137.2, 136.1, 133.5, 130.1, 128.7, 128.3, 123.4, 42.2.

2-(4-(But-3-en-1-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5fb).



Yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 5.9–5.8 (m, 1H), 5.06 (ddt, *J* = 17.0, 1.5, 1.0 Hz, 1H), 5.00 (ddd, *J* = 10.0, 1.5, 1.0 Hz, 1H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.40 (dtt, *J* = 7.5, 7.5, 1.0 Hz, 2H), 1.36 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 145.2, 137.9, 134.8, 127.9, 114.9, 83.6, 35.5, 35.3, 24.8. TLC: R_f 0.56 (hexane/EtOAc = 10:1). IR (neat) 2978.2, 2931.0, 1641.5, 1612.6, 1517.1, 1452.5, 1399.4, 1361.8, 1320.3, 1272.1, 1214.2, 1145.8, 1089.8, 1022.3, 962.5, 912.4, 860.3, 825.6 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{23}O_2BNa$: $[M+Na]^+$, 281.1683. Found: *m/z* 281.1683.

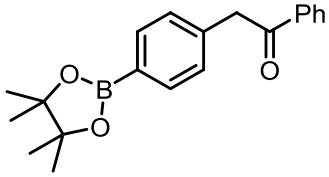
2-(4-(Buta-2,3-dien-1-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5fe).



White solid. ^{1}H NMR ($CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 5.27 (dt, *J* = 7.0, 7.0 Hz, 1H), 4.73 (dt, *J* = 7.0, 3.0 Hz, 2H), 3.38 (dt, *J* = 7.0, 3.0 Hz, 2H), 1.35 (s, 12 H). ^{13}C NMR

($CDCl_3$) δ 143.6, 135.2, 134.9, 128.0, 127.8, 89.2, 83.6, 75.2, 35.2, 24.8. Mp. 33.0–33.4 °C. TLC: R_f 0.47 (hexane/EtOAc = 10:1). IR (KBr) 2979.2, 1954.9, 1612.6, 1513.2, 1399.4, 1364.7, 1325.2, 1267.3, 1211.4, 1143.8, 1089.8, 1020.4, 963.5, 893.1, 860.3, 839.1, 823.6, 739.7, 659.7 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{21}O_2BNa$: $[M+Na]^+$, 279.1527. Found: *m/z* 279.1515.

1-Phenyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (5ff).



Yellow solid. ^1H NMR ($CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.54 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.30 (s, 2H), 1.33 (s, 12H). ^{13}C NMR ($CDCl_3$) δ 197.4, 137.7, 136.4, 135.1, 133.1, 130.1, 128.8, 128.6, 128.4, 83.7, 45.8, 24.8. Mp. 94.2–95.0 °C. TLC: R_f 0.43 (hexane/EtOAc = 4:1). IR (KBr) 2938.0, 2935.8, 1671.4, 1612.6, 1400.4, 1363.7, 1331.9, 1276.9, 1143.8, 1092.7, 1019.4, 966.4, 862.2, 694.4, 654.9 cm^{-1}. HRMS (ESI) Calcd for $C_{20}H_{23}O_3BK$: $[M+K]^+$, 361.1372. Found: *m/z* 361.1359.

References and Notes

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7. (a) Sada, M.; Uchiyama, M.; Matsubara, S. *Synlett* **2014**, *25*, 2831. (b) Sada, M.; Komagawa, S.; Uchiyama, M.; Kobata, M.; Mizuno, T.; Utimoto, K.; Oshima, K.; Matsubara, S. *J. Am. Chem. Soc.* **2010**, *132*, 17452. (c) Haraguchi, R.; Matsubara, S. *Synthesis* **2014**, *46*, 2272.
8. Yoshino, H.; Toda, N.; Kobata, M.; Ukai, K.; Oshima, K.; Utimoto, K.; Matsubara, S. *Chem. Eur. J.* **2006**, *12*, 721.
9. (a) Kanemoto, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Chem. Lett.* **1987**, *16*, 5. (b) Goliaszewski, A.; Schwartz, J. *Organometallics* **1985**, *4*, 417.
10. To perform the cross-coupling between the formed arenylmethylzinc iodide and iodoarene by Pd catalyst, the author found that LiCl (1.0 eq) plays a crucial role. As shown in Scheme 5, 4-methoxyphenylmethylzinc iodide, which was prepared from 4-methoxy-1-iodobenzene and bis(iodozincio)methane in the presence of Pd catalyst, was treated with *p*-tolyl iodide in the presence of a stoichiometric amount of LiCl and an additional Pd catalyst (PEPPSI-IPr) to afford 1-methoxy-4-(4-methylbenzyl)benzene in 81% yield. Without the addition of LiCl, no cross-coupling product was observed.

11. Fieser, L. F. and Fieser, M. *Reagents for Organic Synthesis*, Wiley: New York, 1967; Vol. 1. p. 1276.

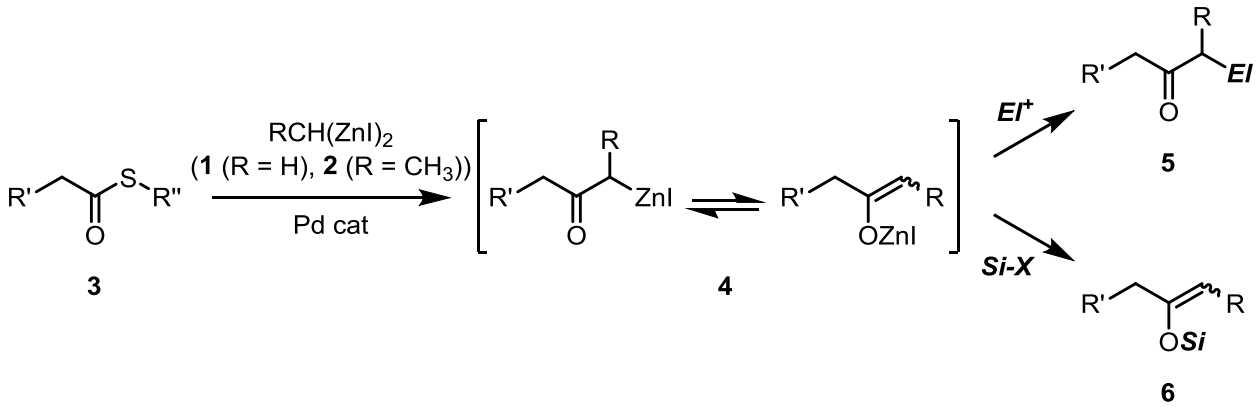
Chapter 2

Chemo- and Regioselective Preparation of Zinc Enolate from Thiol Esters by Palladium Catalyzed Cross-Coupling Reaction

The palladium catalyzed cross-coupling reaction of thiol esters with bis(iodozincio)methane or 1,1-bis(iodozincio)ethane gave Reformatsky-type enolates. They can react with some electrophiles to give the corresponding adducts and were also trapped by silylation reagents to afford silyl enol ethers. As the method applicable to the thiol ester carrying ketone moiety, it afforded zinc enolates carrying ketone in the same molecule

Introduction

Bis(iodozincio)methane (**1**) and 1,1-bis(iodozincio)ethane (**2**), which are easily prepared from the corresponding *gem*-diiodoalkane and zinc powder in the presence of Pb catalyst, have been utilized in organic reactions.[1,2] These reagents work as a nucleophile to carbonyl compounds as a dianion equivalent with the function as a bidentate Lewis acid. Especially, bis(iodozincio)methane (**1**) has offered various specific and characteristic molecular transformations, such as Wittig-type methylenation reaction of easily enolizable ketones,[3] nucleophilic cyclopropanation reaction of 1,2-diketones,[4] ring contraction via 1,4-addition to cyclic enones,[5] and so on.[6] It can also work as a cross-coupling-partner with organic halides and their equivalents;[7] iodozinciomethylation of organic halides by a transition-metal catalyzed cross-coupling reaction resulted in the homologative organozinc reagent formation.[8] Using this strategy, Matsubara had tried to prepare a zinc enolate through the coupling reaction of **1** with acylating reagents. However, treatment of acyl chloride with *gem*-dizinc **1** in the presence of Pd catalysis afforded symmetrical 1,3-diketones.[9] The formation of the duplicated acylation of *gem*-dizinc **1** was observed, regardless of the stoichiometric relationship. The high reactivity of acyl chloride cannot ignore the existence of the formed zinc enolate equivalent, which was quenched immediately with the starting acyl chloride to give the symmetrical 1,3-diketone. In order to use the formed zinc enolate equivalent as a synthetic tool, the milder acylating reagent, which is hard to react with the zinc enolate, should be used. From this viewpoint, the author chose a thiol ester, which had been used for the ketone synthesis by a cross-coupling with alkylzinc species.[10] As a result, he can perform chemoselective cross-coupling of *gem*-dizinc **1** or **2** with a thiol ester carrying various functional group;[11] the transformation gave a route to obtain the zinc enolate carrying even ketone moiety, that had been difficult to be prepared by the classical method.[12] The obtained zinc enolates **4** can be used as a *C*-nucleophile and also as a precursor for silyl enol ethers (Scheme 1).



Scheme 1. Preparation and Reaction of the Zinc Enolate by Pd-Catalyzed Zincioalkylation of a Thiol Ester.

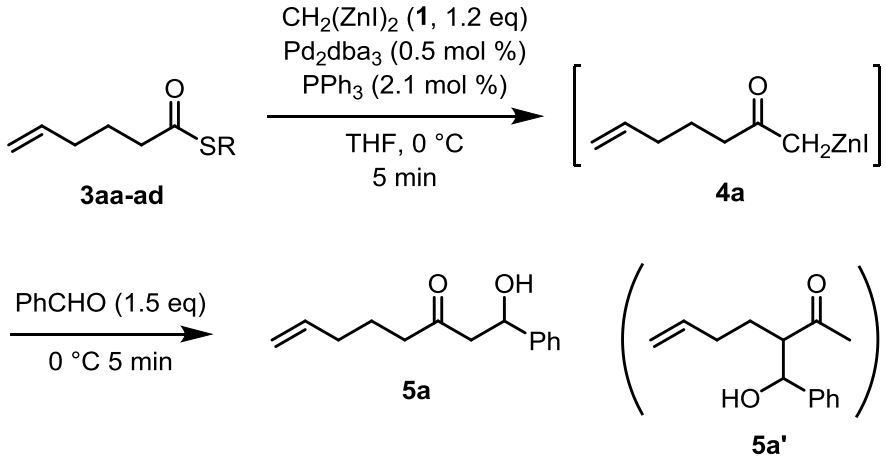
Results and Discussion

According to palladium catalyzed cross-coupling reaction of *S*-ethyl alkanethioate and ethylzinc iodide,[10,13] the author started the cross-coupling reaction of bis(iodozincio)methane (**1**) and a thiol ester[14] using Pd/PPh_3 catalyst. As shown in Table 1, arenethiol esters of 5-hexenoic acid **3aa-ac** were treated with bis(iodozincio)methane (**1**) in the presence of the catalyst, prepared from Pd_2dba_3 and triphenylphosphine, and reacted subsequently with benzaldehyde. The electron density of the benzene ring of thiols affected the yield. The aldol product **5a** was obtained quantitatively, starting from 4-nitrobenzenethiol ester **3ac** (entry 3). Regioisomeric aldol product **5a'**, which may be formed by an isomerization of the initially formed enolate, was not observed. Use of the ethane thiol **3ad** ester as a substrate, which is a typical substrate for Fukuyama ketone synthesis,[9] resulted in the recovery of the starting material in this case (entry 4).

Various electrophiles can be applied as a substrate to the obtained enolate, as shown in Table 2. A reaction with acyl cyanides gave 1,3-diketones. A conjugate addition was not observed in the reaction with (*E*)-MeCH=CHCOPh (entry 7). Tolerance of functional groups in this enolate

formation was also appealed: Primary bromide (entry 11), silyl ether (entry 14), and ester (entry 15) were intact during the reaction. Bromobenzene (entry12) did not disturb the formation of the enolate, although it often interacts with palladium catalyst.

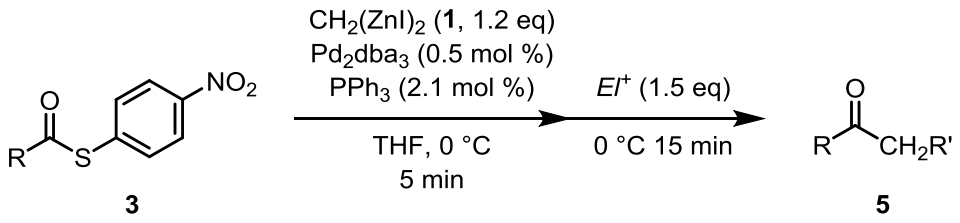
Table 1. Preparation and Reaction with Benzaldehyde of the Zinc Enolate from Thiol Ester **3aa-ad**.[a]



entry	R	Yield of **5a** (%)[b]	Yield of **5a'** (%)[b]	Recovery of **3** (%)[b]
1	Ph (**3aa**)	90	<1	10
2	4-$MeOC_6H_4$ (**3ab**)	74	<1	21
3	4-$NO_2C_6H_4$ (**3ac**)	>99	<1	<1
4	Et (**3ad**)	<1	<1	87

[a] Reactions were carried out using *gem*-dizinc **1** (1.2 mmol), thiol ester **3** (1.0 mmol), Pd_2dba_3 (0.005 mmol), PPh_3 (0.021 mmol), and PhCHO (1.5 mmol) in THF (8.3 mL).
[b] Yields of **5a** and **5a'** and recovery of **3** were determined by ^1H NMR using dibromomethane as an internal standard.

Table 2. Reaction of the Enolate from Thiol Esters **3** with Various Electrophiles.[a]



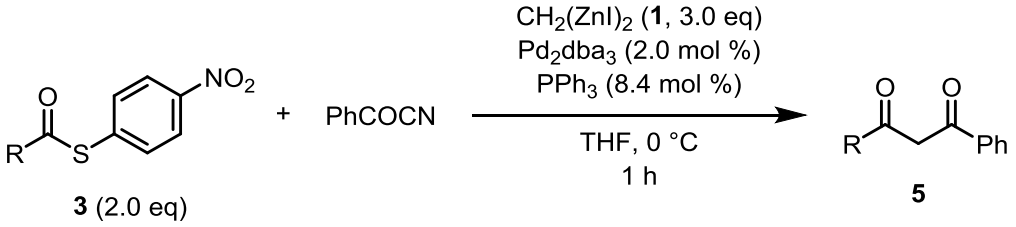
Entry	R	El^+	R' in **5**	Yield of **5** (%)[b]
1	$Ph(CH_2)_2$ (**3b**)	PhCOCN	PhCO	89 (**5ba**)
2	$Ph(CH_2)_2$ (**3b**)	MeCOCN	MeCO	70 (**5bb**)
3	$Ph(CH_2)_2$ (**3b**)	PhCHO	PhCH(OH)	99 (**5bc**)
4	$Ph(CH_2)_2$ (**3b**)	EtCHO	EtCH(OH)	99 (**5bd**)
5	$Ph(CH_2)_2$ (**3b**)	PhCOMe	PhCMe(OH)	86 (**5be**)
6	$Ph(CH_2)_2$ (**3b**)	Cyclohexanone	1-Hydroxycyclohexyl	99 (**5bf**)
7	$Ph(CH_2)_2$ (**3b**)	(*E*)-MeCH=CHCOPh	(*E*)-MeCH=CHCPh(OH)	62 (**5bg**)
8	Ph (**3c**)	PhCOCN	PhCO	80 (**5c**)
9	$CH_2=CH(CH_2)_3$ (**3ac**)	PhCOCN	PhCO	96 (**5aa**)
10	$Br(CH_2)_7$ (**3d**)	PhCOCN	PhCO	93 (**5d**)
11	4-$BrC_6H_4(CH_2)_2$ (**3e**)	PhCOCN	PhCO	80 (**5e**)
12	$PhO(CH_2)_{10}$ (**3f**)	PhCOCN	PhCO	85 (**5f**)
13	$TBSO(CH_2)_{11}$ (**3g**)	PhCOCN	PhCO	84 (**5g**)
14	$EtO_2C(CH_2)_5$ (**3h**)	PhCOCN	PhCO	93 (**5h**)

[a] Reactions were carried out using *gem*-dizinc **1** (1.2 mmol), thiol ester **3** (1.0 mmol), Pd_2dba_3 (0.005 mmol), PPh_3 (0.021 mmol), and El^+ (1.5 mmol) in THF (8.3 mL). [b] Isolated yields.

The preparation of the zinc enolate, which has ketone group in the same molecule, is quite useful.[15] Treatment of a thiol ester carrying a keto group **3i** with bis(iodozincio)methane (**1**) in the presence of palladium catalyst gave a sluggish mixture, which might be formed by a reaction of the ketone group and the formed enolate. Mixing an electrophile, benzoyl cyanide, in advance, however, prevented this homo-condensation. As shown in Table 3, the results by the

following procedure were shown: A mixture of thiol esters with keto group **3i-m** and benzoyl cyanide was treated with the dizinc **1** in the presence of palladium catalyst. These reactions gave triketones in excellent yields. The initially formed zinc enolate reacted with benzoyl cyanide, which is more electrophilic than ketone. It reacted with benzoyl cyanide without transposing to the other methyl ketone moiety in the same molecule. The formation and reaction of enolate from thiol esters proceeded chemo- and regioselectively.

Table 3. Preparation of Triketone **5i-m** by a Reaction of Benzoyl Cyanide with Enolates from Thiol Esters Carrying Acyl Group **3i-m**.[a]



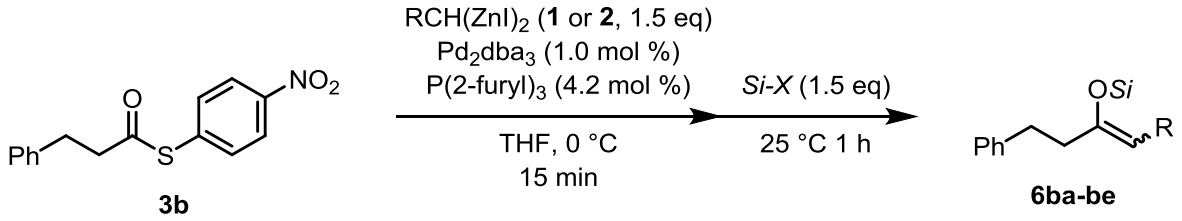
Entry	R	Yield of **5** (%)[b]
1	$CH_3CO(CH_2)_5$ (**3i**)	92 (**5i**)
2	$CH_3CO(CH_2)_8$ (**3j**)	72 (**5j**)
3	4-$CH_3COC_6H_4(CH_2)_2$ (**3k**)	83 (**5k**)
4	$CH_3COCH(CH_3)CH_2$ (**3l**)	94 (**5l**)
5[c]	$CH_3COCH_2CH(CH_3)$ (**3m**)	79 (**5m**)

[a] Reactions were carried out using *gem*-dizinc **1** (3.0 mmol), thiol ester **3** (2.0 mmol), Pd_2dba_3 (0.02 mmol), PPh_3 (0.084 mmol), and PhCOCN (1.0 mmol) in THF (5.8 mL). [b] Isolated yields. [c] P(2-furyl)$_3$ (0.084 mmol) were used instead of PPh_3.

To broaden the scope of this method, the formed zinc enolates were transformed into the silyl enol ethers. The silyl enol ethers have been important reagents especially for cross-aldol reactions, but the selective preparation of those compounds are still needed.[16] For example, it is not so easy to realize the regioselective preparation from an internal ketone, such as 3-hexanone. When the zinc enolates prepared from thiol ester and *gem*-dizinc **1** or **2** are trapped by silylating

reagents, it is possible to construct the silyl enol ether of methyl- and ethyl ketones carrying functional groups regio- and chemoselectively.

Table 4. Preparation of Silyl Enol Ethers **6ba-be** by a Reaction of Silylation Reagents with Enolates from Thiol Ester **3b**.[a]

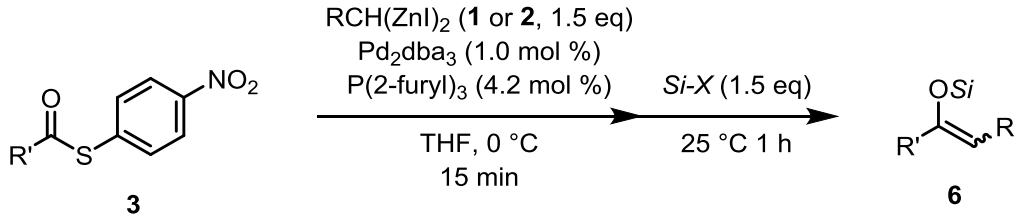


Entry	$RCH(ZnI)_2$	*Si-X*	Yield of **6** (%)[b]	*Z*:*E*
1	$CH_2(ZnI)_2$ (**1**)	Me_3SiCl	96 (**6ba**)	–
2	$CH_2(ZnI)_2$ (**1**)	Me_3SiCN	92 (**6ba**)	–
3	$CH_2(ZnI)_2$ (**1**)	Me_3SiOTf	>99 (**6ba**)	–
4	$CH_2(ZnI)_2$ (**1**)	*t*-$BuMe_2SiCl$	32 (**6bb**)	–
5	$CH_2(ZnI)_2$ (**1**)	*t*-$BuMe_2SiCN$	92 (**6bb**)	–
6	$CH_2(ZnI)_2$ (**1**)	*t*-$BuMe_2SiOTf$	89 (**6bb**)	–
7	$CH_3CH(ZnI)_2$ (**2**)	Me_3SiCl	93 (**6bc**)	79:21
8	$CH_3CH(ZnI)_2$ (**2**)	$PhMe_2SiCl$	34 (**6bd**)	70:30
9	$CH_3CH(ZnI)_2$ (**2**)	*t*-$BuMe_2SiCl$	34 (**6be**)	96:4
10	$CH_3CH(ZnI)_2$ (**2**)	*t*-$BuMe_2SiCN$	60 (**6be**)	93:7
11	$CH_3CH(ZnI)_2$ (**2**)	*t*-$BuMe_2SiOTf$	72 (**6be**)	93:7

[a] Reactions were carried out using *gem*-dizinc **1** or **2** (1.5 mmol), thiol ester **3b** (1.0 mmol), Pd_2dba_3 (0.01 mmol), $P(2\text{-furyl})_3$ (0.042 mmol), and *Si-X* (1.5 mmol) in THF (8.3 mL). [b] Yields were determined by ^1H NMR using dibromomethane as an internal standard.

As shown in Table 4, *S*-(4-nitrophenyl) 3-phenylpropanethioate (**3b**) was treated with *gem*-dizinc **1** or **2** in the presence of palladium catalyst and the mixture were treated with various silylation reagents.

Table 5. Preparation of Silyl Enol Ethers **6** by a Reaction of Silylation Reagents with Enolates from Various Thiol Esters **3**.[a]



entry	R'	*gem*-dizinc	*Si-X*	Yield of **6** (%)[b]	*Z*:*E*
1	CH_2=CH$(CH_2)_3$ (**3ac**)	**1**	Me_3SiCl	94 (**6aa**)	–
2	Ph (**3c**)	**1**	Me_3SiCl	70 (**6ca**)	–
3	Br$(CH_2)_7$ (**3d**)	**1**	Me_3SiCl	79 (**6da**)	–
4	4-Br$C_6H_4(CH_2)_2$ (**3e**)	**1**	Me_3SiCl	76 (**6ea**)	–
5	PhO$(CH_2)_{10}$ (**3f**)	**1**	Me_3SiCl	79 (**6fa**)	–
6	$EtO_2C(CH_2)_5$ (**3h**)	**1**	Me_3SiCl	96 (**6ha**)	–
7	CH_2=CH$(CH_2)_3$ (**3ac**)	**2**	*t*-BuMe_2SiOTf	66 (**6ab**)	90:10
8	4-Br$C_6H_4(CH_2)_2$ (**3e**)	**2**	*t*-BuMe_2SiOTf	67 (**6eb**)	93:7
9	$EtO_2C(CH_2)_5$ (**3h**)	**2**	*t*-BuMe_2SiOTf	60 (**6hb**)	93:7
10	$CH_3(CH_2)_2$ (**3n**)	**2**	*t*-BuMe_2SiOTf	58 (**6nb**)	90:10
11	3-Furanyl (**3o**)	**1**	Me_3SiCl	63 (**6oa**)	–
12	3-Thienyl (**3p**)	**1**	Me_3SiCl	59 (**6pa**)	–

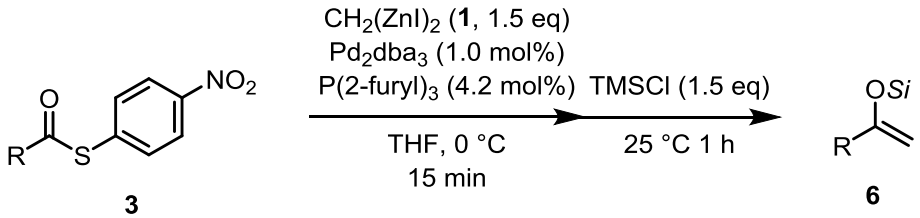
[a] Reactions were carried out using *gem*-dizinc **1** or **2** (1.5 mmol), thiol ester **3** (1.0 mmol), Pd_2dba_3 (0.01 mmol), P(2-furyl)$_3$ (0.042 mmol), and *Si-X* (1.5 mmol) in THF (8.3 mL).
[b] Isolated yields.

In this preparation of silyl enol ether, the palladium catalyst prepared from Pd_2dba_3 and tris(2-furyl)phosphine gave the good yields. Trimethylsilyl triflate gave the best yield among the used trimethylsilylation reagents (entries 1-3). The reactions of 1,1-bis(iodozincio)ethane (**2**) gave the corresponding silyl enol ethers **6** as a mixture of *E/Z*-isomers. Use of *tert*-butyldimethylsilylation gave the sterically less hindered *Z*-enolate more diastereoselectively

compared to trimethylsilylation or dimethylphenylsilylation (entries 7-11).

As shown in Table 5, various thiol esters were examined for the preparation of silyl enol ethers. Thiol esters carrying primary bromide (entry 3), aryl bromide (entries 4, 8), and ester (entries 6, 9) were transformed into the corresponding silyl enol ethers in good yields. When 1,1-bis(iodozincio)ethane was used, the produced silyl enol ethers had *Z*-configuration selectively.[17] Especially, the transformation shown in entry 10 gave (*Z*)-*tert*-butyl(hex-2-en-3-yloxy)dimethylsilane, which is hard to prepare selectively from the corresponding ketone, 3-hexanone.[18]

Table 6. Preparation of Silyl Enol Ethers Having Acyl Group in the Same Molecule **6**.[a]



3 **6**

Entry	R	Yield of **6** (%)[b]
1	$CH_3CO(CH_2)_5$ (**3i**)	82 (**6i**)
2	4-$CH_3COC_6H_4(CH_2)_2$ (**3k**)	97 (**6k**)
3	$CH_3COCH(CH_3)CH_2$ (**3l**)	58 (**6l**)
4	$CH_3COCH_2CH(CH_3)$ (**3m**)	62 (**6m**)
5	$CH_3CO(CH_2)_4$ (**3q**)	65 (**6q**)

[a] Reactions were carried out using *gem*-dizinc **1** (1.5 mmol), thiol ester **3** (1.0 mmol), Pd_2dba_3 (0.01 mmol), P(2-furyl)$_3$ (0.042 mmol), and TMSCl (1.5 mmol) in THF (5.8 mL). [b] Isolated yields.

As shown in Table 6, treatment of a mixture of the thiol ester carrying keto group and chlorotrimethylsilane with bis(iodozincio)methane in the palladium catalyst gave the corresponding silyl enol ether carrying acyl group in the same molecule. In entries 3 and 4, two possible kinetic enolates from 3-methylhexane-2,5-dione **6k**,**l** were prepared selectively. The

classical deprotonation method from 3-methylhexane-2,5-dione cannot yield selectively.

Conclusion

This zinciomethylation of thiol esters offers an efficient method to give zinc enolates carrying additional ketone regio-, chemo-, and stereoselectively. The enolates can be isolated as the corresponding silyl enol ethers, which are important nucleophilic reagents for organic synthesis. The preparation of the silyl enol ether, which carries ketone moiety in the same molecule, is one of the most useful applications of this method.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. All aldehydes, ketones, acyl cyanide, and silylation reagents listed in Chapter 2 were commercially available.

General procedure for the preparation and reaction of zinc enolate from thiol ester

To a solution of Pd_2dba_3 (0.005 mmol) in THF (0.8 mL), triphenylphosphine (0.021 mmol) was added at 25 °C. The mixture was stirred for 10 min. To a solution, *p*-nitrobenzene thiol ester of 5-hexenoicacid (**3ac**, 1.0 mmol) in THF (1.0 mL) and bis(iodozincio)methane (**1**, 0.45 M, 1.2 mmol, 2.7 mL) in THF were added subsequently at 0 °C. The resulting mixture was stirred for 5 min at the same temperature. A solution of electrophile (1.5 mmol) in THF (1.0 mL) was added at 0 °C. The whole was stirred for 5 min at the same temperature, then poured into sat. NH_4Claq and extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give compound **5**.

Procedure for the synthesis of triketone 5i-m

To a solution of Pd_2dba_3 (0.01 mmol) in THF (1.0 mL), triphenylphosphine (0.042 mmol) was added at 25 °C. The mixture was stirred for 10 min. To a solution, benzoyl cyanide (0.5 mmol) in THF (0.5 mL) and *p*-nitrobenzene thiol ester of carboxylic acid (**3**, 1.0 mmol) in THF (1.0 mL), bis(iodozincio)methane (**1**, 0.45 M, 1.5 mmol, 3.3 mL) in THF was added dropwise at 0 °C. The resulting mixture was stirred for 1 h at the same temperature, then poured into sat. NH_4Claq and extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the triketone **5i-m**.

General procedure for the preparation of 6 except 6i-l,q

Tri(2-furyl)phosphine (0.082 mmol) in THF (1.0 mL) was added at 25 °C to a solution of Pd_2dba_3 (0.02 mmol) in THF (1.0 mL) and the mixture was stirred for 15 min. *gem*-dizinc (**1** or **2**, 0.45 M, 3.0 mmol) in THF and *p*-nitrobenzene thiol ester of carboxylic acid (**3**, 2.0 mmol) in THF (1.0 mL) were added subsequently at 0 °C. The resulting mixture was stirred for 15 min at the same temperature. Silylation reagent (3.0 mmol) was added to the reaction mixture. The resulting mixture was stirred for 6 h at 25 °C. Et_3N (1.0 mL) was added to the mixture, then poured into sat. $NaHCO_3$aq and extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by rapid silica gel column chromatography to give compound **6**.

Procedure for the preparation of 6i-l,q

To a solution of Pd_2dba_3 (0.02 mmol) in THF (1.0 mL), tri(2-furyl)phosphine (0.082 mmol) in THF (1.0 mL) was added at 25 °C. The mixture was stirred for 10 min. To this solution, chlorotrimethylsilane (3.0 mmol, 0.4 mL) and *p*-nitrobenzene thiol ester of ketoacid (3**i-l**,**q** 2.0 mmol) in THF (2.0 mL) were added subsequently at 0 °C and a solution of bis(iodozincio)methane (**1**, 0.45 M, 3.0 mmol) in THF was added dropwise at 0 °C. The resulting mixture was stirred for 5 min at the same temperature and then stirred for an additional 15 min at 25 °C. Et_3N (1.0 mL) was added to the mixture, then poured into sat. $NaHCO_3$aq and extracted with Et_2O. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation to give compound **6**.

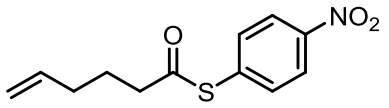
Preparation of 1,1-bis(iodozincio)ethane (2)

A mixture of zinc powder (150 mmol), 1,1-diiodoethane (1.0 mmol), and $PbCl_2$ (0.005 mmol) in THF (5.0 mL) was sonicated for 1 h in an ultrasonic cleaner bath under Ar. When pyrometallurgy zinc dust was used instead of pure zinc, it is not necessary to add $PbCl_2$. Both

of pure zinc and pyrometallurgy zinc are commercially available. To the mixture, 1,1-diiodoethane (50 mmol) in THF (45 mL) was added dropwise over 30 min at 0 °C with vigorous stirring. The mixture was stirred for 4 h at 25 °C. After the stirring was stopped, the reaction vessel was allowed to stand undisturbed for several hours. Excess zinc was separated by sedimentation. ^{1}H NMR (300 MHz, 20 °C) δ –0.08 (q, *J* = 7.8 Hz, 1H), 1.45 (d, *J* = 7.8 Hz, 3H). ^{1}H NMR spectra of the obtained supernatant showed a quartet at –0.08 ppm at 0 °C, which corresponded to the methyne proton of **2**. The supernatant was used for the further reaction as a solution of **2** in THF (0.1–0.5 M). The concentration of **2** was estimated by ^{1}H NMR analysis using 2,2,3,3-tetramethylbutane as an internal standard. 1.1-Bis(iodozincio)ethane in THF can be kept unchanged at least for two days in a sealed reaction vessel.

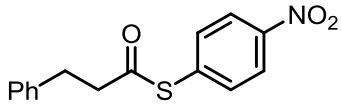
Characterization data

***S*-(4-Nitrophenyl) hex-5-enethioate (3ac)**.



^{1}H NMR ($CDCl_3$) δ 8.24 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.59 (dd, *J* = 9.0, 2.0 Hz, 2H), 5.77 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.05 (m, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.14 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.83 (tt, *J* = 7.5, 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 195,0, 147.9, 137.1, 136.3, 134.6, 123.9, 115.9, 43.2, 32.7, 24.4. TLC: R_f 0.43 (hexane/EtOAc = 5:1). IR (neat) 3077.6, 2932.9, 1715.8, 1600.0, 1578.8, 1520.9, 1478.5, 1398.5, 1344.4, 1309.7, 1177.6, 1109.1, 1058.0, 1013.6, 995.3, 966.4, 920.1, 853.5, 743.6, 731.1, 683.8 cm^{-1}. HRMS (APCI$^+$) Calcd for $C_{12}H_{14}NO_3S$: $[M+H]^+$, 252.0682. Found: *m/z* 252.0689.

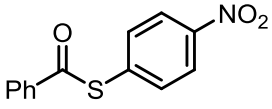
***S*-(4-Nitrophenyl) 3-phenylpropanethioate (3b)**.



Yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.25 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.57 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.24 (m, 3H), 3.04 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 194.4, 148.0, 139.4, 136.1, 134.7, 128.6, 128.3, 126.6, 123.9, 45.5, 31.2. Mp. 78.5–79.0 °C. TLC: R_f 0.53 (hexane/EtOAc = 4:1). IR (KBr) 3105.5,

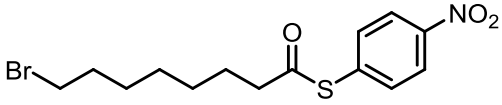
1696.5, 1601.0, 1578.8, 1520.9, 1347.3, 1308.8, 1277.9, 1055.1, 964.5, 855.5, 745.5, 697.3 cm^{-1}. HRMS (ESI) Calcd for $C_{15}H_{13}NO_3SNa$: $[M+Na]^+$, 310.0508. Found: *m/z* 310.0502.

***S*-(4-Nitrophenyl) benzothioate (3c)**: CAS RN [1219-32-5].



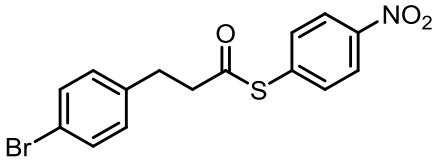
Yellow solid. ^1H NMR ($CDCl_3$) δ 8.16 (dd, *J* = 9.0, 2.5 Hz, 2H), 8.02 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.72 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.66 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.53 (dd, *J* = 8.0, 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 188.0, 148.2, 136.0, 135.9, 135.4, 134.3, 129.0, 127.6, 124.0.

***S*-(4-nitrophenyl) 8-bromooctanethioate (3d).**



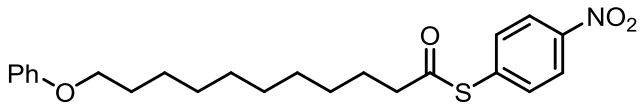
White oil. ^1H NMR ($CDCl_3$) δ 8.24 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.59 (dd, *J* = 9.0, 2.0 Hz, 2H), 3.40 (t, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.85 (tt, *J* = 7.0, 7.0 Hz, 2H), 1.73 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.39 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 195.2, 148.0, 136.3, 134.6, 123.9, 44.0, 33.9, 32.6, 28.6, 28.3, 27.8, 25.3. TLC: R_f 0.47 (hexane/EtOAc = 5:1). IR (neat) 2932.9, 2856.7, 1715.8, 1706.1, 1599.1, 1578.8, 1518.0, 1473.7, 1343.5, 1309.7, 1109.1, 1013.6, 957.7, 853.5, 743.6, 683.8 cm^{-1}. HRMS (ESI) Calcd for $C_{14}H_{18}BrNO_3SNa$: $[M+Na]^+$, 382.0083. Found: *m/z* 382.0074.

***S*-(4-Nitrophenyl) 3-(4-bromophenyl)propanethioate (3e).**



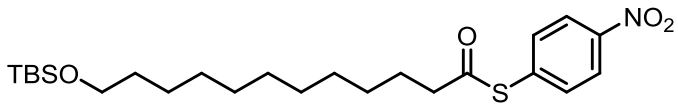
Yellow solid. ^1H NMR ($CDCl_3$) δ 8.25 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.56 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.43 (dd, *J* = 8.5, 2.0 Hz, 2H), 7.09 (dd, *J* = 8.5, 2.0 Hz, 2H), 3.00 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 194.2, 138.3, 134.7, 131.7, 130.1, 126.3, 124.4, 124.0, 120.4, 45.2, 30.5. Mp. 118.0–118.8 °C. TLC: R_f 0.33 (hexane/EtOAc = 5:1). IR (KBr) 3105.5, 2924.2, 1697.4, 1604.8, 1576.9, 1488.2, 1474.6, 1406.2, 1347.3, 1307.8, 1271.1, 1105.3, 1053.2, 1011.7, 968.3, 852.6, 807.2, 743.6 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{12}BrNO_3S$: $[M]^+$, 364.9721. Found: *m/z* 364.9717.

***S*-(4-Nitrophenyl) 11-phenoxyundecanethioate (3f).**



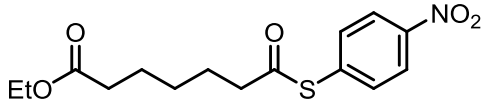
White solid. ^{1}H NMR ($CDCl_3$) δ 8.25 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.59 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.28 (dd, *J* = 9.0, 7.5 Hz, 2H), 6.93 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.89 (dd, *J* = 9.0, 1.0 Hz, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.75 (m, 4H), 1.37 (m, 12H). ^{13}C NMR ($CDCl_3$) δ 195.3, 159.0, 148.0, 136.5, 134.6, 129.4, 123.9, 120.4, 114.4, 67.8, 44.2, 29.4, 29.3, 29.3, 29.3, 29.2, 28.9, 26.0, 25.5. Mp. 55.5–56.0 °C. TLC: R_f 0.33 (hexane/EtOAc = 10:1). IR (KBr) 2928.1, 2917.5, 2850.0, 1735.0, 1602.0, 1499.7, 1472.7, 1438.0, 1307.8, 1271.1, 1252.8, 1242.2, 1207.5, 1174.7, 1083.1, 1014.6, 891.2, 815.9, 752.3, 696.3 cm^{-1}. HRMS (ESI) Calcd for $C_{23}H_{29}NO_4SNa$: $[M+Na]^+$, 438.1710. Found: *m/z* 438.1706.

***S*-(4-Nitrophenyl) 12-((*tert*-butyldimethylsilyl)oxy)dodecanethioate (3g).**



Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 9.5, 2.0 Hz, 2H), 7.59 (dd, *J* = 9.5, 2.0 Hz, 2H), 3.59 (t, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 1.72 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.50 (tt, *J* = 7.0, 7.0 Hz, 2H), 1.27 (m, 14H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 195.2, 147.9, 136.5, 134.6, 123.8, 63.3, 44.1, 32.8, 29.5, 29.5, 29.4, 29.3, 29.2, 28.9, 25.9, 25.7, 25.4, 18.3, –5.3. TLC: R_f 0.67 (hexane/EtOAc = 10:1). IR (neat) 2927.1, 2854.8, 1714.8, 1600.0, 1579.8, 1522.9, 1477.5, 1343.5, 1255.7, 1097.5, 1013.6, 847.8, 775.4, 743.6 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{42}NO_4SSi$: $[M+H]^+$, 468.2598. Found: *m/z* 468.2594.

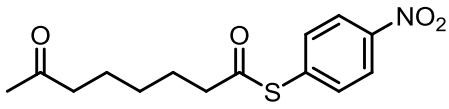
Ethyl 7-((4-nitrophenyl)thio)-7-oxoheptanoate (3h).



Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.23 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.58 (dd, *J* = 9.0, 2.0 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.74 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.65 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.40 (m, 2H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 195.0, 173.4, 147.9, 136.3, 134.6, 123.8, 60.3, 43.8, 33.9, 28.2, 25.0, 24.4, 14.2. TLC: R_f 0.40

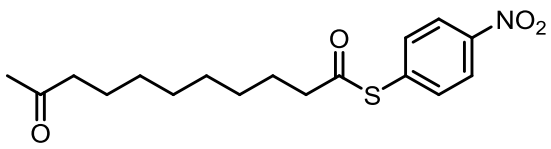
(hexane/EtOAc = 3:1). IR (neat) 3102.6, 2967.6, 2935.8, 1715.8, 1600.0, 1578.8, 1520.9, 1478.5, 1397.5, 1371.5, 1344.4, 1309.7, 1243.2, 1110.1, 1047.4, 992.4, 972.2, 886.3, 853.5, 801.5, 744.6, 684.8 cm^{-1}. HRMS (ESI) Calcd for $C_{15}H_{19}NO_5SNa$: $[M+Na]^+$, 348.0876. Found: *m/z* 348.0867.

_S_-(4-Nitrophenyl) 7-oxooctanethioate (3i).



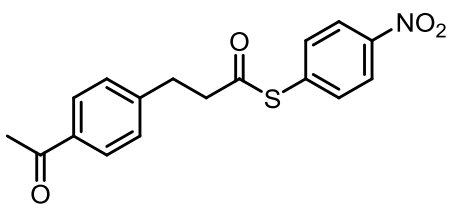
White solid. ^1H NMR ($CDCl_3$) δ 8.24 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.59 (dd, *J* = 9.0, 2.5 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.14 (s, 3H), 1.74 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.60 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.37 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 208.7, 195.1, 148.0, 136.3, 134.7, 123.9, 43.8, 43.2, 30.0, 28.3, 25.2, 23.1. Mp. 44.1–44.5 °C. TLC: R_f 0.27 (hexane/EtOAc = 3:1). IR (KBr) 2948.3, 2934.8, 2929.0, 1725.4, 1598.1, 1578.8, 1524.8, 1519.0, 1513.2, 1464.0, 1374.3, 1337.7, 1316.5, 1106.2, 1032.9, 1027.1, 969.3, 857.4, 852.6, 747.5, 732.0 cm^{-1}. HRMS (ESI) Calcd for $C_{14}H_{17}NO_4SNa$: $[M+Na]^+$, 318.0770. Found: *m/z* 318.0763.

_S_-(4-Nitrophenyl) 10-oxoundecanethioate (3j).



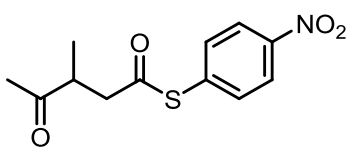
White solid. ^1H NMR ($CDCl_3$) δ 8.24 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.59 (dd, *J* = 9.0, 2.5 Hz, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.71 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.56 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.31 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 209.3, 195.2, 148.0, 136.4, 134.6, 123.9, 44.1, 43.7, 29.9, 29.1, 29.0, 29.0, 28.8, 25.4, 23.7. Mp. 54.5–55.0 °C. TLC: R_f 0.27 (hexane/EtOAc = 4:1). IR (KBr) 2931.0, 2851.9, 1709.0, 1700.3, 1598.1, 1577.8, 1513.2, 1471.8, 1404.2, 1340.6, 1283.7, 1207.5, 1162.2, 1106.2, 1050.3, 1012.7, 951.9, 854.5, 754.2, 745.5 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{23}NO_4SNa$: $[M+Na]^+$, 360.1240. Found: *m/z* 360.1231.

***S*-(4-Nitrophenyl) 3-(4-acetylphenyl)propanethioate (3k).**



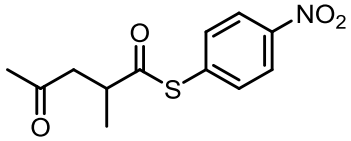
White solid. ^{1}H NMR ($CDCl_3$) δ 8.25 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.92 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.56 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.31 (dd, *J* = 8.0, 2.0 Hz, 2H), 3.06 (m, 4H), 2.60 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.7, 194.1, 145.0, 135.7, 135.7, 134.7, 128.8, 128.6, 128.5, 124.0, 44.9, 31.0, 26.6. Mp. 60.2–60.6 °C. TLC: R_f 0.27 (hexane/EtOAc = 3:1). IR (KBr) 3093.0, 2964.7, 1699.4, 1679.1, 1671.4, 1605.8, 1535.4, 1415.8, 1360.8, 1348.3, 1307.8, 1266.3, 1186.3, 1054.1, 956.7, 852.6, 823.6, 769.6, 744.6, 673.2 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{15}NO_4SNa$: $[M+Na]^+$, 352.0614. Found: *m/z* 352.0605.

***S*-(4-Nitrophenyl) 3-methyl-4-oxopentanethioate (3l).**



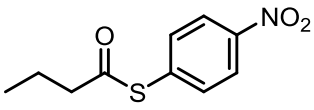
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.20 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.56 (dd, *J* = 9.0, 2.5 Hz, 2H), 3.18 (dd, *J* = 16.5, 8.5 Hz, 1H), 3.10 (m, 1H), 2.69 (dd, *J* = 16.5, 5.0 Hz, 1H), 2.19 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 209.7, 194.2, 148.0, 135.9, 134.7, 123.8, 46.0, 42.9, 28.2, 16.3. TLC: R_f 0.30 (hexane/EtOAc = 3:1). IR (neat) 3101.7, 2974.4, 2919.4, 1790.0, 1707.1, 1599.1, 1578.8, 1521.9, 1458.3, 1344.4, 1227.7, 1174.7, 1109.1, 1088.9, 999.2, 920.1, 853.5, 744.6 cm^{-1}. HRMS (ESI) Calcd for $C_{12}H_{13}NO_4SNa$: $[M+Na]^+$, 290.0457. Found: *m/z* 290.0453.

***S*-(4-Nitrophenyl) 2-methyl-4-oxopentanethioate (3m).**



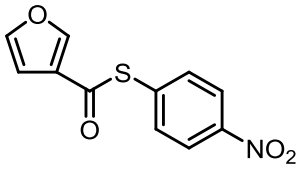
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.20 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.58 (m, 2H), 3.24 (m, 1H), 3.01 (dd, *J* = 18.5, 8.5 Hz, 1H), 2.58 (dd, *J* = 18.5, 5.5 Hz, 1H), 2.02 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 205.7, 198.7, 147.9, 136.2, 134.7, 123.8, 46.7, 43.5, 29.8, 17.7. TLC: R_f 0.27 (hexane/EtOAc = 3:1). IR (neat) 3101.7, 2976.3, 2934.8, 1751.4, 1714.8, 1599.1, 1577.8, 1520.9, 1478.5, 1457.3, 1398.5, 1344.4, 1310.7, 1172.8, 1108.2, 1083.1, 954.8, 892.1, 853.5, 744.6, 684.8 cm^{-1}. HRMS (ESI) Calcd for $C_{12}H_{13}NO_4SNa$: $[M+Na]^+$, 290.0457. Found: *m/z* 290.0452.

***S*-(4-Nitrophenyl) butanethioate (3n).**



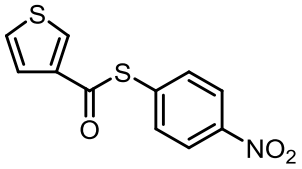
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.22 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.58 (dd, *J* = 9.0, 2.0 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.75 (tq, *J* = 7.5, 7.5 Hz, 2H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 195.1, 147.9, 136.4, 134.6, 123.8, 45.9, 19.0, 13.4. TLC: R_f 0.54 (hexane/EtOAc = 5:1). IR (neat) 3102.6, 2938.7, 1728.3, 1600.0, 1578.8, 1520.0, 1465.0, 1397.5, 1371.5, 1344.4, 1309.7, 1178.6, 1148.7, 1090.8, 1013.6, 853.5, 744.6, 684.8 cm^{-1}. HRMS (ESI) Calcd for $C_{10}H_{11}NO_3SNa$: $[M+Na]^+$, 248.0352. Found: *m/z* 248.0348.

***S*-(4-Nitrophenyl) furan-3-carbothioate (3o).**



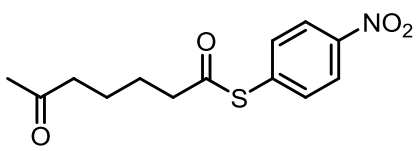
White solid. ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, *J* = 9.0, 2.5 Hz, 2H), 8.20 (dd, *J* = 1.5, 1.0 Hz, 1H), 7.69 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.52 (dd, *J* = 2.0, 1.5 Hz, 1H), 6.81 (dd, *J* = 2.0, 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 180.8, 148.2, 146.7, 144.6, 135.3, 135.1, 125.9, 123.9, 108.2. Mp. 129.2–130.0 °C. TLC: R_f 0.43 (hexane/EtOAc = 4:1). IR (KBr) 3132.5, 3101.7, 2968.6, 1700.3, 1600.0, 1517.1, 1348.3, 1283.7, 1159.3, 1086.9, 1013.6, 843.9, 811.1, 742.6 cm^{-1}. HRMS ($APCI^+$) Calcd for $C_{11}H_8NO_4S$: $[M+H]^+$, 250.0164. Found: *m/z* 250.0169.

***S*-(4-Nitrophenyl) thiophene-3-carbothioate (3p).**



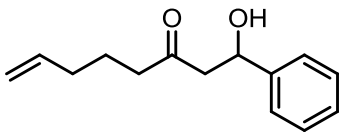
White solid. ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, *J* = 9.0, 2.0 Hz, 2H), 8.24 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.70 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.58 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.41 (dd, *J* = 5.0, 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 181.2, 139.5, 135.8, 135.2, 134.6, 132.0, 127.1, 126.0, 123.9. Mp. 143.3–144.0 °C. TLC: R_f 0.43 (hexane/EtOAc = 4:1). IR (KBr) 3094.9, 2965.7, 2937.7, 1723.5, 1675.3, 1600.0, 1512.3, 1480.4, 1343.5, 1227.7, 1158.3, 1107.2, 1014.6, 959.6, 849.7, 795.7, 743.6, 682.8 cm^{-1}. HRMS (ESI) Calcd for $C_{11}H_7NO_3S_2Na$: $[M+Na]^+$, 287.9760. Found: *m/z* 287.9754.

***S*-(4-Nitrophenyl) 6-oxoheptanethioate (3q).**



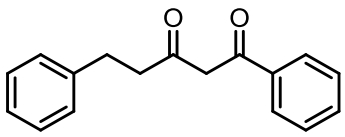
White solid. ^{1}H NMR ($CDCl_3$) δ 8.24 (dd, *J* = 9.5, 2.0 Hz, 2H), 7.59 (dd, *J* = 9.5, 2.0 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.15 (s, 3H), 1.72 (m, 2H), 1.64 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 208.2, 194.9, 148.0, 136.2, 134.7, 123.9, 43.8, 43.0, 30.0, 24.8, 22.8. Mp. 56.5–57.0 °C. TLC: R_f 0.33 (hexane/EtOAc = 2:1). IR (KBr) 3094.0, 2947.4, 2870.2, 1709.0, 1696.5, 1598.1, 1577.8, 1526.7, 1461.1, 1405.2, 1342.5, 1234.5, 1166.0, 1107.2, 1089.8, 1039.7, 965.4, 854.5, 769.6, 744.6 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{15}NO_4SNa$: $[M+Na]^+$, 304.0614. Found: *m/z* 304.0606.

1-Hydroxy-1-phenyloct-7-en-3-one (5a).



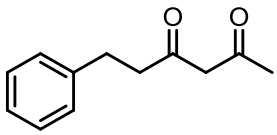
^{1}H NMR ($CDCl_3$) δ 7.25 (m, 4H), 7.18 (m, 1H), 5.65 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.06 (dt, *J* = 9.0, 3.0 Hz, 1H), 4.90 (m, 2H), 2.76 (dd, *J* = 17.0, 9.0 Hz, 1H), 2.68 (dd, *J* = 17.0, 3.0 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.96 (m, 2H), 1.60 (quint, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 211.3, 142.7, 137.7, 128.5, 127.6, 125.6, 115.4, 69.9, 51.1, 42.7, 32.9, 22.4. TLC: R_f 0.40 (hexane/EtOAc = 3:1). IR (KBr) 3417.0, 3073.7, 3031.3, 2931.9, 1707.1, 1640.5, 1517.1, 1452.5, 1405.2, 1371.5, 1338.7, 1089.8, 1062.8, 1001.1, 913.3, 760.0, 700.2 cm^{-1}. HRMS (ESI) Calcd for $C_{14}H_{18}O_2Na$: $[M+Na]^+$, 241.1199. Found: *m/z* 241.1194.

1,5-Diphenylpentane-1,3-dione (5ba): CAS RN [71298-03-8].



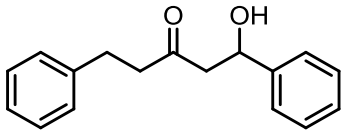
^{1}H NMR ($CDCl_3$) δ 7.86–7.85 (m, 2H), 7.54–7.51 (m, 1H), 7.46–7.43 (m, 2H), 7.32–7.29 (m, 2H), 7.24–7.21 (m, 3H), 6.14 (s, 1H), 3.02 (t, *J* = 8.0 Hz, 2H), 2.76 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 195.8, 183.1, 140.7, 134.8, 132.3, 128.6, 128.5, 128.3, 127.0, 126.2, 96.3, 41.0, 31.6.

6-Phenylhexane-2,4-dione (5bb): CAS RN [52393-50-7].



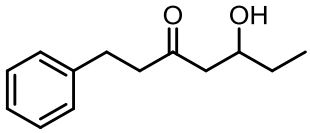
^{1}H NMR ($CDCl_3$) δ 7.31–7.27 (m, 2H), 7.22–7.18 (m, 3H), 5.48 (s, 0.84H), 3.56 (s, 0.32H), 2.95–2.90 (m, 2H), 2.86–2.83 (m, 0.32H), 2.60 (t, J = 7.5 Hz, 1.68H), 2.20 (s, 0.48H), 2.04 (s, 2.52H). ^{13}C NMR ($CDCl_3$) δ 203.2, 202.0, 193.2, 191.0, 140.7, 140.5, 128.53, 128.47, 128.30, 128.26, 126.23, 126.19, 100.0, 58.0, 45.2, 40.0, 31.4, 30.9, 29.4, 24.8.

1-Hydroxy-1,5-diphenylpentan-3-one (5bc): CAS RN [62731-45-7].



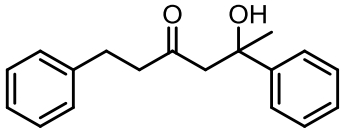
^{1}H NMR ($CDCl_3$) δ 7.34–7.33 (m, 4H), 7.30–7.27 (m, 3H), 7.22–7.19 (m, 1H), 7.18–7.16 (m, 2H), 5.16 (dd, J = 9.5, 3.0 Hz, 1H), 2.92 (t, J = 7.5 Hz, 2H), 2.85 (dd, J = 17.5, 9.5 Hz, 1H), 2.77 (t, J = 7.5 Hz, 2H), 2.76 (dd, J = 17.5, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 210.3, 142.7, 140.6, 128.9, 128.5, 128.3, 127.7, 126.2, 125.6, 69.9, 51.3, 45.1, 29.4.

5-Hydroxy-1-phenylheptan-3-one (5bd).



^{1}H NMR ($CDCl_3$) δ 7.30–7.27 (m, 2H), 7.21–7.20 (m, 1H), 7.19–7.17 (m, 2H), 3.98–3.93 (m, 1H), 2.91 (t, J = 7.5 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.58 (dd, J = 17.5, 3.0 Hz, 1H), 2.49 (dd, J = 17.5, 9.0 Hz, 1H), 1.55–1.38 (m, 2H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 211.2, 140.7, 128.5, 128.2, 126.2, 68.9, 48.8, 45.0, 29.5, 29.3, 9.8. TLC: R_f 0.30 (hexane/EtOAc = 3:1). IR (neat) 3467.2, 3026.4, 2964.7, 2918.4, 2878.9, 2850.0, 2308.9, 1710.9, 1700.3, 1654.0, 1559.5, 1540.2, 1507.4, 1457.3, 1339.6, 1110.1, 1030.0, 982.8, 745.5, 697.3, 668.4 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{19}O_2$: $[M+H]^+$, 207.1380. Found: *m/z* 207.1378.

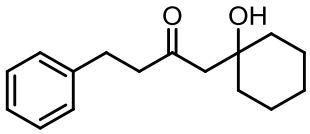
5-Hydroxy-1,5-diphenylhexan-3-one (5be): CAS RN [925421-43-8].



^{1}H NMR ($CDCl_3$) δ 7.41–7.40 (m, 2H), 7.35–7.31 (m, 2H), 7.27–7.23 (m, 3H), 7.20–7.17 (m, 1H), 7.07–7.06 (m, 2H), 3.16 (d, J

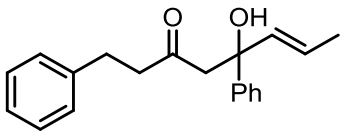
= 16.5 Hz, 1H), 2.80 (d, *J* = 16.5 Hz, 1H), 2.81–2.67 (m, 3H), 2.62–2.55 (m, 1H), 1.51 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 211.8, 147.1, 140.4, 128.5, 128.3, 128.2, 126.7, 126.1, 124.3, 73.3, 53.4, 46.0, 30.6, 29.0.

1-(1-Hydroxycyclohexyl)-4-phenylbutan-2-one (5bf).



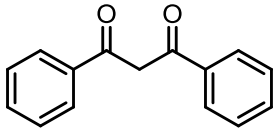
^{1}H NMR ($CDCl_3$) δ 7.30–7.26 (m, 2H), 7.21–7.17 (m, 3H), 3.55 (bs, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.76 (d, *J* = 7.5. Hz, 2H), 2.56 (s, 2H), 1.70–1.60 (m, 4H), 1.55–1.49 (m, 1H), 1.42–1.31 (m, 4H), 1.29–1.21 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 212.2, 140.6, 128.5, 128.3, 126.2, 70.7, 52.3, 46.2, 37.5, 29.3, 25.6, 21.9. TLC: R_f 0.47 (hexane/EtOAc = 3:1). IR (neat) 3491.3, 3027.4, 2931.0, 2857.7, 1701.3, 1496.8, 1453.4, 1405.2, 1363.7, 1312.6, 1267.3, 1168.9, 1095.6, 969.3, 745.5, 699.2 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{23}O_2$: $[M+H]^+$, 247.1693. Found: *m/z* 247.1690.

(*E*)-5-Hydroxy-1,5-diphenyloct-6-en-3-one (5bg).



^{1}H NMR ($CDCl_3$) δ 7.40–7.38 (m, 2H), 7.34–7.31 (m, 2H), 7.28–7.22 (m, 3H), 7.20–7.17 (m, 1H), 7.10–7.08 (m, 2H), 5.69 (dq, *J* = 15.0, 1.5 Hz, 1H), 5.57 (ddq, *J* = 15.0, 6.5, 1.5 Hz, 1H), 4.76 (bs, 1H), 3.09 (d, *J* = 16.5 Hz, 1H), 2.95 (d, *J* = 16.5 Hz, 1H), 2.86–2.71 (m, 3H), 2.68–2.61 (m, 1H), 1.69 (ddd, *J* = 6.0, 1.5, 1.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 211.5, 145.3, 140.5, 135.9, 128.5, 128.2, 128.2, 126.9, 126.2, 125.0, 124.6, 75.3, 52.2, 46.1, 29.0, 17.7. Mp. 59.5–60.2 °C. TLC: R_f 0.40 (hexane/EtOAc = 10:1). IR (KBr) 3473.0, 2837.4, 1681.0, 1595.2, 1576.9, 1507.4, 1474.6, 1450.5, 1363.7, 1339.6, 1175.7, 1107.2, 1079.2, 979.9, 854.5, 840.0, 758.1, 737.8, 700.2, 690.6 cm^{-1}. HRMS (ESI) Calcd for $C_{20}H_{23}O_2$: $[M+H]^+$, 295.1693. Found: *m/z* 295.1691.

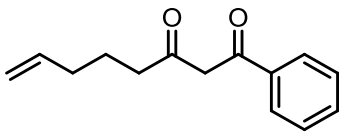
1,3-Diphenylpropane-1,3-dione (5c): CAS RN [120-46-7].



^{1}H NMR ($CDCl_3$) δ 8.01–7.99 (m, 4H), 7.58–7.55 (m, 2H), 7.52–7.48 (m, 4H), 6.87 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 185.8, 135.5, 132.5, 128.7, 127.2,

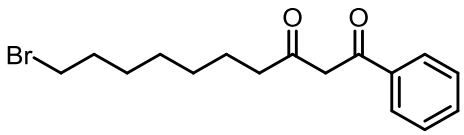
93.1.

1-Phenyloct-7-ene-1,3-dione (5aa): CAS RN [131223-44-4].



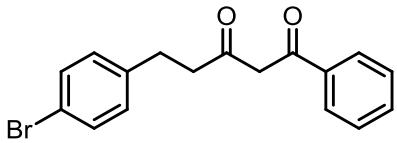
^{1}H NMR ($CDCl_3$) δ 7.90–7.87 (m, 2H), 7.54–7.51 (m, 1H), 7.47–7.43 (m, 2H), 6.18 (s, 1H), 5.82 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.06 (ddt, *J* = 17.0, 3.5, 1.5 Hz, 1H), 5.01 (ddd, *J* = 10.5, 2.0, 1.5 Hz, 1H), 2.45 (t, *J* = 8.0. Hz, 2H), 2.14 (dddt, *J* = 7.5, 7.0, 1.5, 1.5 Hz, 2H), 1.80 (ddt, *J* = 8.0, 7.5, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 196.6, 183.4, 137.8, 134.0, 132.2, 128.6, 127.0, 115.4, 96.2, 38.4, 33.1, 24.8.

10-Bromo-1-phenyldecane-1,3-dione (5d).



^{1}H NMR ($CDCl_3$) δ 7.90–7.87 (m, 2H), 7.54–7.51 (m, 1H), 7.47–7.43 (m, 2H), 6.17 (s, 1H), 3.41 (t, *J* = 7.0 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.86 (tt, *J* = 7.0, 6.5 Hz, 2H), 1.69 (tt, *J* = 7.5, 6.5 Hz, 2H), 1.48–1.35 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 196.9, 183.4, 135.0, 132.2, 128.6, 127.0, 96.1, 39.2, 33.9, 32.7, 29.0, 28.5, 28.0, 25.7. TLC: R_f 0.70 (hexane/EtOAc = 10:1). IR (KBr) 2920.4, 2852.8, 1737.0, 1559.5, 1494.9, 1457.3, 1404.2, 1366.6, 1303.0, 1279.8, 1258.6, 1217.1, 1143.8, 1078.3, 929.7, 766.7, 691.5 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{22}BrO_2$: $[M+H]^+$, 325.0798. Found: *m/z* 325.0787.

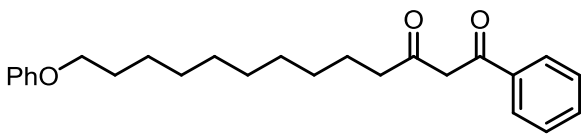
5-(4-Bromophenyl)-1-phenylpentane-1,3-dione (5e).



^{1}H NMR ($CDCl_3$) δ 7.86–7.84 (m, 2H), 7.54–7.51 (m, 1H), 7.47–7.43 (m, 2H), 7.43–7.34 (m, 2H), 7.12–7.10 (m, 2H), 6.12 (s, 1H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.73 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 195.5, 183.0, 139.6, 134.6, 132.4, 131.6, 130.1, 128.6, 127.0, 120.0, 96.4, 40.7, 30.9. Mp. 51.5–52.0 °C. TLC: R_f 0.64 (hexane/EtOAc = 10:1). IR (KBr) 3059.2, 2930.0, 1599.1, 1533.5, 1488.2, 1298.2, 1227.7, 1102.4, 1073.4, 1000.1, 925.9, 821.7, 755.2, 680.9 cm^{-1}.

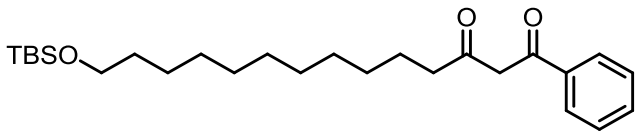
HRMS (ESI) Calcd for $C_{17}H_{16}BrO_2$: $[M+H]^+$, 331.0328. Found: *m/z* 331.0355.

13-Phenoxy-1-phenyltridecane-1,3-dione (5f).



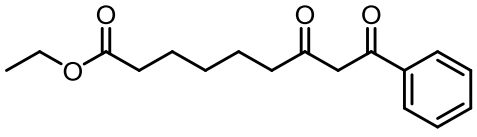
^{1}H NMR ($CDCl_3$) δ 7.89–7.88 (m, 2H), 7.53–7.50 (m, 1H), 7.46–7.43 (m, 2H), 7.29–7.25 (m, 2H), 6.94–6.89 (m, 3H), 6.17 (s, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.77 (tt, *J* = 6.5, 6.5 Hz, 2H), 1.68 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.48–1.27 (m, 12H). ^{13}C NMR ($CDCl_3$) δ 197.0, 183.4, 159.0, 135.0, 132.2, 129.3, 128.5, 126.9, 120.4, 114.4, 96.0, 67.8, 39.2, 29.5, 29.3, 29.3, 29.2, 29.2, 26.0, 25.8. Mp. 70.5–71.0 °C. TLC: R_f 0.63 (hexane/EtOAc = 10:1). IR (KBr) 2932.9, 2916.5, 2850.9, 1602.9, 1575.9, 1497.8, 1473.7, 1337.7, 1303.0, 1274.0, 1251.9, 1172.8, 1146.7, 1080.2, 1012.7, 879.6, 749.4, 691.5 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{33}O_3$: $[M+H]^+$, 381.2424. Found: *m/z* 381.2416.

14-((*tert*-Butyldimethylsilyl)oxy)-1-phenyltetradecane-1,3-dione (5g).



^{1}H NMR ($CDCl_3$) δ 7.89–7.87 (m, 2H), 7.54–7.50 (m, 1H), 7.47–7.44 (m, 2H), 6.17 (s, 1H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.68 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.52–1.47 (m, 2H), 1.38–1.25 (m, 14H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 197.0, 183.5, 135.1, 132.2, 128.6, 127.0, 96.1, 63.2, 39.3, 32.9, 29.6, 29.5, 29.5, 29.4, 29.4, 29.3, 26.0, 25.9, 25.8, 18.4, –5.3. TLC: R_f 0.57 (hexane/EtOAc = 10:1). IR (neat) 3065.0, 2927.1, 2854.8, 2648.4, 1723.5, 1603.9, 1575.9, 1463.1, 1360.8, 1300.1, 1255.7, 1182.4, 1097.5, 1028.1, 1005.9, 954.8, 835.2, 774.5, 694.4 cm^{-1}. HRMS (ESI) Calcd for $C_{26}H_{45}O_3Si$: $[M+H]^+$, 433.3132. Found: *m/z* 433.3127.

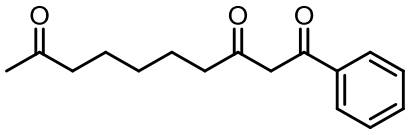
Ethyl-7,9-dioxo-9-phenylnonanoate (5h).



^{1}H NMR ($CDCl_3$) δ 7.90–7.87 (m, 2H), 7.54–7.50 (m, 1H), 7.47–7.43 (m, 2H), 6.17 (s, 1H), 4.12 (q, *J* = 7.0 Hz,

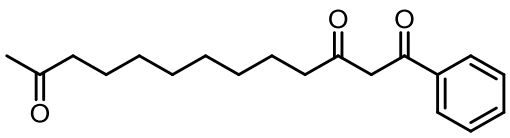
2H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.74–1.64 (m, 4H), 1.44–1.38 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 196.6, 183.4, 173.6, 134.9, 132.2, 128.6, 127.0, 96.1, 62.2, 39.0, 34.1, 28.7, 25.4, 24.6, 14.2. TLC: R_f 0.40 (hexane/EtOAc = 5:1). IR (neat) 3082.4, 2918.4, 2850.9, 2369.7, 1735.0, 1599.1, 1570.1, 1459.2, 1412.9, 1369.5, 1340.6, 1291.4, 1260.5, 1181.5, 1087.9, 1028.1, 853.5, 767.7, 697.3 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{23}O_4$: $[M+H]^+$, 291.1591. Found: *m/z* 291.1586.

1-Phenyldecane-1,3,9-trione (5i).



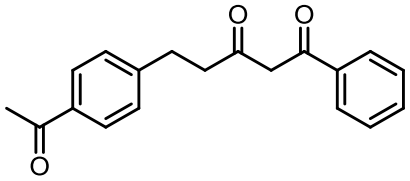
^{1}H NMR ($CDCl_3$) δ 7.89–7.87 (m, 2H), 7.54–7.51 (m, 1H), 7.47–7.43 (m, 2H), 6.17 (s, 1H), 2.45 (t, *J* = 7.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.14 (s, 3H), 1.70 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.62 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.40–1.34 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 209.0, 196.7, 183.4, 134.9, 132.3, 128.6, 127.0, 96.1, 43.4, 39.0, 29.9, 28.7, 25.5, 23.4. Mp. 57.5–58.2 °C. TLC: R_f 0.33 (hexane/EtOAc = 3:1). IR (KBr) 2937.7, 2866.3, 1705.2, 1614.5, 1598.1, 1575.9, 1462.1, 1411.0, 1360.8, 1345.4, 1295.3, 1261.5, 1144.8, 1088.9, 1069.6, 947.1, 774.5, 695.4 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{21}O_3$: $[M+H]^+$, 261.1485. Found: *m/z* 261.1482.

1-Phenyltridecane-1,3,12-trione (5j).



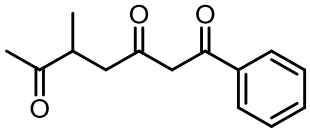
^{1}H NMR ($CDCl_3$) δ 7.89–7.87 (m, 2H), 7.53–7.50 (m, 1H), 7.47–7.43 (m, 2H), 6.17 (s, 1H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.67 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.56 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.37–1.26 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 209.4, 197.0, 183.4, 135.0, 132.2, 128.6, 127.0, 96.1, 43.7, 39.2, 29.9, 29.2, 29.2, 29.2, 29.1, 25.8, 23.8. Mp. 34.8–35.5 °C. TLC: R_f 0.60 (hexane/EtOAc = 3:1). IR (KBr) 3098.8, 2930.0, 2852.8, 2549.0, 1705.2, 1616.4, 1595.2, 1576.9, 1507.4, 1499.7, 1410.0, 1341.6, 1101.4, 950.0, 929.7, 854.5, 839.1, 740.7, 692.5 cm^{-1}. HRMS (ESI) Calcd for $C_{19}H_{27}O_3$: $[M+H]^+$, 303.1955. Found: *m/z* 303.1947.

5-(4-Acetylphenyl)-1-phenylpentane-1,3-dione (5k).



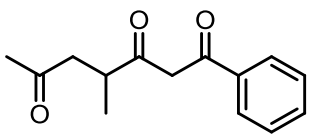
^{1}H NMR ($CDCl_3$) δ 7.91–7.89 (m, 2H), 7.86–7.83 (m, 1H), 7.54–7.51 (m, 2H), 7.47–7.43 (m, 2H), 7.33–7.32 (m, 2H), 6.13 (s, 1H), 3.08 (t, *J* = 7.5 Hz, 2H), 2.78 (t, *J* = 7.5 Hz, 2H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.8, 195.4, 182.9, 146.4, 135.4, 134.6, 132.4, 128.7, 128.6, 128.6, 127.0, 96.3, 40.4, 31.4, 26.6. Mp. 50.9–51.5 °C. TLC: R_f 0.53 (hexane/EtOAc = 2:1). IR (KBr) 3065.0, 2918.4, 1683.9, 1602.9, 1570.1, 1494.9, 1460.2, 1406.2, 1360.8, 1302.0, 1267.3, 1177.6, 1142.9, 1108.2, 1079.2, 1033.9, 1013.6, 957.7, 868.0, 824.6, 779.3, 697.3 cm^{-1}. HRMS (ESI) Calcd for $C_{19}H_{19}O_3$: $[M+H]^+$, 295.1329. Found: *m/z* 295.1322.

5-Methyl-1-phenylheptane-1,3,6-trione (5l).



^{1}H NMR ($CDCl_3$) δ 7.86–7.85 (m, 2H), 7.53–7.50 (m, 1H), 7.46–7.43 (m, 2H), 6.17 (s, 1H), 3.13 (ddq, *J* = 8.0, 7.0, 6.0 Hz, 1H), 2.94 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.44 (dd, *J* = 16.0, 6.0 Hz, 1H), 2.25 (s, 3H), 1.18 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 211.1, 196.6, 181.0, 134.3, 132.3, 128.6, 126.9, 96.7, 42.8, 42.3, 28.5, 16.6. Mp. 35.1–36.0 °C. TLC: R_f 0.60 (hexane/EtOAc = 2:1). IR (KBr) 3403.5, 3095.9, 2973.4, 2877.9, 1712.9, 1598.1, 1560.5, 1462.1, 1427.4, 1396.5, 1371.5, 1336.7, 1281.8, 1213.3, 1174.7, 1150.6, 1082.1, 1068.6, 951.9, 932.6, 834.4, 770.6, 692.5 cm^{-1}. HRMS (ESI) Calcd for $C_{14}H_{17}O_3$: $[M+H]^+$, 233.1172. Found: *m/z* 233.1170.

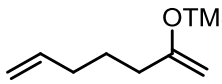
4-Methyl-1-phenylheptane-1,3,6-trione (5m).



^{1}H NMR ($CDCl_3$) δ 7.88–7.86 (m, 2H), 7.53–7.50 (m, 1H), 7.46–7.43 (m, 2H), 6.23 (s, 1H), 3.08 (ddq, *J* = 7.5, 7.5, 5.0 Hz, 1H), 3.02 (dd, *J* = 17.5, 7.5 Hz, 1H), 2.51 (dd, *J* = 17.5, 5.0 Hz, 1H), 2.18 (s, 3H), 1.22 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 206.9, 201.2, 181.3, 134.4, 132.2, 128.6, 126.9, 95.4, 46.5, 38.7, 30.3, 17.9. Mp. 30.5–31.0 °C. TLC: R_f 0.63 (hexane/EtOAc = 2:1). IR (KBr) 2968.6, 1781.3, 1710.9, 1612.6, 1576.9, 1516.1, 1464.0, 1392.7, 1373.4, 1339.6, 1275.0, 1153.5, 1122.6,

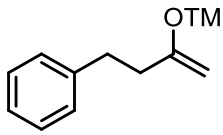
1067.7, 942.3, 853.5, 802.8, 781.2, 693.4 cm^{-1}. HRMS (ESI) Calcd for $C_{14}H_{17}O_3$: $[M+H]^+$, 233.1172. Found: *m/z* 233.1169.

(Hepta-1,6-dien-2-yloxy)trimethylsilane (6aa).



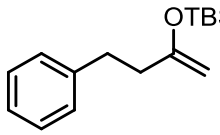
^1H NMR ($CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.0, 2.0 Hz, 1H), 5.01 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.96 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.05 (s, 2H), 2.06 (dt, *J* = 7.5, 6.5 Hz, 2H), 2.02 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.55 (tt, *J* = 7.5, 7.5 Hz, 2H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 159.4, 138.9, 114.8, 90.2, 36.1, 33.3, 26.3, 0.3. IR (neat) 3077.6, 2957.0, 2863.5, 1638.6, 1458.3, 1437.0, 1251.9, 1225.8, 1172.8, 1100.4, 1035.8, 958.7, 911.4, 841.0, 752.3, 694.4 cm^{-1}. HRMS (ESI) Calcd for $C_{10}H_{20}OSiK$: $[M+K]^+$, 223.0915. Found: *m/z* 223.0943.

Trimethyl((4-phenylbut-1-en-2-yl)oxy)silane (6ba) : CAS RN [59417-89-9].



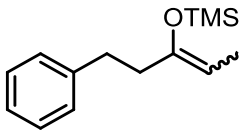
^1H NMR ($CDCl_3$) δ 7.30–7.26 (m, 2H), 7.21–7.17 (m, 3H), 4.07 (d, *J* = 0.5 Hz, 1H), 4.06 (d, *J* = 0.5 Hz, 1H), 2.79 (dd, *J* = 8.0, 8.0 Hz, 2H), 2.34 (dd, *J* = 8.0, 8.0 Hz, 2H), 0.22 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 158.9, 142.1, 128.6, 128.5, 125.9, 90.4, 38.5, 33.6, 0.3.

***tert*-Butyldimethyl((4-phenylbut-1-en-2-yl)oxy)silane (6bb)**.



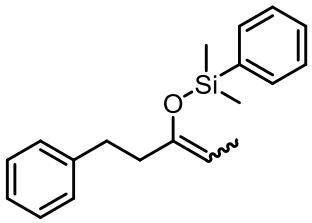
^1H NMR ($CDCl_3$) δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (m, 2H), 4.07 (bs, 2H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.36 (t, *J* = 8.0 Hz, 2H), 0.98 (s, 9H), 0.20 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 158.8, 141.9, 128.4, 128.3, 125.8, 90.1, 38.6, 33.4, 25.7, 18.1, –4.7. IR (neat) 3112.3, 3028.4, 2957.0, 2930.0, 2858.6, 2361.9, 1654.0, 1635.7, 1496.8, 1472.7, 1361.8, 1292.4, 1257.6, 1221.0, 1160.2, 1149.6, 1077.3, 1031.0, 1005.0, 838.1, 810.1, 780.2, 697.3 cm^{-1}. HRMS (EI) Calcd for $C_{16}H_{26}OSi$: $[M]^+$, 262.1753. Found: *m/z* 262.1748.

Trimethyl((5-phenylpent-2-en-3-yl)oxy)silane (6bc).



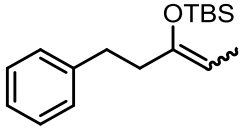
^{1}H NMR ($CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (m, 3H), 4.65 (q, *J* = 7.0 Hz, 0.21H), 4.59 (q, *J* = 7.0 Hz, 0.79H), 2.79 (t, *J* = 8.0 Hz, 2H), 2.37 (t, *J* = 8.0 Hz, 0.42H), 2.30 (t, *J* = 8.0 Hz, 1.58H), 1.53 (dt, *J* = 7.0, 1.0 Hz, 2.37H), 1.46 (d, *J* = 7.0 Hz, 0.63H), 0.23 (s, 7.11H), 0.20 (s, 1.89H). ^{13}C NMR ($CDCl_3$) δ 150.4, 142.0, 128.3, 128.3, 125.8, 102.7, 38.8, 33.7, 10.7, 0.6. IR (neat) 2929.0, 1676.2, 1454.4, 1331.9, 1252.8, 1192.1, 1105.3, 1092.7, 1041.6, 995.3, 912.4, 898.9, 843.9, 750.3, 698.3 cm^{-1}. HRMS (EI) Calcd for $C_{14}H_{22}OSi$: $[M]^+$, 234.1440. Found: *m/z* 234.1431.

Dimethyl(phenyl)((5-phenylpent-2-en-3-yl)oxy)silane (6bd).



^{1}H NMR ($CDCl_3$) δ 7.68 (dd, *J* = 4.0, 2.0 Hz, 2H), 7.43 (m, 3H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 2H), 4.65 (q, *J* = 7.0 Hz, 0.30H), 4.59 (q, *J* = 6.5 Hz, 0.70H), 2.79 (t, *J* = 8.0 Hz, 0.60H), 2.71 (t, *J* = 8.0 Hz, 1.40H), 2.37 (t, *J* = 8.0 Hz, 0.60H), 2.23 (t, *J* = 8.0 Hz, 1.40H), 1.54 (dt, *J* = 6.5, 1.0 Hz, 2.10H), 1.42 (d, *J* = 6.5 Hz, 0.90H), 0.51 (s, 4.20H), 0.47 (s, 1.80H). ^{13}C NMR ($CDCl_3$) δ 150.4, 141.9, 137.9, 133.3, 129.8, 128.3, 128.2, 127.9, 125.7, 103.1, 38.7, 33.8, 10.8, –0.9. IR (neat) 3068.9, 2958.0, 2917.5, 2861.5, 1678.1, 1496.8, 1454.4, 1428.4, 1381.1, 1327.1, 1252.8, 1191.1, 1118.8, 1041.6, 998.2, 898.9, 832.3, 787.0, 743.6, 698.3 cm^{-1}. HRMS (EI) Calcd for $C_{19}H_{24}OSi$: $[M]^+$, 296.1596. Found: *m/z* 296.1588.

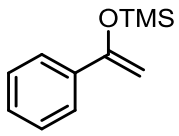
***tert*-Butyldimethyl((5-phenylpent-2-en-3-yl)oxy)silane (E/Z mixture, 93/7) (6be)**.



^{1}H NMR ($CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.19 (m, 3H), 4.64 (q, *J* = 7.0 Hz, 0.07H), 4.56 (q, *J* = 7.0 Hz, 0.93H), 2.80 (t, *J* = 8.5 Hz, 2H), 2.31 (t, *J* = 8.5 Hz, 2H), 1.55 (d, *J* = 7.0 Hz, 2.79H), 1.45 (d, *J* = 7.0 Hz, 0.21H), 1.01 (s, 8.37H), 0.97 (s, 0.63H), 0.17 (s, 5.58H), 0.09 (s, 0.42H). ^{13}C NMR ($CDCl_3$) δ 150.5, 142.0, 128.3, 128.3, 125.8, 102.4, 38.8, 33.9, 25.8, 10.8, 1.0, –4.0. IR (neat) 3027.4, 2958.9, 2921.3, 2862.5,

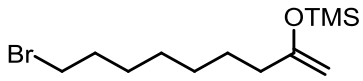
2360.0, 2342.7, 1676.2, 1604.8, 1496.8, 1454.4, 1382.1, 1331.9, 1220.0, 1192.1, 1105.3, 1041.6, 993.4, 912.4, 844.9, 751.3, 698.3 cm^{-1}. HRMS (EI) Calcd for $C_{17}H_{28}OSi$: $[M]^+$, 276.1909. Found: *m/z* 276.1906.

Trimethyl((1-phenylvinyl)oxy)silane (6ca) : CAS RN [13735-81-4].



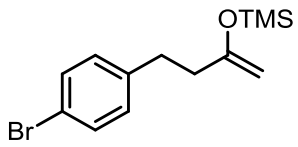
^1H NMR ($CDCl_3$) δ 7.62–7.52 (m, 2H), 7.35–7.25 (m, 3H), 4.92 (d, *J* = 2.0 Hz, 1H), 4.43 (d, *J* = 2.0 Hz, 1H), 0.27 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 155.9, 137.7, 128.4, 128.2, 125.4, 91.3, 0.3.

((9-Bromonon-1-en-2-yl)oxy)trimethylsilane (6da).



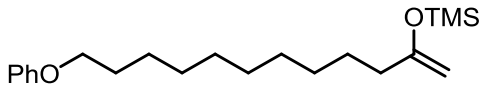
^1H NMR ($CDCl_3$) δ 4.03 (bs, 2H), 3.40 (t, *J* = 7.0 Hz, 2H), 2.00 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.85 (ddt, *J* = 7.5, 7.5, 7.0 Hz, 2H), 1.48–1.38 (m, 4H), 1.36–1.26 (m, 4H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 159.7, 90.0, 36.6, 34.1, 33.0, 29.0, 28.8, 28.3, 26.9, 0.3. IR (neat) 2960.9, 2932.9, 2857.7, 2360.0, 2331.1, 1654.0, 1635.7, 1628.0, 1459.2, 1433.2, 1251.9, 1216.2, 1117.8, 1016.5, 844.9, 752.3, 666.4 cm^{-1}. HRMS (EI) Calcd for $C_{12}H_{25}BrOSi$: $[M]^+$, 292.0858. Found: *m/z* 292.0851.

((4-(4-Bromophenyl)but-1-en-2-yl)oxy)trimethylsilane (6ea).



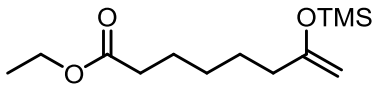
^1H NMR ($CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 4.04 (d, *J* = 1.0 Hz, 1H), 4.02 (d, *J* = 1.0 Hz, 1H), 2.73 (dd, *J* = 8.0, 6.5 Hz, 2H), 2.30 (dd, *J* = 8.0, 6.5 Hz, 2H), 0.21 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 158.4, 141.0, 131.5, 130.4, 119.7, 90.6, 38.3, 33.0, 0.3. IR (neat) 2958.9, 1654.0, 1631.9, 1617.4, 1488.2, 1349.3, 1340.6, 1292.4, 1252.8, 1219.1, 1152.5, 1100.4, 1072.5, 1031.0, 1011.7, 921.1, 846.8, 753.2, 684.8 cm^{-1}. HRMS (EI) Calcd for $C_{13}H_{18}BrOSi$: $[M–H]^+$, 297.0313. Found: *m/z* 297.0312.

Trimethyl((12-phenoxydodec-1-en-2-yl)oxy)silane (6fa).



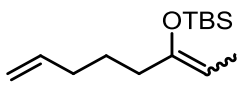
^{1}H NMR ($CDCl_3$) δ 7.30–7.25 (m, 2H), 6.95–6.85 (m, 3H), 4.04 (bs, 2H), 3.95 (t, *J* = 6.5 Hz, 2H), 2.00 (dd, *J* = 7.0, 7.0 Hz, 2H), 1.78 (ddt, *J* = 7.0, 7.0, 6.5 Hz, 2H), 1.50–1.40 (m, 4H), 1.40–1.26 (m, 10H), 0.21 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 159.8, 159.3, 129.6, 120.1, 114.7, 89.9, 68.0, 36.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.3, 27.0, 26.3, 0.3. IR (neat) 3109.4, 3040.9, 2927.1, 2854.8, 1632.8, 1602.0, 1497.8, 1468.9, 1387.8, 1301.0, 1251.9, 1171.8, 1107.2, 1014.6, 846.8, 814.0, 752.3, 690.6 cm^{-1}. HRMS (EI) Calcd for $C_{21}H_{36}O_2Si$: $[M]^+$, 348.2485. Found: *m/z* 348.2480.

Ethyl-7-((trimethylsilyl)oxy)oct-7-enoate (6ga).



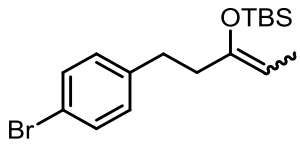
^{1}H NMR ($CDCl_3$) δ 4.12 (q, *J* = 7.5 Hz, 2H), 4.03 (bs, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.00 (t, *J* = 7.5 Hz, 2H), 1.63 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.47 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.33 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.25 (t, *J* = 7.5 Hz, 3H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 159.5, 90.1, 60.4, 36.5, 34.5, 28.8, 26.7, 25.0, 14.6, 0.3. IR (neat) 2938.7, 2863.5, 2360.0, 2331.1, 1739.9, 1735.0, 1252.8, 1181.5, 1139.0, 1087.9, 1014.6, 916.2, 845.8, 752.3, 685.7, 673.2 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{27}O_3Si$: $[M+H]^+$, 259.1724. Found: *m/z* 259.1722.

***tert*-Butyldimethyl(octa-2,7-dien-3-yloxy)silane (E/Z mixture, 90/10) (6ab)**.



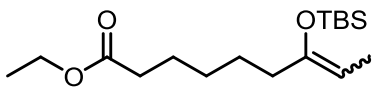
^{1}H NMR ($CDCl_3$) δ 5.80 (ddt, *J* = 17.0, 10.5, 6.5 Hz, 1H), 5.01 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.95 (dd, *J* = 17.0, 2.0 Hz, 1H), 4.63 (q, *J* = 7.0 Hz, 0.10H), 4.49 (q, *J* = 7.0 Hz, 0.90H), 2.05 (dt, *J* = 7.5, 6.5 Hz, 2H), 2.00 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.55 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.52 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 8.10H), 0.94 (s, 0.90H), 0.12 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 151.1, 138.9, 114.7, 102.1, 36.2, 33.4, 26.5, 26.0, 18.5, 11.0, –3.8. IR (neat) 3067.0, 2956.0, 2858.6, 1642.5, 1472.7, 1383.0, 1361.8, 1330.9, 1254.8, 1193.0, 1045.5, 910.4, 837.1, 777.4 cm^{-1}. HRMS (EI) Calcd for $C_{14}H_{28}OSi$: $[M]^+$, 240.1909. Found: *m/z* 240.1906.

((5-(4-Bromophenyl)pent-2-en-3-yl)oxy)(*tert*-butyl)dimethylsilane (E/Z mixture, 93/7) (6eb).



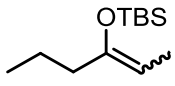
^{1}H NMR ($CDCl_3$) δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 4.61 (q, *J* = 7.0 Hz, 0.07H), 4.48 (q, *J* = 6.5 Hz, 0.93H), 2.77–2.67 (m, 2H), 2.32 (dd, *J* = 8.0, 7.5 Hz, 1.86H), 2.25 (dd, *J* = 8.0, 7.5 Hz, 0.14H), 1.51 (d, *J* = 6.5 Hz, 2.79H), 1.41 (d, *J* = 6.5 Hz, 0.21H), 0.98 (s, 8.37H), 0.94 (s, 0.63H), 0.14 (s, 5.58H), 0.13 (s, 0.42H). ^{13}C NMR ($CDCl_3$) δ 150.1, 141.1, 131.5, 130.3, 119.7, 103.0, 38.7, 33.3, 26.0, 18.5, 11.0, –3.7. IR (neat) 3024.5, 2955.1, 2930.0, 2857.7, 1489.1, 1471.8, 1404.2, 1388.8, 1331.9, 1253.8, 1193.0, 1100.4, 1043.5, 1012.7, 904.7, 838.1, 806.3, 778.3, 697.3 cm^{-1}. HRMS (EI) Calcd for $C_{17}H_{26}BrOSi$: $[M–H]^+$, 353.0936. Found: *m/z* 353.0935.

Ethyl-7-((*tert*-butyldimethylsilyl)oxy)non-7-enoate (E/Z mixture, 93/7) (6hb).



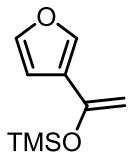
^{1}H NMR ($CDCl_3$) δ 4.61 (q, *J* = 7.0 Hz, 0.07H), 4.48 (q, *J* = 7.0 Hz, 0.93H), 4.12 (q, *J* = 7.0 Hz, 2H), 2.29 (t, *J* = 8.0 Hz, 2H), 1.98 (t, *J* = 8.0 Hz, 2H), 1.62 (tt, *J* = 8.0, 7.5 Hz, 2H), 1.51 (d, *J* = 7.0 Hz, 3H), 1.47 (tt, *J* = 8.0, 8.0 Hz, 2H), 1.31 (tt, *J* = 8.0, 7.5 Hz, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.95 (s, 9H), 0.11 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 159.5, 151.2, 102.0, 60.4, 36.6, 34.5, 28.9, 26.9, 26.0, 25.1, 18.5, 14.4, 11.0, –3.8. IR (neat) 2951.2, 2930.0, 2858.6, 2361.9, 1739.9, 1676.2, 1601.0, 1472.7, 1465.0, 1462.1, 1330.9, 1302.0, 1252.8, 1193.0, 1181.5, 1099.5, 1036.8, 1005.9, 939.4, 894.0, 838.1, 806.3, 777.4, 692.5 cm^{-1}. HRMS (EI) Calcd for $C_{17}H_{33}O_3Si$: $[M–H]^+$, 313.2199. Found: *m/z* 313.2191.

***tert*-Butyl(hex-2-en-3-yloxy)dimethylsilane (E/Z mixture, 95/5) (6nb)**.



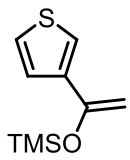
^{1}H NMR ($CDCl_3$) δ 4.63 (q, *J* = 6.5 Hz, 0.05H), 4.48 (q, *J* = 6.5 Hz, 0.95H), 2.03 (t, *J* = 7.0 Hz, 0.10H), 1.96 (t, *J* = 7.5 Hz, 1.90H), 1.52 (d, *J* = 6.5 Hz, 3H), 1.47 (tq, *J* = 7.5, 7.5 Hz, 2H), 0.95 (s, 9H), 0.89 (t, *J* = 7.5 Hz, 3H), 0.12 (s, 5.70H), 0.11 (s, 0.30H). ^{13}C NMR ($CDCl_3$) δ 151.3, 101.8, 38.9, 26.0, 20.5, 18.5, 13.9, 11.0, –3.8. IR (neat) 2958.9, 2930.0, 2859.6, 2808.5, 2360.0, 2331.1, 1672.4, 1465.0, 1253.8, 1194.0, 1110.1, 914.3, 837.1, 777.4, 665.5 cm^{-1}. HRMS (EI) Calcd for $C_{12}H_{26}OSi$: $[M]^+$, 214.1753. Found: *m/z* 214.1752.

((1-(Furan-3-yl)vinyl)oxy)trimethylsilane (6oa).



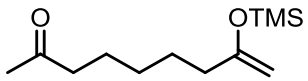
^{1}H NMR ($CDCl_3$) δ 7.49 (bs, 1H), 7.33 (t, *J* = 2.0 Hz, 1H), 6.45 (dd, *J* = 1.0, 1.0 Hz, 1H), 4.56 (d, *J* = 1.5 Hz, 1H), 4.30 (d, *J* = 1.5 Hz, 1H), 0.25 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 150.0, 143.2, 140.2, 125.3, 108.0, 90.8, 0.1. IR (neat) 2959.9, 2917.5, 2904.0, 2850.0, 2377.4, 1319.4, 1253.8, 1168.0, 1100.4, 1070.5, 1009.8, 956.7, 843.9, 795.7 cm^{-1}. HRMS (EI) Calcd for $C_9H_{14}O_2Si$: $[M]^+$, 182.0763. Found: *m/z* 182.0762.

Trimethyl((1-(thiophen-3-yl)vinyl)oxy)silane (6pa): CAS RN [101306-15-4].



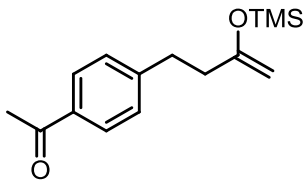
^{1}H NMR ($CDCl_3$) δ 7.36 (dd, *J* = 3.0, 1.0 Hz, 1H), 7.24 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.20 (dd, *J* = 5.0, 1.5 Hz, 1H), 4.76 (d, *J* = 1.5 Hz, 1H), 4.37 (d, *J* = 1.5 Hz, 1H), 0.27 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 152.1, 140.3, 125.6, 125.2, 121.8, 90.8, 0.1.

8-((Trimethylsilyl)oxy)non-8-en-2-one (6i).



^{1}H NMR ($CDCl_3$) δ 4.03 (bs, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 2.00 (t, *J* = 7.5 Hz, 2H), 1.58 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.46 (tt, *J* = 7.5, 7.5 Hz, 2H), 1.30 (tt, *J* = 7.5, 7.5 Hz, 2H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 209.3, 159.2, 89.9, 47.7, 36.2, 29.9, 28.5, 26.5, 23.6, 0.1. IR (neat) 3111.3, 2940.6, 2860.6, 2361.9, 2321.4, 1718.7, 1430.3, 1358.9, 1252.8, 1222.9, 1168.9, 1145.8, 1092.7, 1016.5, 895.0, 845.8, 755.2, 684.8 cm^{-1}. HRMS (ESI) Calcd for $C_{12}H_{25}O_2Si$: $[M+H]^+$, 229.1618. Found: *m/z* 229.1617.

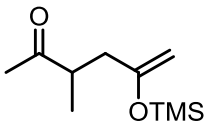
1-(4-(3-((Trimethylsilyl)oxy)but-3-en-1-yl)phenyl)ethan-1-one (6k).



^{1}H NMR ($CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 4.04 (d, *J* = 1.0 Hz, 1H), 4.03 (d, *J* = 1.0 Hz, 1H), 2.84 (dd, *J* = 8.0, 6.5 Hz, 2H), 2.58 (s, 3H), 2.34 (dd, *J* = 8.0, 6.5 Hz, 2H), 0.21 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 198.0, 158.2, 147.9, 135.3, 128.8, 128.6, 90.6, 38.0, 33.0, 26.7, 0.3. IR (neat) 2958.9, 2931.9, 1685.9, 1635.7, 1607.7, 1430.3, 1412.9, 1338.7, 1290.4, 1268.3, 1252.8, 1221.0, 1182.4, 1154.5, 1112.0, 1032.0, 1005.9, 954.8, 923.9, 847.8, 755.2, 685.7 cm^{-1}. HRMS (EI)

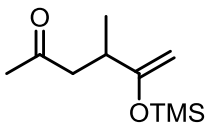
Calcd for $C_{15}H_{22}O_2Si$: $[M]^+$, 262.1389. Found: *m/z* 262.1388.

3-Methyl-5-((trimethylsilyl)oxy)hex-5-en-2-one (6l).



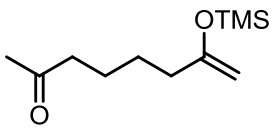
^{1}H NMR ($CDCl_3$) δ 4.05 (bs, 1H), 4.04 (bs, 1H), 2.74 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.40 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.16 (s, 3H), 2.06 (ddq, *J* = 13.5, 6.5, 6.5 Hz, 1H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 212.0, 156.5, 91.3, 44.5, 39.8, 28.3, 15.7, –0.1. IR (neat) 2963.8, 2920.4, 2360.0, 2312.8, 1714.8, 1635.7, 1576.9, 1510.3, 1457.3, 1338.7, 1287.5, 1251.9, 1091.8, 1012.7, 842.9, 742.6, 668.4 cm^{-1}. HRMS (ESI) Calcd for $C_{10}H_{21}O_2Si$: $[M+H]^+$, 201.1305. Found: *m/z* 201.1302.

4-Methyl-5-((trimethylsilyl)oxy)hex-5-en-2-one (6m).



^{1}H NMR ($CDCl_3$) δ 4.06 (bs, 1H), 3.99 (bs, 1H), 2.67 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.36 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.16 (s, 3H), 2.07 (ddq, *J* = 13.5, 6.5, 6.5 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.20 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 208.3, 162.0, 88.3, 48.5, 36.0, 30.4, 18.4, 0.0. IR (neat) 2965.7, 2917.5, 2850.0, 2598.2, 2375.4, 2310.8, 1717.7, 1539.3, 1253.8, 1010.7, 844.9, 665.5 cm^{-1}. HRMS (ESI) Calcd for $C_{10}H_{21}O_2Si$: $[M+H]^+$, 201.1305. Found: *m/z* 201.1305.

7-((Trimethylsilyl)oxy)oct-7-en-2-one (6q).



^{1}H NMR ($CDCl_3$) δ 4.03 (bs, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 2.01 (t, *J* = 7.5 Hz, 2H), 1.58 (m, 2H), 1.45 (m, 2H), 0.19 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 209.2, 158.9, 90.1, 43.6, 36.2, 29.9, 26.3, 23.2, 0.1. IR (neat) 2942.5, 2859.6, 1718.7, 1715.8, 1672.4, 1635.7, 1433.2, 1412.0, 1357.9, 1252.8, 1222.9, 1169.9, 1145.8, 1016.5, 846.8, 755.2, 683.8 cm^{-1}. HRMS (EI) Calcd for $C_{11}H_{22}O_2Si$: $[M]^+$, 214.1389. Found: *m/z* 214.1386.

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Chapter 3

Preparation of the Zinc Enolate Equivalent of Amides by Zinciomethylation of Isocyanates: Catalytic Asymmetric Reformatsky-Type Reaction

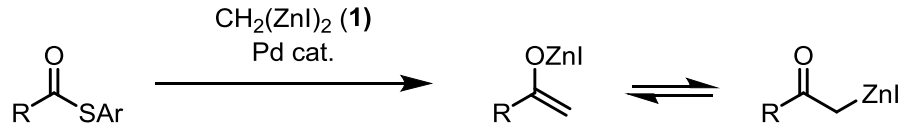
Bis(iodozincio)methane transforms isocyanates into the enolate equivalent of amides via zinciomethylation. The reactivity of the enolate equivalent as a nucleophile toward aldehydes depends on the R group of the isocyanate. For the enolate equivalent formed from phenyl isocyanate, the addition of a catalytic amount of an optically active amino alcohol, which acts as an activator, leads to a catalytic asymmetric Reformatsky-type reaction.

Introduction

Organozinc reagents have been widely used as versatile nucleophiles, which possess reasonable reactivity and high compatibility with various functional groups.[1] Some classical methods, such as metal–zinc exchange, deprotonation, and halogen–zinc exchange, have been utilized to prepare these reagents. These methods are problematic, as the conditions used are often too harsh for some functional groups in the target organozinc species. However, the use of complex reagent systems has changed the situation dramatically. For example, it has been shown that the insertion of zinc into organic halides is facilitated in the presence of a stoichiometric amount of lithium chloride.[2] Amide zincates[3] and the zinc–magnesium–lithium complex base, $(tmp)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$,[4] have been shown to be useful reagents to provide heteroarylzinc compounds by deprotonation. These reagents have led to a renewed interest in organozinc species as an indispensable tool for organic synthesis.[5] To increase the value of organozinc reagents as synthetic tools, a completely different strategy for the preparation of these reagents may be significant.

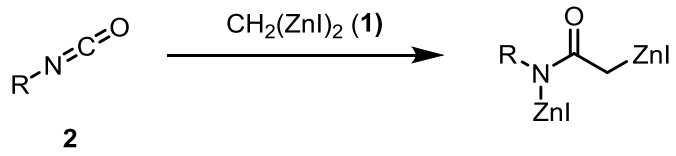
Bis(iodozincio)methane (**1**),[6] which is easily obtained from diiodomethane and zinc powder,[7] has two C–Zn bonds at the same carbon. A number of specific molecular transformations, based on its reactivity as a *gem*-dimetal species, have been shown.[8] Among these transformations, a zinciomethylation reaction can be focused on as a new method for the preparation of organozinc species.[9] For example, a palladium-catalyzed cross-coupling reaction of iodobenzene with **1** gave a benzylzinc reagent. Moreover, treatment of acylating reagents with **1** gives α-iodozinciocarbonyl compounds, which can tautomerize into the corresponding enolates. In fact, treatment of a thioester with dizinc **1** and trimethylsilyl chloride in the presence of a palladium catalyst gave the corresponding silyl enolate via Fukuyama coupling [Scheme 1, (1)].[10] In this study, the author focus on the use of isocyanates as electrophiles [Scheme 1, (2)]. He discuss the synthesis and reactivity of the zinc enolate equivalent of amides, which can be prepared by the addition of dizinc **1** to isocyanates **2**.[11]

(1) Preparation of Zinc Enolate



(Ar = 4-$NO_2C_6H_4$)

(2) Preparation of Zinc Enolate Equivalent



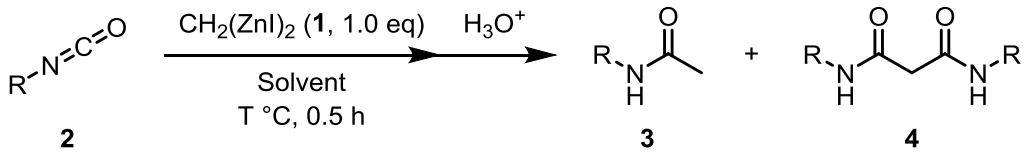
Scheme 1. Homologative Preparation of Zinc Enolate: (1) Cross-Coupling Reaction of Thiol Esters with **1**; (2) Nucleophilic Addition of **1** to Isocyanates **2**.

Results and Discussion

Various isocyanates were treated with dizinc **1** (Table 1). A tetrahydrofuran solution of **1** (0.13 M, 1.5 mL) was added to a solution of the isocyanate **2** (0.2 mmol) in solvent (4 mL). The resulting reaction mixture was quenched with a saturated aqueous solution of ammonium chloride. At 25 °C, benzoyl isocyanate (**2a**, R = Bz) gave the corresponding amide **3a** and the diamide **4a**; the diamide **4a** is the adduct of the initial zinciomethylated product with another equivalent of isocyanate **2a** (Table 1, entry 1). Lowering the reaction temperature (–60 °C), to prevent the formation of **4a** gave **3a** selectively (Table 1, entry 3). Aryl and alkyl isocyanates **2b**–**e** were less electrophilic than **2a** in the reaction with dizinc **1**. To complete the addition of **1** to phenyl isocyanate (**2b**), a higher reaction temperature (80 °C) was required (Table 1, entries 4 and 5). The use of toluene as a less polar solvent did not affect the yield of **3b** (Table 1, entry 6). The addition of substituents to the aryl isocyanates to tune the electron density on the benzene ring resulted in a slight decrease in the yield (Table 1, entries 7 and 8). An alkyl (cyclohexyl)

isocyanate also gave the corresponding amide **3e** at 80 °C (Table 1, entry 9).

Table 1. Reaction of Dizinc **1** with Isocyanates **2**.[a]

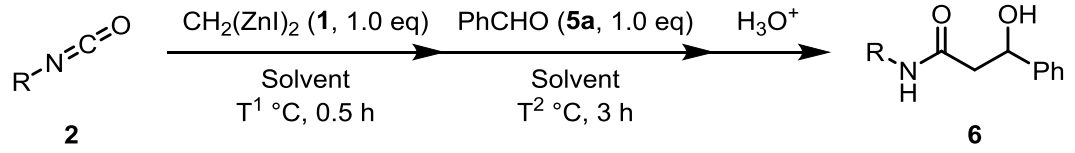


entry	R	Solvent	T (°C)	Yield of **3** (%)[b]	Yield of **4** (%)[b]
1	Bz (**2a**)	THF	25	6 (**3a**)	88 (**4a**)
2	Bz (**2a**)	THF	0	32 (**3a**)	62 (**4a**)
3	Bz (**2a**)	THF	–60	73 (**3a**)	16 (**4a**)
4	Ph (**2b**)	THF	25	48 (**3b**)	<1
5	Ph (**2b**)	THF	80	99 (**3b**)	<1
6	Ph (**2b**)	Toluene	80	99 (**3b**)	<1
7	4-$MeOC_6H_4$ (**2c**)	THF	80	88 (**3c**)	<1
8	4-$F_3CC_6H_4$ (**2d**)	THF	80	96 (**3d**)	<1
9	Cy (**2e**)	THF	80	95 (**3e**)	<1

[a] Reactions were carried out using *gem*-dizinc **1** (0.2 mmol) and isocyanate **2** (0.2 mmol), in the solvent (4.0 mL). [b] Yields were determined by ^{1}H NMR using dibromomethane as an internal standard.

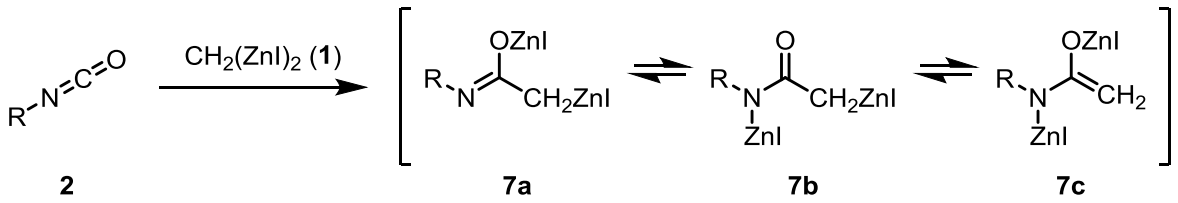
The addition of benzaldehyde in place of the aqueous workup was examined to perform a Reformatsky-type reaction. The corresponding enolate equivalent formed from benzoyl isocyanate (**2a**) showed high nucleophilicity toward benzaldehyde (**5a**), even at –40 °C, and gave the adduct **6aa** in 90% yield (Table 2, entry 1). In the case of the enolate equivalent formed from phenyl isocyanate (**2b**), a higher reaction temperature (140 °C) was required to give the corresponding adduct **6ba** in reasonable yield (Table 2, entry 5). The other isocyanates, **2c**–**e**, also gave the corresponding adducts **6ca**–**ea** in poor yields at 25 °C (Table 2, entries 6–8).

Table 2. Reformatsky-Type Reaction Starting from Dizinc **1** and Isocyanates **2**.[a]

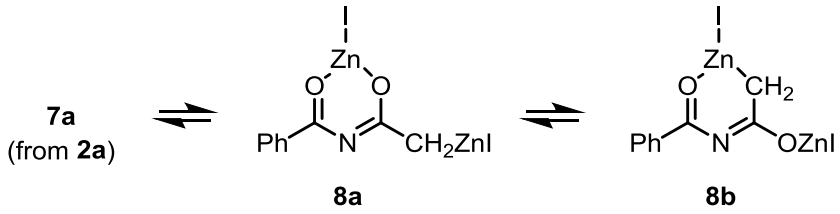


entry	R	Solvent	T^1 (°C)	T^2 (°C)	Yield of **6** (%)[b]
1	Bz (**2a**)	THF	–60	–40	90 (**6aa**)
2	Ph (**2b**)	THF	80	–40	<5 (**6ba**)
3	Ph (**2b**)	THF	80	25	13 (**6ba**)
4	Ph (**2b**)	Toluene	80	25	20 (**6ba**)
5	Ph (**2b**)	Toluene	80	140	85 (**6ba**)
6	4-$MeOC_6H_4$ (**2c**)	Toluene	80	25	22 (**6ca**)
7	4-$F_3CC_6H_4$ (**2d**)	Toluene	80	25	39 (**6da**)
8	Cy (**2e**)	Toluene	80	25	6 (**6ea**)

[a] Reactions were carried out using *gem*-dizinc **1** (0.2 mmol), isocyanate **2** (0.2 mmol), and PhCHO (**5a**, 0.2 mmol) in the solvent (4.0 mL). [b] Yields were determined by ^{1}H NMR using dibromomethane as an internal standard.



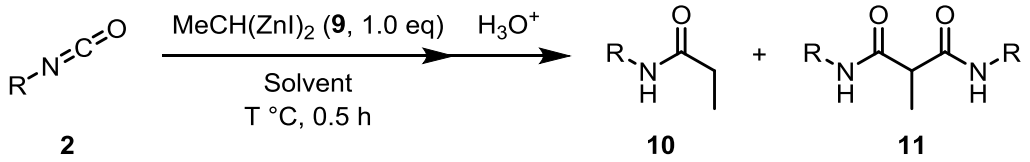
Scheme 2. Possible Structures of the Adduct Formed from Dizinc **1** and an Isocyanate **2**.



Scheme 3. Possible Chelation of the Enolate Equivalent **7a** Formed from **1** and **2a**.

The enolate equivalent adduct of dizinc **1** and an isocyanate **2** has three possible forms, **7a**–**c** (Scheme 2). Although these structures are in equilibrium, the contribution of each structure depends on the R group. ^{1}H NMR analysis of the mixture resulting from the reaction of dizinc **1** and benzoyl isocyanate (**2a**) or phenyl isocyanate (**2b**) in tetrahydrofuran-d_8 gave some insight on the preferred structure of the formed enolate equivalents. The singlet peak at –1.3 ppm from the reaction of **1** and **2a** (R = Bz) suggests the formation of imine-like **7a**, while the singlet peak at 1.8 ppm from the reaction of **1** and **2b** (R = Ph) implies the formation of *C*-enolate **7b**.[12] The upfield chemical shift of the enolate equivalent from **2a** implies this compound has a stronger anionic character than that of the enolate equivalent from **2b**. The higher nucleophilicity observed for the **2a** enolate equivalent in the reaction with aldehydes can be understood in this way. As shown in Scheme 3, it is also plausible that enolate equivalent **7a**, formed from **2a**, may form chelated structures **8a** and **8b**. There is some enhancement of negative charge on the α-carbon atom in **8b**.

Table 3. Reaction of Dizinc **9** with Isocyanates **2**.[a]



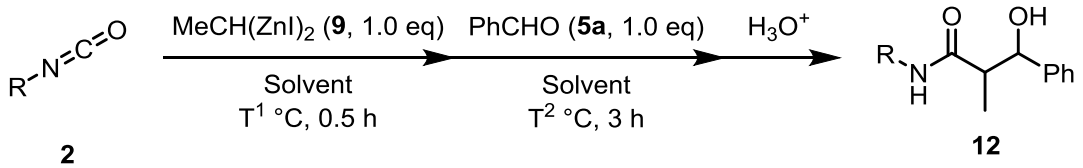
entry	R	Solvent	T (°C)	Yield of **10** (%)[b]	Yield of **11** (%)[b]
1	Bz (**2a**)	THF	–20	53 (**10a**)	<1
2	Bz (**2a**)	THF	–40	48 (**10a**)	<1
3	Ph (**2b**)	THF	–60	53 (**10a**)	<1
4	Ph (**2b**)	THF	25	<1	<1
5	Ph (**2b**)	THF	80	13 (**10b**)	<1
6	Ph (**2b**)	Toluene	80	22 (**10b**)	<1

[a] Reactions were carried out using *gem*-dizinc **9** (0.2 mmol) and isocyanate **2** (0.2 mmol), in the solvent (4.0 mL). [b] Yields were determined by ^{1}H NMR using dibromomethane as an internal standard.

Treatment of 1,1-diiodoethane with zinc powder in the presence of a lead catalyst also gives the corresponding *gem*-dizinc reagent, 1,1-bis(iodozincio)ethane (**9**). The reaction of **9** and isocyanates **2** affords the zinc enolate equivalent of propionamide. As shown in Table 3, the formation of the enolate equivalent was evaluated by the yield of the protonated amide products.

The Reformatsky-type reaction was also examined for the enolate equivalents formed from dizinc **9** and isocyanates **2**. As shown in Table 4 (entry 1), the enolate equivalent formed from **9** and **2a** reacted with benzaldehyde (**5a**) to give the adduct **12aa** in 47% yield with a *syn/anti* diastereoselectivity of 6:1.[13] The reactivity of the enolate equivalent formed from **9** and **2b** was too low to undergo the Reformatsky-type reaction with **5a** (Table 4, entries 2–4). The low reactivity to aldehyde at 25 °C of the enolate equivalents of amides prepared from dizinc **1** and phenyl isocyanate (**2b**) or cyclohexyl isocyanate **(2e**) (Table 2, entries 4 and 8), implied the possibility of asymmetric induction of the Reformatsky-type reaction in the presence of a catalytic amount of an optically active activator.

Table 4. Reformatsky-Type Reaction Starting from Dizinc **9** and Isocyanates **2**.[a]

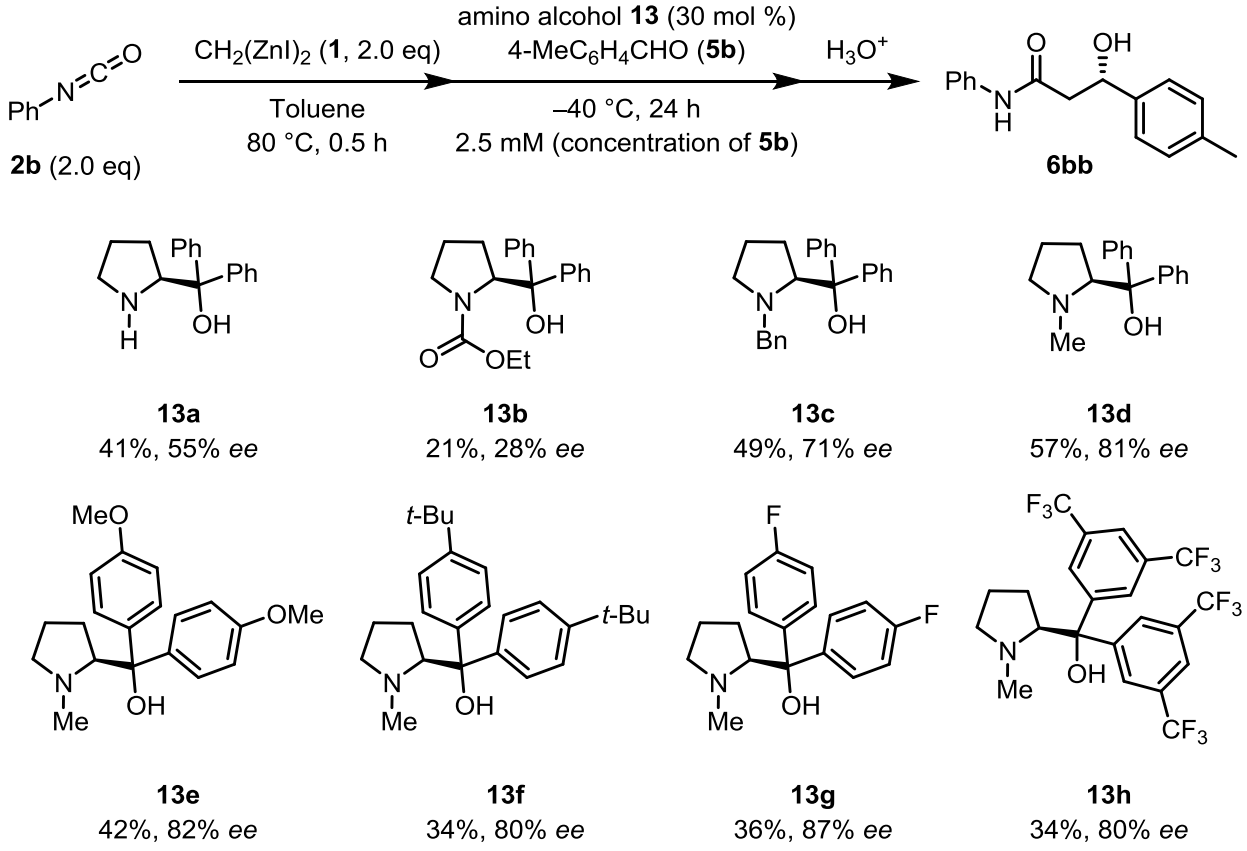


entry	R	Solvent	T^1 (°C)	T^2 (°C)	Yield of **12** (%)[b]	*syn*:*anti*
1	Bz (**2a**)	THF	–60	–40	47 (**12aa**)	6:1
2	Ph (**2b**)	Toluene	80	–40	<1 (**12ba**)	–
3	Ph (**2b**)	Toluene	80	25	<1 (**12ba**)	–
4	Ph (**2b**)	Toluene	80	140	<1 (**12ba**)	–

[a] Reactions were carried out using *gem*-dizinc **9** (0.2 mmol) isocyanate **2** (0.2 mmol), and PhCHO (**5a**, 0.2 mmol) in the solvent (4.0 mL). [b] Yields were determined by ^{1}H NMR using dibromomethane as an internal standard.

Although a variety of catalytic asymmetric alkylations of aldehydes using organozinc

reagents have been developed,[14] examples of the catalytic asymmetric Reformatsky-type reaction using a zinc enolate are limited.[15] Several examples of the Reformatsky reaction using stoichiometric amounts of a chiral source[16] and a few examples of catalytic asymmetric zinc enolate aldol reactions[17] have already been reported.

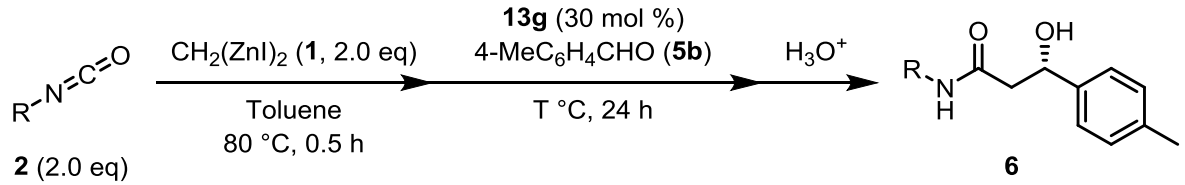


Scheme 4. Asymmetric Induction in the Reaction of the Enolate Equivalent Formed from **1** and **2b** with *p*-Tolylaldehyde (**5b**) in the Presence of L-Proline-Derived Amino Alcohols **13**.

Optically active amino alcohols **13**, which were derived from L-proline, were added in a catalytic amount (30 mol %) to activate the enolate equivalent **7** formed from dizinc **1** and phenyl isocyanate (**2b**) for the addition to *p*-tolylaldehyde (**5b**) (Scheme 4). In all cases, asymmetric induction was observed. Among the structures of **13**, (*S*)-bis(4-fluorophenyl)(1-methylpyrrolidin-2-yl)methanol (**13g**) induced the highest

enantioselectivity (87% *ee*). The reactions in Scheme 4 were performed under dilution conditions to ensure a slow reaction rate, as the milder conditions may benefit the asymmetric induction: in each case, the concentration of **5b** was 2.5 mM. More concentrated conditions were examined, which resulted in slightly lower enantioselectivities (Table 5, entries 1 and 2).

Table 5. Optimization of the Catalytic Asymmetric Reformatsky-Type Reaction Using the Enolate Equivalent Formed from **1** and **2b** or **2e** in the Presence of **13g**.[a]

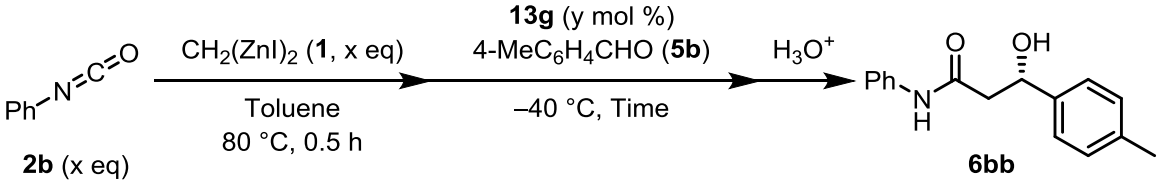


entry	R	T (°C)	Concn of **5b** (mM)	Yield of **6** (%)[b]	ee (%)
1	Ph (**2b**)	–40	10.0	88 (**6bb**)	73
2	Ph (**2b**)	–40	5.0	59 (**6bb**)	79
3	Ph (**2b**)	–40	2.5	36 (**6bb**)	87
4	Ph (**2b**)	0	2.5	36 (**6bb**)	61
5	Cy (**2e**)	–40	2.5	5 (**6eb**)	45
6	Cy (**2e**)	0	2.5	3 (**6eb**)	60

[a] Reactions were carried out using *gem*-dizinc **1** (0.2 mmol) and isocyanate **2** (0.2 mmol), *p*-tolylaldehyde (**5b**, 0.1 mmol), and aminoalcohol **13g** (0.03 mmol) in toluene (10.0 mL for entry 1, 20.0 mL for entry 2, 40 mL for entry 3–6). [b] Isolated yields.

As indicated in Table 2, successful asymmetric induction was also expected in the case of the less reactive enolate equivalent **7** formed from dizinc **1** and cyclohexyl isocyanate (**2e**); unfortunately, the yields and enantioselectivity obtained for the asymmetric Reformatsky-type reaction were inferior to those obtained for the enolate equivalent formed from **1** and phenyl isocyanate (**2b**) (Table 5, entries 5 and 6).

Table 6. Optimization of the Reaction of the Enolate Equivalent Formed from **1** and **2b** with *p*-Tolylaldehyde (**5b**) in the Presence of a Catalytic Amount of **13g**.[a]

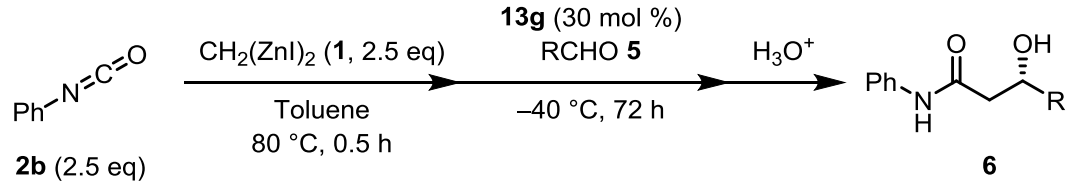


entry	x (eq)	y (mol %)	Time (h)	Yield of **6bb** (%)[b]	ee (%)
1	2.0	30	24	36	87
2	2.0	30	48	35	83
3	2.0	30	72	52	84
4	2.5	30	72	99	84
5	2.5	20	72	68	81
6	2.5	10	72	56	75

[a] Reactions were carried out using *gem*-dizinc **1** (0.2 mmol for entry 1–3, 0.25 mmol for entry 4–6) and phenylisocyanate (**2b**, 0.2 mmol for entry 1–3, 0.25 mmol for entry 4–6), *p*-tolylaldehyde (**5b**, 0.1 mmol), and aminoalcohol **13g** (0.03 mmol for entry 1–4, 0.02 mmol for entry 5, 0.01 mmol for entry 6) in toluene (40.0 mL). [b] Isolated yields.

Optimization of the reaction parameters for the addition of the enolate equivalent **7** formed from dizinc **1** and phenyl isocyanate (**2b**) to *p*-tolylaldehyde (**5b**) in the presence of **13g** was examined (Table 6). When the reaction was performed by adding 2.5 equivalents of the enolate to **5b** in the presence of 30 mol % **13g** for 72 hours, the adduct **6bb** was obtained in 99% yield with 84% *ee* (Table 6, entry 4). When less catalyst was used, the yield of the product was decreased (Table 6, entries 5 and 6).

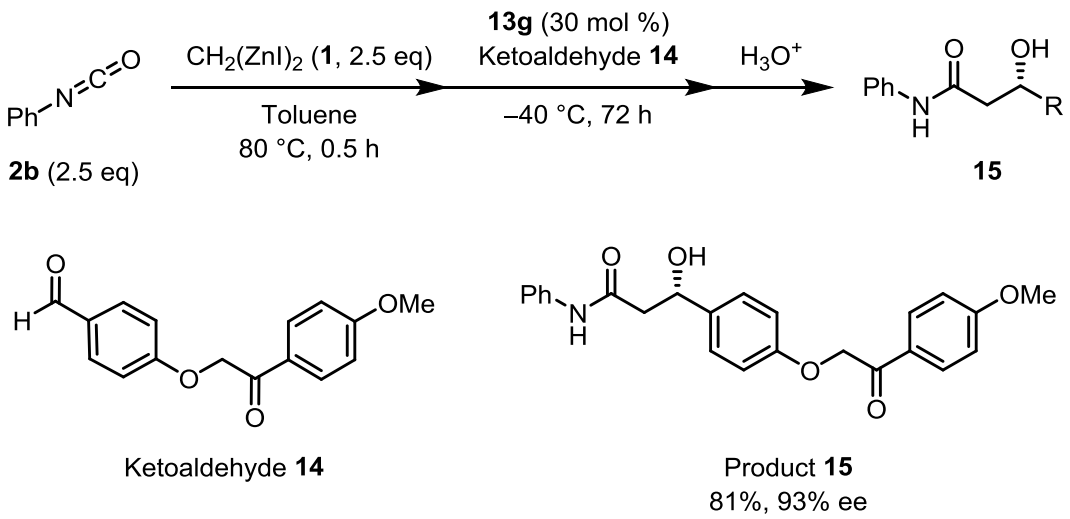
Table 7. Examples of the Reaction of **7** Formed from **1** and **2b** with Aldehydes **5** in the Presence of a Catalytic Amount of **13g**.[a]



Entry	R	Yield of **6** (%)[b]	ee (%)
1	4-MeC_6H_4	99 (**6bb**)	84
2	2-MeC_6H_4	91 (**6bc**)	84
3	4-FC_6H_4	77 (**6bd**)	89
4	4-ClC_6H_4	76 (**6be**)	79
5	4-BrC_6H_4	47 (**6bf**)	77
6	4-$MeOC_6H_4$	65 (**6bg**)	94
7	4-*t*-BuC_6H_4	57 (**6bh**)	84
8	Mes	63 (**6bi**)	84
9	2-Naph	89 (**6bj**)	88
10	2-Thienyl	73 (**6bk**)	94
11	2-Furyl	92 (**6bl**)	76
12	Me	45 (**6bm**)	76
13	*t*-Bu	49 (**6bn**)	83

[a] Reactions were carried out using *gem*-dizinc **1** (0.25 mmol) and phenylisocyanate (**2b**, 0.25 mmol), aldehyde **5** (0.1 mmol), and aminoalcohol **13g** (0.03 mmol) in toluene (40.0 mL). [b] Isolated yields.

As shown in Table 7, the reactions of this enolate equivalent with various aldehydes were examined using the conditions of entry 4 in Table 6. In all cases, the products **6bb**–**bn** were obtained with over 76% *ee*. Compared to previously reported catalytic asymmetric Reformatsky-type reactions, the present results show competitive optical yields.



Scheme 5. Asymmetric Induction in the Chemoselective Reformatsky-Type Reaction.

The moderate reactivity of the enolate equivalent **7** can realize an asymmetric Reformatsky-type reaction with aldehydes even in the presence of a keto group. As shown in Scheme 5, treatment of keto aldehyde **14** with the enolate equivalent **7** formed from dizinc **1** and phenyl isocyanate (**2b**) in the presence of amino alcohol **13g** (30 mol %) afforded the corresponding product **15** in 81% yield with 93% *ee*; the keto group in the substrate remained intact.

Conclusion

In conclusion, the enolate equivalents prepared from isocyanates and dizinc compounds have only moderate nucleophilicity, which can be enhanced by the addition of a catalytic amount of a 2-amino alcohol. When the added 2-amino alcohol is optically active, moderate to good asymmetric induction is observed. In addition, the asymmetric Reformatsky-type reaction with aldehydes can be performed chemoselectively, even in the presence of a keto group. This reaction of a dizinc compound with an isocyanate is a novel strategy for obtaining an amide enolate equivalent, which has unique reactivity. The reasonable catalytic asymmetric induction in these reactions was accomplished with an optically active Lewis base, not with an optically active Lewis acid.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification. Aldehydes **5a-5n** were commercially available. All isocyanates listed in Chapter 3 were commercially available. Chiral aminoalcohols **13a**–**13h** were prepared according to the literature.[18] Bis(iodozincio)methane (**1**) and 1,1-bis(iodozincio)ethane (**9**) were prepared by the method described in Chapter 2.

General procedure for asymmetric synthesis of *β*-hydroxy amides 6bb–6bn and 15

To a solution of phenyl isocyanate (**2b**, 0.25 mmol) in toluene (4.0 mL), dizinc **1** (0.13 M in THF, 2.0 mL, 0.25 mmol) was added dropwise at 80 °C under argon. After being stirred for 30 min at 80 °C, the mixture was diluted with toluene (30 mL) at –40 °C. To the resulting mixture, (*S*)-bis(4-fluorophenyl)(1-methylpyrrolidin-2-yl)methanol (**13g**, 0.03 mmol) in toluene (2.0 mL) and aldehyde **5** (0.1 mmol) in toluene (2.0 mL) were added. The resulting mixture was stirred at –40 °C for 72 h, then poured into sat. NH_4Claq and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the corresponding *β*-hydroxy amides **6.**

Procedure for Reformatsky-type reaction for the formation of 6aa

To a solution of benzoyl isocyanate (**2a**, 0.2 mmol) in THF (4.0 mL), dizinc **1** (0.13 M in THF, 0.2 mmol) was added dropwise at –60 °C under argon. The reaction mixture was stirred for 30 min at –60 °C. After the reaction mixture was warmed to –40 °C, benzaldehyde (**5a**, 0.2 mmol) was added to the resulting mixture. The resulting mixture was stirred at –40 °C for 3 h, then poured into sat. NH_4Claq and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure,

and the residue was purified by silica gel column chromatography to give compound **6aa**.

General procedure for Reformatsky-type reaction for the formation of 6ba-6ea

To a solution of isocyanate **2** (0.2 mmol) in THF or toluene (4.0 mL), dizinc **1** (0.13 M in THF, 0.2 mmol) was added dropwise at 80 °C under argon. The reaction mixture was stirred for 30 min at 80 °C. Then, benzaldehyde (**5a**, 0.2 mmol) was added to the resulting mixture at 25 °C. The mixture was stirred at 25 °C for 3 h, then poured into sat. NH_4Claq and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the corresponding *β*-hydroxy amides **6**.

General Procedure for Preparation of Aminoalcohols 13 except for 13c

To a solution of proline (3.45 g, 30 mmol) in MeOH (60 mL), K_2CO_3 (4.15 g, 30 mmol) and ethyl carbonochloridate (6.51g, 60 mmol) were added sequentially at 25 °C. After the mixture being stirred for 12 h at 25 °C, MeOH was removed by evaporation. The residue was dissolved in $CHCl_3$ / water (40 mL / 40 mL). The aqueous phase was extracted with $CHCl_3$ (25 mL × 4). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. Without any purification, (*S*)-1-ethyl-2-methyl pyrrolidine-1,2-dicarboxylate was used for next step. To a solution of arylmagnesium bromide (40 mmol, 1.0 M in THF) was added dropwise the obtained (*S*)-1-ethyl 2-methyl pyrrolidine-1,2-dicarboxylate (2.01 g, 10 mmol) in THF (10 mL) at 0 °C under Ar. After being stirred for 3 h at 0 °C, the resulting mixture was poured into 1 M HClaq and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (hexane / ethyl acetate) gave the corresponding (*S*)-ethyl-2-(hydroxydiarylmethyl)pyrrolidine-1-carboxylate. Next, to a solution of lithium aluminium hydride (0.33 g, 8.8 mmol) in THF (10 mL) was added the obtained (*S*)-ethyl-2-(hydroxydiarylmethyl)pyrrolidine-1-carboxylate at 0 °C and was stirred for 30 min at

90 °C under Ar. To the reaction mixuture was added sequentially water (0.33 mL), 15% NaOHaq (0.33 mL), and water (1.0 mL) at 0 °C. The mixture was separated by filtration through glass filter G3 and the filtrate was concentrated in vacuo. Purification by silica gel column chromatography using $CHCl_3$ as an eluent gave the corresponding aminoalcohol (**7**). Instead of the reduction by lithium aluminium hydride, hydrolysis of (*S*)-ethyl-2-(hydroxydiphenylmethyl)- pyrrolidine-1-carboxylate by potassium hydroxide gave (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**7a**). To a solution of (*S*)-ethyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (0.98 g, 3.0 mmol) in MeOH (10 mL) was added KOH (1.68 g, 30 mmol) at 25 °C and for 4 h under MeOH reflux. The resulting mixture was poured into water and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Purification by silica gel column chromatography using $CHCl_3$ / MeOH (v/v = 20/1) as an eluent gave (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**7a**) in 48% yield.

Procedure for Preparation of Aminoalcohols 13c

To a solution of proline (1.15 g, 10 mmol) in EtOH (15 mL) was added dropwise at 0 °C. After the mixture being stirred at 60 °C for 30 min, EtOH was removed by evaporation. The obtained residue was used to next step without any purification. To a solution of obtained residue (1.79 g, 10 mmol) in acetone (10 mL) were added K_2CO_3 (2.76 g, 20 mmol) and benzyl bromide (3.40 g, 15 mmol) in acetone (5 mL) at 25 °C for 12 h. The mixture was separated by filtration through glass filter G3 and filtrate was concentrated in vacuo. Purification by silica gel column chromatography using ($CHCl_3$ / MeOH) as an eluent gave the (*S*)-ethyl 1-benzylpyrrolidine-2-carboxylate. To a solution of phenylmagnesium bromide (8.34 mL, 8.34 mmol, 1.0 M in THF) was added dropwise (*S*)-ethyl 1-benzylpyrrolidine-2-carboxylate (0.65 g, 2.78 mmol) in THF (1.66 mL) at 25 °C over 5 min. The reaction mixture was allowed to stir at 25 °C for 3 h and was quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Purification by silica gel column

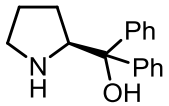
chromatography using ($CHCl_3$ / MeOH) as an eluent gave (*S*)-(1-benzylpyrrolidin-2-yl)diphenylmethanol (**7c**).

Procedure for Preparation of 4-(2-(4-methoxyphenyl)-2-oxoethoxy)benzaldehyde (14)

4-Hydroxybenzaldehyde (0.86 g, 7.0 mmol), 2-bromo-1-(4-methoxyphenyl)ethanone (1.60 g, 7.0 mmol), and K_2CO_3 (1.94 g, 14.0 mmol) were dissolved in DMF (7.0 mL), and the solution was stirred for 1 h at 25 °C. The resulting mixture was poured into HClaq (20%) at 0 °C. Then, the formed white solid was separated by filtration through glass filter G3 and the residue was washed with water. The obtained white solid was purified by recrystallization from EtOH to give ketoaldehyde **14c** (1.00 g, 53%) as a white solid.

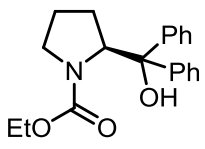
Characterization Data

(*S*)-Diphenyl(pyrrolidin-2-yl)methanol (13a): CAS RN [112068-01-6].



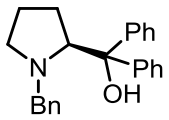
White solid. ^{1}H NMR ($CDCl_3$) δ 7.58 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.50 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.29 (m, 4H), 7.17 (m, 2H), 4.26 (t, *J* = 7.5 Hz, 2H), 3.04 (m, 1H), 2.95 (m, 1H), 1.66 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 148.2, 145.4, 128.2, 127.9, 126.4, 126.3, 125.9, 125.5, 77.1, 64.5, 46.8, 26.3, 25.5.

(*S*)-Ethyl 2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (13b): CAS RN [152326-82-4].



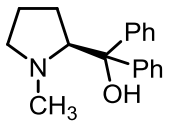
White solid. ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 4H), 7.29 (m, 6H), 6.08 (s, 1H), 4.93 (dd, *J* = 9.0, 3.5 Hz, 1H), 4.12 (m, 2H), 3.41 (d, *J* = 8.0 Hz, 1H), 2.95 (s, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 1.49 (m, 1H), 1.23 (t, *J* = 7.5 Hz, 3H), 0.79 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 158.4, 146.4, 143.7, 128.2, 127.9, 127.6, 127.4, 123.9, 127.2, 127.1, 81.6, 66.0, 61.9, 47.7, 29.7, 23.0, 14.6.

(*S*)-(1-Benzylpyrrolidin-2-yl)diphenylmethanol (13c): CAS RN [118970-95-9].



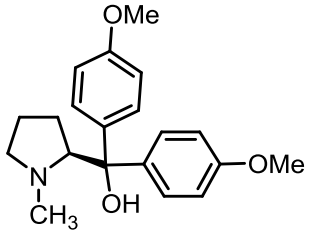
White solid. ^{1}H NMR ($CDCl_3$) δ 7.73 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.58 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.23 (m, 8H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 2H), 4.94 (s, 1H), 3.98 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.22 (d, *J* = 12.5 Hz, 1H), 3.03 (d, *J* = 12.5 Hz, 1H), 2.92 (m 1H), 2.36 (m, 1H), 1.97 (m, 1H), 1.76 (m, 1H), 1.64 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 148.1, 146.7, 139.7, 128.6, 128.2, 128.1, 128.1, 126.8, 126.4, 126.2, 125.6, 125.6, 77.9, 70.7, 60.6, 55.5, 29.8, 24.1.

(*S*)-(1-Methylpyrrolidin-2-yl)diphenylmethanol (13d): CAS RN [110529-22-1].



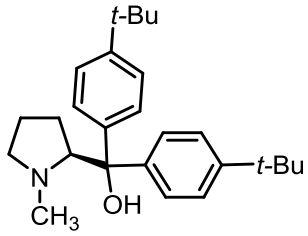
White solid. ^{1}H NMR ($CDCl_3$) δ 7.65 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.55 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.28 (dt, *J* = 7.0, 3.0 Hz, 4H), 7.15 (m, 2H), 4.79 (s, 1H), 3.63 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.12 (m, 1H), 2.46 (m, 1H), 1.92 (m, 1H), 1.83 (s, 3H), 1.68 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 148.3, 146.7, 128.0, 128.0, 126.1, 126.1, 125.5, 125.4, 77.4, 72.0, 59.2, 43.0, 29.9, 24.0.

(*S*)-Bis(4-methoxyphenyl)(1-methylpyrrolidin-2-yl)methanol (13e).



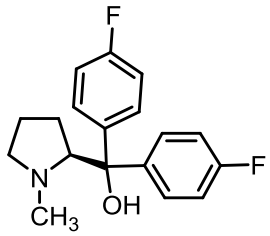
White solid. $[\alpha]_D^{20}$ 24.5 (*c* 1.02, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.50 (d, *J* = 4.0 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 3.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.98 (t, *J* = 2.5 Hz, 1H), 5.49 (m, 1H), 3.79 (d, *J* = 3.5 Hz, 1H), 2.90 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 169.3, 146.3, 137.2, 129.1, 126.8, 125.0, 124.7, 123.8, 120.1, 67.2, 45.8. Mp. 81.0–81.3 °C. TLC: R_f 0.34 (chloroform/methanol = 10:1). IR (KBr) 3367.9, 2952.2, 2905.9, 2863.5, 2811.4, 2038.9, 1605.8, 1507.4, 1456.3, 1372.4, 1296.2, 1285.6, 1243.2, 1170.8, 1139.0, 1028.1, 850.6, 823.6, 811.1, 648.2, 581.6. cm^{-1}. HRMS (ESI) Calcd for $C_{20}H_{26}NO_3$: $[M+H]^+$, 328.1907. Found: *m/z* 328.1909.

(*S*)-Bis(4-(*tert*-butyl)phenyl)(1-methylpyrrolidin-2-yl)methanol (13f).



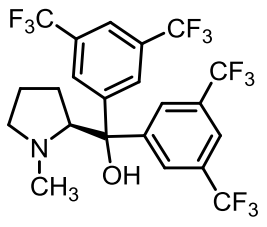
White solid. $[\alpha]_D^{20}$ 17.9 (*c* 0.84, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.50 (d, *J* = 4.0 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 3.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.98 (t, *J* = 2.5 Hz, 1H), 5.49 (m, 1H), 3.79 (d, *J* = 3.5 Hz, 1H), 2.90 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 169.3, 146.3, 137.2, 129.1, 126.8, 125.0, 124.7, 123.8, 120.1, 67.2, 45.8. Mp. 71.8.–72.2 °C. TLC: R_f 0.45 (chloroform/methanol = 10:1). IR (KBr) 3367.9, 2963.8, 2904.0, 2869.2, 2786.3, 2362.9, 1507.4, 1460.2, 1406.2, 1362.8, 1316.5, 1268.3, 1203.6, 1110.1, 1041.6, 823.6, 708.9, 583.5. cm^{-1}. HRMS (ESI) Calcd for $C_{26}H_{38}NO$: $[M+H]^+$, 380.2948. Found: *m/z* 380.2951.

(*S*)- Bis(4-fluorophenyl)(1-methylpyrrolidin-2-yl)methanol (13g): CAS RN [350236-79-2].



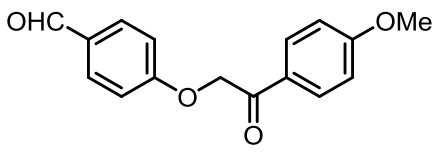
White solid. ^{1}H NMR ($CDCl_3$) δ 7.56 (dd, *J* = 9.0, 5.5 Hz, 2H), 7.46 (dd, *J* = 9.0, 5.5 Hz, 2H), 6.96 (m, 4H), 4.82 (s, 1H), 3.54 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.11 (m, 1H), 2.45 (m, 1H), 1.87 (m, 1H), 1.84 (s, 3H), 1.66 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 162.2, 160.3, 144.0, 142.5, 127.0 (d, *J* = 8.3 Hz), 127.0 (d, *J* = 8.3 Hz), 114.9 (d, *J* = 4.5 Hz), 114.8 (d, *J* = 4.0 Hz), 76.9, 72.0, 59.1, 43.0, 29.8, 23.9.

(*S*)-Bis(3,5-bis(trifluoromethyl)phenyl)(1-methylpyrrolidin-2-yl)methanol (13h): CAS RN [350236-79-2].



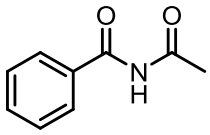
White solid. ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 2H), 7.99 (s, 2H), 7.74 (d, *J* = 7.5 Hz, 2H), 5.30 (s, 1H), 3.72 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.19 (m, 1H), 2.56 (q, *J* = 9.0 Hz, 1H), 1.87 (m, 4H), 1.72 (m, 2H), 1.50 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 149.8, 147.9, 132.0 (q, *J* = 33.5 Hz), 131.9 (q, *J* = 33.7 Hz), 125.8, 125.5, 123.2, (q, *J* = 277.1 Hz), 121.2, (q, *J* =3.8 Hz), 121.1, (q, *J* = 3.8 Hz), 76.5, 71.7, 58.8, 42.7, 29.9, 23.6.

4-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzaldehyde (**14**): CAS RN [901414-44-6].



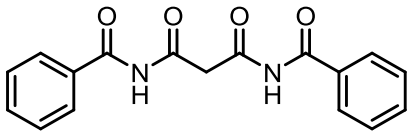
White solid. ^{1}H NMR ($CDCl_3$) δ 9.88 (s, 1H), 7.98 (d, *J* = 9.0 Hz, 2H), 7.83 (d, *J* = 7.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 5.33 (s, 2H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 191.8, 190.6, 164.3, 163.0, 131.9, 130.6, 130.5, 127.3, 115.0, 114.2, 70.4, 55.6.

***N*-Acetylbenzamide (3a):** CAS RN [1575-95-7].



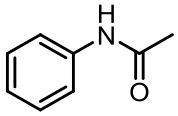
Yellow oil. ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 2.62 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 173.1, 165.5, 133.3, 132.7, 129.1, 127.5, 25.5.

***N*^{1},*N*^{3}-Dibenzoylmalonamide (4a).**



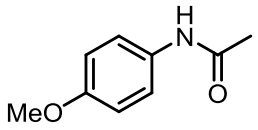
White solid. ^{1}H NMR ($CDCl_3$) δ 8.79 (s, 2H), 7.87 (d, *J* = 7.8 Hz, 4H), 7.63 (t, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 7.8 Hz, 4H), 4.62 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 168.6, 165.4, 133.5, 132.2, 129.1, 127.7, 48.1. Mp. 181.0–182.0 °C. TLC: R_f 0.36 (hexane/EtOAc = 1:1). IR (KBr) 3326.4, 3278.2, 2958.9, 2930.0, 1722.5, 1710.9, 1685.9, 1673.3, 1599.1, 1469.8, 1357.9, 1317.4, 1257.6, 1202.7, 1159.3, 706.9 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{15}N_2O_4$: $[M+H]^+$, 311.1026. Found: *m/z* 311.1012.

***N*-Phenylacetamide (3b):** CAS RN [103-84-4].



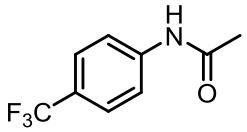
White solid. ^{1}H NMR ($CDCl_3$) δ 7.51 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.4, 137.9, 128.9, 124.3, 119.8, 24.5.

***N*-(4-Methoxyphenyl)acetamide (3c):** CAS RN [51-66-1].



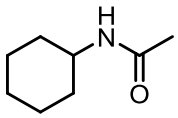
White solid. ^{1}H NMR ($CDCl_3$) δ 7.38 (dt, *J* = 9.0, 3.5 Hz, 2H), 7.34 (s, 1H), 6.84 (dt, *J* = 9.5, 3.5 Hz, 2H), 3.78 (s, 3H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.3, 156.4, 131.0, 121.9, 114.1, 55.4, 24.3.

***N*-(4-(Trifluoromethyl)phenyl)acetamide (3d):** CAS RN [349-97-3].



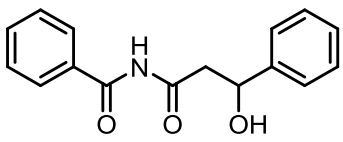
White solid. ^{1}H NMR ($CDCl_3$) δ 7.64 (d, *J* = 8.5, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.44 (s, 1H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.5, 140.4, 126.3 (q, *J* = 15.0 Hz), 125.9, 124.0 (q, *J* = 1080.0 Hz), 119.3, 24.7. ^{19}F NMR ($CDCl_3$) δ –62.6.

***N*-Cyclohexylacetamide (3e):** CAS RN [1124-53-4].



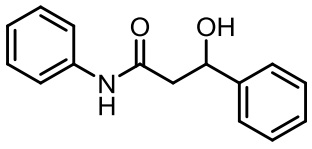
White solid. ^{1}H NMR ($CDCl_3$) δ 5.45 (s, 1H), 3.73 (m, 1H), 1.94 (s, 3H), 1.89 (m, 2H), 1.64 (m, 3H), 1.33 (m, 2H), 1.12 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 169.0, 48.2, 33.2, 25.5, 24.8, 23.6.

***N*-(3-Hydroxy-3-phenylpropanoyl)benzamide (6aa).**



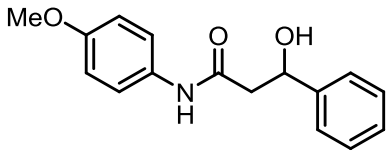
White solid. ^{1}H NMR ($CDCl_3$) δ 9.03 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 6.9 Hz, 1H), 5.27 (m, 1H), 3.40 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 174.6, 165.5, 142.4, 133.5, 132.4, 129.0, 128.6, 127.8, 127.7, 125.8, 70.1, 46.5. Mp. 125.5–126.0 °C. TLC: R_f 0.30 (hexane/EtOAc = 1:1). IR (KBr) 3475.9, 3286.8, 1700.3, 1668.5, 1510.3, 1469.8, 1375.3, 1304.9, 1248.0, 1183.4, 1032.0, 910.4, 770.6, 705.0 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{15}NO_3Na$: $[M+Na]^+$, 292.0944. Found: *m/z* 290.0937.

3-Hydroxy-*N*,3-diphenylpropanamide (6ba): CAS RN [4198-15-6].



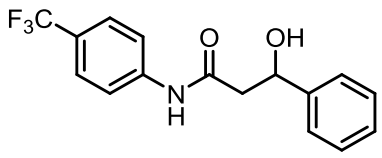
White solid. ^{1}H NMR ($CDCl_3$) δ 9.18 (s, 1H), 7.40 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.17 (t, *J* = 7.0 Hz, 2H), 7.11 (m, 3H), 6.90 (t, *J* = 7.5 Hz, 1H), 5.08 (d, *J* = 3.5 Hz, 1H), 4.99 (m, 1H), 2.62 (dd, *J* = 15.0, 9.5 Hz, 1H), 2.53 (dd, *J* = 15.0, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.9, 143.6, 138.0, 128.3, 128.0, 127.0, 125.3, 123.4, 119.6, 70.2, 45.7.

3-Hydroxy-*N*-(4-methoxyphenyl)-3-phenylpropanamide (6ca).



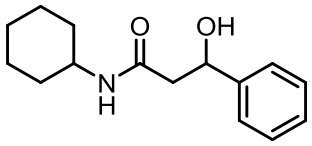
White solid. ^{1}H NMR ($CDCl_3$) δ 8.92 (s, 1H), 7.34 (t, *J* = 9.3 Hz, 4H), 7.25 (t, *J* = 9.3 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.74 (td, *J* = 8.7, 3.3 Hz,, 2H), 5.04 (m, 2H), 3.69 (s, 3H), 2.64 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 169.9, 155.9, 143.6, 131.1, 128.2, 127.2, 125.4, 121.6, 113.7, 70.5, 55.2, 45.5. Mp. 140.5–141.0 °C. TLC: R_f 0.32 (hexane/EtOAc = 1:1). IR (KBr) 3287.8, 3253.1, 1656.0, 1604.8, 1552.8, 1511.3, 1414.9, 1303.0, 1248.0, 1181.5, 1065.7, 1035.8, 967.3, 832.3, 776.4, 757.1, 698.3 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{17}NO_3Na$: $[M+Na]^+$, 294.1101. Found: *m/z* 294.1091.

3-Hydroxy-3-phenyl-*N*-(4-(trifluoromethyl)phenyl)propanamide (6da).



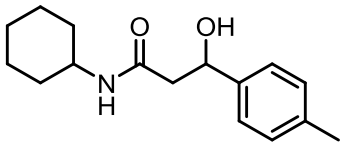
White solid. ^{1}H NMR ($CDCl_3$) δ 9.56 (s, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 2H), 7.02 (t, *J* = 7.5 Hz, 2H), 6.93 (t, *J* = 8.1 Hz, 1H), 5.00 (d, *J* = 3.9 Hz, 1H), 4.85 (m, 1H), 2.50 (dd, *J* = 15.0, 9.3 Hz, 1H), 2.37 (dd, *J* = 14.7, 3.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 170.2, 143.5, 141.4, 127.9, 127.0, 125.4 (q, *J* = 14.4 Hz,), 125.2, 124.4, 123.4 (q, *J* = 844.8 Hz,), 119.0, 70.0, 46.0. ^{19}F NMR ($CDCl_3$) δ –62.3 ppm. Mp. 191.2–192.0 °C. TLC: R_f 0.50 (hexane/EtOAc = 1:1). IR (KBr) 3335.1, 1661.8, 1603.9, 1532.5, 1456.3, 1411.0, 1331.9, 1252.8, 1151.6, 1113.0, 1071.5, 1019.4, 973.1, 912.4, 888.3, 866.1, 836.2, 758.1, 702.1 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{15}F_3NO_2$: $[M+H]^+$, 310.1049. Found: *m/z* 310.1036.

***N*-Cyclohexyl-3-hydroxy-3-phenylpropanamide (6ea).**



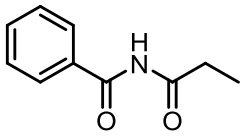
White solid. ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H), 5.55 (d, J = 7.2 Hz, 1H), 5.09 (m, 1H), 4.31 (d, J = 3.0 Hz, 1H), 3.77 (m, 1H), 2.53 (m, 2H), 1.88 (m, 2H), 1.65 (m, 3H), 1.33 (m, 2H), 1.10 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 170.8, 143.0, 128.5, 127.6, 125.6, 70.9, 48.2, 44.7, 33.0, 25.4, 24.8. Mp. 129.2–129.5 °C. TLC: R_f 0.43 (hexane/EtOAc = 1:2). IR (KBr) 3302.3, 3087.2, 3023.6, 2933.9, 2854.8, 1638.6, 1553.7, 1450.5, 1360.8, 1207.5, 1054.1, 1020.4, 984.7, 893.1, 698.3 cm^{-1}. HRMS (ESI) Calcd for $C_{15}H_{21}NO_2Na$: $[M+Na]^+$, 270.1465. Found: *m/z* 270.1456.

_N_-Cyclohexyl-3-hydroxy-3-(*p*-tolyl)propanamide (6eb).



White solid. ^{1}H NMR ($CDCl_3$) δ 7.25 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 5.57 (d, J = 6.9 Hz, 1H), 5.06 (m, 1H), 4.17 (d, J = 3.0 Hz, 1H), 3.77 (m, 1H), 2.51 (m, 2H), 2.33 (s, 3H), 1.89 (m, 2H), 1.65 (m, 3H), 1.34 (m, 2H), 1.11 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 170.8, 140.1, 137.3, 129.1, 125.5, 70.8, 48.2, 44.8, 33.0, 25.4, 24.8, 21.1. Mp. 137.5–137.9 °C. TLC: R_f 0.27 (hexane/EtOAc = 1:1). IR (KBr) 3301.3, 3080.5, 2932.9, 2852.8, 1641.5, 1639.6, 1548.9, 1447.6, 1363.7, 1245.1, 1204.6, 1062.8, 1028.1, 983.7, 889.2, 817.9, 722.4, 686.7 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{23}NO_2Na$: $[M+Na]^+$, 284.1621. Found: *m/z* 284.1612.

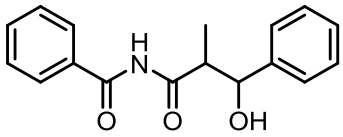
_N_-Propionylbenzamide (10a): CAS RN [28358-79-4].



White solid. ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1H), 7.87 (dt, J = 7.0, 1.5 Hz, 2H), 7.61 (tt, J = 7.5, 1.5 Hz, 1H), 7.50 (tt, J = 7.5, 1.0 Hz, 2H), 3.04 (q, J = 7.5 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 177.1, 165.5, 133.2, 132.8, 129.0, 127.6, 31.2, 8.2.

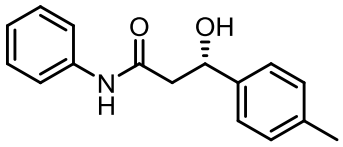
_N_-(3-Hydroxy-2-methyl-3-phenylpropanoyl)benzamide (12aa, including 14% diastereo

mixture).



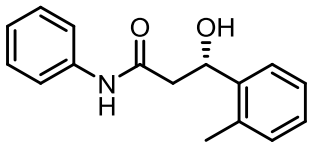
Colorless oil. ^{1}H NMR ($CDCl_3$) δ 9.07 (s, 1H), 7.85 (m, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.34 (m, 5H), 5.24 (s, 1H), 3.75 (m, 1H), 3.17 (d, *J* = 1.5 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 177.8, 165.2, 141.0, 133.3, 132.8, 129.0, 128.3, 127.7, 127.6, 126.0, 73.3, 47.2, 10.2. TLC: R_f 0.50 (hexane/EtOAc = 1:2). IR (neat) 3410.3, 2981.1, 2937.7, 1730.2, 1680.1, 1601.0, 1507.4, 1484.3, 1369.5, 1264.4, 1159.3, 1121.7, 1027.1, 701.2, 665.5 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{18}NO_3$: $[M+H]^+$, 284.1281. Found: *m/z* 284.1268.

(*S*)-3-Hydroxy-*N*-phenyl-3-(p-tolyl)propanamide (6bb).



Yield: 99%, 84% *ee*, white solid. $[\alpha]_D^{20}$ –83.3 (*c* 0.06, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.26 (m, 4H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 5.09 (m, 1H), 4.68 (d, *J* = 3.0 Hz, 1H), 2.74 (dd, *J* = 15.0, 9.5 Hz, 1H), 2.65 (dd, *J* = 15.5, 3.0 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.1, 140.5, 138.1, 137.1, 129.0, 128.7, 125.5, 123.9, 119.9, 70.5, 45.9, 21.0. Mp. 181.0–182.0 °C. TLC: R_f 0.45 (hexane/EtOAc = 1:1). IR (KBr) 3330.2, 1657.9, 1601.0, 1540.2, 1498.8, 1442.8, 1363.7, 1064.8, 815.9, 752.3, 691.5, 502.5 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{17}NO_2Cl$: $[M+Cl]^-$, 290.0942. Found: *m/z* 290.0956. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 17.6 mn, t_{major} = 20.0 mn.

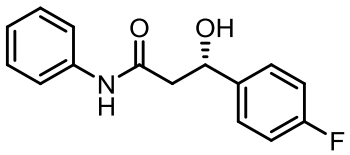
(*S*)-3-Hydroxy-*N*-phenyl-3-(*o*-tolyl)propanamide (6bc).



Yield: 91%, 84% *ee*, white solid. $[\alpha]_D^{20}$ –41.7 (*c* 0.12, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H), 7.54 (m, 3H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.26 (m, 1H), 7.21 (dt, *J* = 1.5, 8.5 Hz, 1H), 7.14 (m, 2H), 5.45 (td, *J* = 2.5, 10.0 Hz, 1H), 3.31 (d, *J* = 2.5 Hz, 1H), 2.76 (dd, *J* = 15.0, 10.0 Hz, 1H), 2.65 (dd, *J* = 16.0, 2.5 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 169.8, 140.8, 137.6, 134.2, 130.6, 129.1, 127.8,

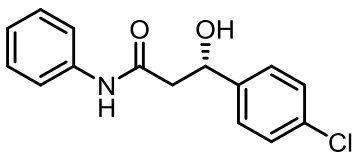
126.6, 125.1, 124.5, 120.1, 67.7, 44.9, 19.0. Mp. 161.2–162.0 °C. TLC: R_f 0.53 (hexane/EtOAc = 1:1). IR (KBr) 3304.2, 1659.8, 1599.1, 1540.2, 1499.7, 1444.8, 1360.8, 1312.6, 1300.1, 1066.7, 1022.3, 756.1, 729.1, 693.4, 498.6 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{17}NO_2Cl$: $[M+Cl]^-$, 290.0942. Found: *m/z* 290.0954. HPLC (Daicel Chiralcel IA, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 14.0 mn, t_{major} = 16.8 mn.

(*S*)-3-(4-Fluorophenyl)-3-hydroxy-*N*-phenylpropanamide (6bd).



Yield: 77%, 89% *ee*, white solid. $[\alpha]_D^{20}$ –20.8 (*c* 0.24, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 8.43 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.38 (dt, *J* = 7.0, 1.5 Hz, 2H), 7.30 (dt, *J* = 7.5, 2.0 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.03 (dt, *J* = 8.5, 1.5 Hz, 2H), 5.16 (d, *J* = 8.5 Hz, 1H), 4.50 (s, 1H), 2.72 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.0, 139.1, 137.9, 128.9, 127.3 (d, *J* = 8.3 Hz), 124.2, 120.0, 119.9, 115.3 (d, *J* = 21.4 Hz), 70.1, 45.9. ^{19}F NMR ($CDCl_3$) δ –95.1 ppm. Mp. 169.0–170.0 °C. TLC: R_f 0.32 (hexane/EtOAc = 1:1). IR (KBr) 3335.1, 1654.0, 1602.9, 1540.2, 1512.3, 1499.7, 1444.8, 1227.7, 831.4, 756.1, 691.5 cm^{-1}. HRMS (ESI) Calcd for $C_{15}H_{14}FNO_2Cl$: $[M+Cl]^-$, 294.0692. Found: *m/z* 294.0706. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 19.0 mn, t_{major} = 16.0 mn.

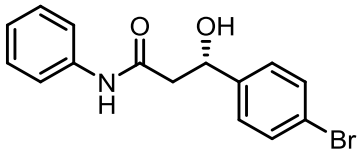
(*S*)-3-(4-Chlorophenyl)-3-hydroxy-*N*-phenylpropanamide (6be).



Yield: 76%, 79% *ee*, white solid. $[\alpha]_D^{20}$ –8.3 (*c* 0.03, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.50 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.34 (m, 6H), 7.14 (t, *J* = 7.0 Hz, 1H), 5.21 (m, 1H), 3.74 (d, *J* = 3.0 Hz, 1H), 2.76 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.70 (dd, *J* = 15.0, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.9, 137.8, 128.9, 128.6, 127.0, 124.3, 120.0, 119.9, 109.7, 70.1, 45.7. Mp. 188.5–189.2 °C. TLC: R_f 0.46 (hexane/EtOAc = 1:1). IR (KBr) 3328.3, 1656.0, 1602.0, 1540.2, 1499.7, 1444.8, 1425.5, 1369.5, 1092.7, 1067.7, 1012.7, 824.6, 756.1, 744.6, 692.5, 500.6 cm^{-1}. HRMS (ESI)

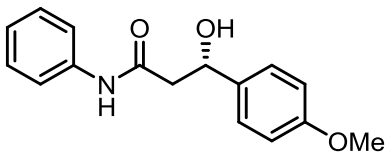
Calcd for $C_{15}H_{13}ClNO_2$: $[M–H]^-$, 274.0640. Found: *m/z* 274.0647. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 17.2 mn, t_{major} = 22.8 mn.

(*S*)-3-(4-Bromophenyl)-3-hydroxy-*N*-phenylpropanamide (6bf).



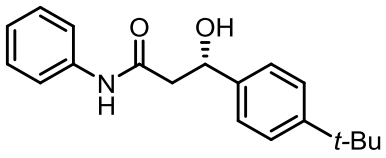
Yield: 47%, 77% *ee,* white solid. $[\alpha]_D^{20}$ 25.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 9.06 (s, 1H), 7.46 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.22 (m, 4H), 7.00 (tt, *J* = 7.0, 1.0 Hz, 1H), 5.13 (d, *J* = 3.5 Hz, 1H), 5.04 (m, 1H), 2.63 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 169.8, 142.7, 138.0, 131.3, 128.6, 127.3, 123.9, 121.0, 119.9, 69.9, 45.6. Mp. 186.0–186.6 °C. TLC: R_f 0.44 (hexane/EtOAc = 1:1). IR (KBr) 3327.4, 1654.0, 1601.0, 1540.2, 1499.7, 1490.1, 1444.8, 1067.7, 1009.8, 821.7, 692.5 cm^{-1}. HRMS (ESI) Calcd for $C_{15}H_{14}BrNO_2Cl$: $[M+Cl]^-$, 353.9891. Found: *m/z* 353.9911. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 41.1 mn, t_{major} = 48.4 mn.

(*S*)-3-Hydroxy-3-(4-methoxyphenyl)-*N*-phenylpropanamide (6bg).



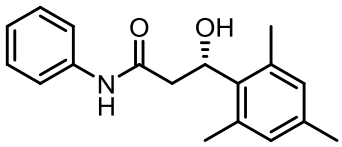
Yield: 64%, 94% *ee,* white solid. $[\alpha]_D^{20}$ –35.7 (*c* 0.07, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.96 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.26 (m, 4H), 7.28 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.06 (td, *J* = 3.0, 9.5 Hz, 1H), 4.79 (d, *J* = 2.5 Hz, 1H), 3.74 (s, 3H), 2.73 (dd, *J* = 15.5, 9.5 Hz, 1H), 2.62 (dd, *J* = 15.0, 3.0 Hz 1H). ^{13}C NMR ($CDCl_3$) δ 170.2, 158.9, 138.1, 135.7, 128.7, 126.8, 123.8, 119.9, 113.7, 70.2, 55.1, 45.9. Mp. 185.0–186.0 °C. TLC: R_f 0.30 (hexane/EtOAc = 1:1). IR (KBr) 3325.4, 1658.9, 1601.0, 1538.3, 1515.1, 1499.7, 1443.8, 1365.7, 1300.1, 1178.6, 1065.7, 1037.8, 829.5, 753.2, 692.5, 502.5 cm^{-1}. HRMS (ESI) Calcd for $C_{16}H_{16}NO_3$: $[M–H]^-$, 270.1136. Found: *m/z* 270.1142. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 37.3 mn, t_{major} = 41.9 mn.

(*S*)-3-(4-(*tert*-Butyl)phenyl)-3-hydroxy-*N*-phenylpropanamide (6bh).



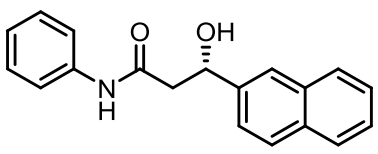
Yield: 57%, 84% *ee,* white solid. $[\alpha]_D^{20}$ –25.0 (*c* 0.20, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.80 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 2H),7.40 (d, *J* = 8.5 Hz, 2H), 7.33 (m, 4H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.20 (m, 1H), 3.35 (d, *J* = 2.5 Hz, 1H), 2.83 (dd, *J* = 15.5, 9.5 Hz, 1H), 2.71 (dd, *J* = 15.0, 3.0 Hz, 1H) 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 169.8, 151.0, 139.7, 137.5, 129.0, 125.6, 125.3, 124.5, 120.0, 70.9, 46.0, 34.6, 31.3. Mp. 110.0–111.0 °C. TLC: R_f 0.61 (hexane/EtOAc = 1:1). IR (KBr) 3298.4, 2961.8, 1669.5, 1603.9, 1554.7, 1499.7, 1442.8, 1312.6, 1060.9, 819.8, 754.2, 690.6, 581.6 cm^{-1}. HRMS (ESI) Calcd for $C_{19}H_{23}NO_2Cl$: $[M+Cl]^-$, 332.1412. Found: *m/z* 332.1425. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 23.3 mn, t_{major} = 19.3 mn.

(*S*)-3-Hydroxy-3-mesityl-*N*-phenylpropanamide (6bi).



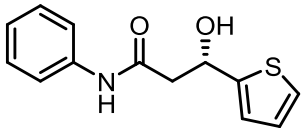
Yield: 63%, 84% *ee,* white solid. $[\alpha]_D^{20}$ –16.9 (*c* 0.74, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.33 (t, *J* = 8.5 Hz, 2H), 7.12 (t, *J* = 7.0 Hz, 1H), 6.83 (s, 2H), 5.65 (d, *J* =10.5 Hz, 1H), 3.14 (dd, *J* = 15.5, 5.5 Hz, 1H), 3.10 (s, 1H), 2.49 (dd, *J* = 15.5, 2.0 Hz 1H), 2.43 (s, 6H) 2.26 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.0, 137.7, 137.2, 136.0, 134.8, 130.3, 129.0, 124.4, 120.0, 68.2, 42.7, 20.7, 20.7. IR (KBr) 3431.5, 3269.5, 2921.3, 1628.0, 1600.0, 1545.1, 1498.8, 1444.8, 1312.6, 1253.8, 1172.8, 1071.5, 850.6, 752.3, 690.6, 351.1 cm^{-1}. Mp. 110.0–111.0 °C. TLC: R_f 0.29 (hexane/EtOAc = 3:1). HRMS (ESI) Calcd for $C_{18}H_{20}NO_2$: $[M–H]^-$, 282.1500. Found: *m/z* 282.1487. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 15.0 mn, t_{major} = 8.5 mn.

(*S*)-3-Hydroxy-3-(naphthalen-2-yl)-*N*-phenylpropanamide (6bj).



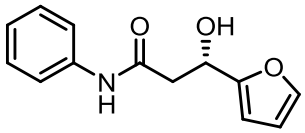
Yield: 89%, 88% *ee,* white solid. $[\alpha]_D^{20}$ –250.0 (*c* 0.02, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 7.87 (s, 1H), 7.81 (m, 3H), 7.52 (t, *J* = 8.5 Hz, 3H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.0 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 5.33 (d, *J* = 9.5 Hz, 1H), 4.79 (s, 1H), 2.85 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.78 (dd, *J* = 15.5, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 170.1, 140.8, 133.2, 132.9, 128.8, 128.3, 127.9, 127.6, 126.1, 125.8, 124.3, 124.1, 123.8, 121.1, 120.0, 70.9, 45.9. Mp. 173.0–174.0 °C. TLC: R_f 0.44 (hexane/EtOAc = 1:1). IR (KBr) 3299.4, 1664.6, 1602.0, 1549.9, 1499.7, 1488.2, 1445.7, 1363.7, 1314.5, 1068.6, 761.0, 744.6 cm^{-1}. HRMS (ESI) Calcd for $C_{19}H_{17}NO_2Cl$: $[M+Cl]^-$, 326.0942. Found: *m/z* 326.0954. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 39.2 mn, t_{major} = 30.7 mn.

(*S*)-3-Hydroxy-*N*-phenyl-3-(thiophen-2-yl)propanamide (6bk).



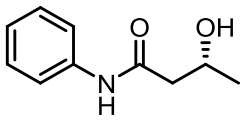
Yield: 73%, 94% *ee,* white solid. $[\alpha]_D^{20}$ –41.7 (*c* 0.12, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.64 (s, 1H), 7.50 (d, *J* = 4.0 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 3.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.98 (t, *J* = 2.5 Hz, 1H), 5.49 (m, 1H), 3.79 (d, *J* = 3.5 Hz, 1H), 2.90 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 169.3, 146.3, 137.2, 129.1, 126.8, 125.0, 124.7, 123.8, 120.1, 67.2, 45.8. Mp. 159.5–160.2 °C. TLC: R_f 0.50 (hexane/EtOAc = 1:1). IR (KBr) 3297.5, 1679.1, 1663.7, 1607.7, 1599.1, 1554.7, 1498.8, 1444.8, 1319.4, 1254.8, 1236.4, 1086.0, 1046.4, 758.1, 700.2, 689.6 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{13}NO_2SCl$: $[M+Cl]^-$, 282.0350. Found: *m/z* 282.0367. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 18.9 mn, t_{major} = 21.4 mn.

(*S*)-3-(Furan-2-yl)-3-hydroxy-*N*-phenylpropanamide (6bl).



Yield: 92%, 76% *ee,* white solid. $[\alpha]_D^{20}$ –31.3 (*c* 0.24, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.40 (m, 1H), 7.34 (t, *J* = 7.0 Hz, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.35 (m, 1H), 6.33 (d, *J* = 3.0 Hz, 1H), 5.24 (m, 1H), 3.62 (d, *J* = 4.5 Hz, 1H), 2.96 (dd, *J* = 16.0, 8.5 Hz, 1H), 2.87 (dd, *J* = 15.5, 3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 169.4, 154.6, 142.3, 137.3, 129.0, 124.7, 120.1, 110.4, 106.5, 64.7, 42.0. Mp. 133.0–134.0 °C. TLC: R_f 0.43 (hexane/EtOAc = 1:1). IR (KBr) 3284.9, 1669.5, 1608.7, 1559.5, 1491.0, 1445.7, 1314.5, 1168.0, 1060.9, 1018.5, 759.0, 744.6, 693.4, 598.0 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{12}NO_2$: $[M–H]^-$, 230.0823. Found: *m/z* 230.0812. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 20/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 19.6 mn, t_{major} = 22.8 mn.

(*R*)-3-Hydroxy-*N*-phenylbutanamide (6bm).



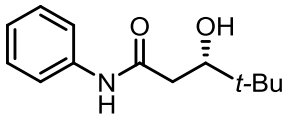
Yield: 45%, 76% *ee,* white solid. $[\alpha]_D^{20}$ –21.2 (*c* 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 4.32 (m, 1H), 3.17 (d, *J* = 3.0 Hz, 1H), 2.55 (dd, *J* = 3.0, 15.5Hz, 1H), 2.48 (dd, *J* = 9.0, 15.5Hz, 1H) 1.30 (d, *J* = 6.5 Hz,3H). ^{13}C NMR ($CDCl_3$) δ 170.3, 137.5, 129.0, 124.5, 120.0, 65.0, 45.2, 23.0. Mp. 102.8–103.5 °C. TLC: R_f 0.28 (hexane/EtOAc = 1:2). IR (KBr) 3250.2, 1662.7, 1601.0, 1553.7, 1500.7, 1445.7, 1338.7, 1319.4, 1128.4, 1064.8, 753.2, 694.4 cm^{-1}. HRMS (ESI) Calcd for $C_{10}H_{13}NO_2Cl$: $[M+Cl]^-$, 214.0629. Found: *m/z* 214.0643. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 33/1, flow rate = 1.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 38.8 mn, t_{major} = 34.7 mn.

The absolute configuration of **6bm** was assigned as (*R*) by comparing the optical rotation with the literature value.[19]

$[\alpha]_D^{20}$ –21.2 (*c* 0.70, CH_2Cl_2) [lit.[6] (*R*)-3-hydroxy-*N*-phenylbutanamide: $[\alpha]_D^{20}$ –28.6 (*c* 1.1, $CHCl_3$)]

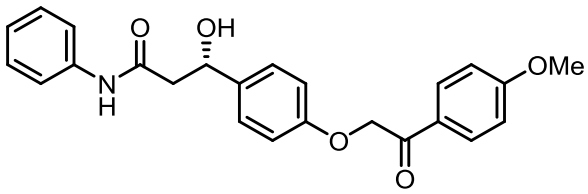
The absolute configurations of other products were assigned analogously.

(*S*)-3-Hydroxy-4,4-dimethyl-*N*-phenylpentanamide (6bn).



Yield: 49%, 83% *ee,* yellow solid. $[\alpha]_D^{20}$ –27.8 (*c* 0.27, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.0 Hz, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 3.79 (d, *J* = 5.0 Hz, 1H), 3.01 (s, 1H), 2.54 (dd, *J* = 2.0, 15.5 Hz, 1H), 2.43 (dd, *J* = 10.5, 15.5 Hz, 1H), 0.96 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 177.1, 137.7, 129.0, 124.4, 120.0, 76.4, 39.2, 34.7, 25.5. Mp. 110.0–111.0 °C. TLC: R_f 0.61 (hexane/EtOAc = 1:1). IR (KBr) 3293.6, 2958.9, 1659.3, 1603.9, 1552.8, 1501.7, 1445.7, 1337.7, 1149.6, 1070.5, 754.2, 702.1, 419.5 cm^{-1}. HRMS (ESI) Calcd for $C_{13}H_{18}NO_2$: $[M–H]^-$, 220.1343. Found: *m/z* 220.1347. HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 33/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 13.0 mn, t_{major} = 18.3 mn.

(*S*)-3-Hydroxy-3-(4-(2-(4-methoxyphenyl)-2-oxoethoxy)phenyl)-*N*-phenylpropanamide (15).

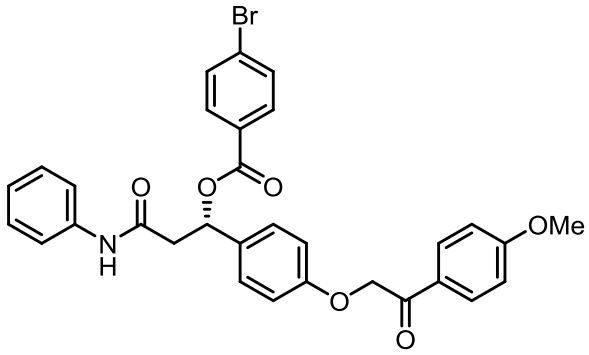


Yield: 81%, 93% *ee,* white solid. $[\alpha]_D^{20}$ 10.0 (*c* 0.25, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 8.00 (d, *J* = 9.0 Hz, 2H), 7.73 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.33 (m, 3H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 5.23 (s , 2H), 5.16 (d, *J* = 9.5 Hz, 1H), 3.89 (s, 3H) , 3.45 (d, *J* = 2.5 Hz, 1H), 2.78 (dd, *J* = 15.5, 9.5 Hz, 1H), 2.67 (dd, *J* = 15.5, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 193.0, 169.7, 164.1, 157.9, 137.5, 135.9, 130.6, 129.0, 127.6, 127.0, 124.5, 120.1, 115.0, 114.1, 70.8, 70.6, 55.5, 46.1. Mp. 142.5–143.0 °C. TLC: R_f 0.38 (hexane/EtOAc = 1:2). IR (KBr) 3514.5, 3265.6, 2920.3, 1681.0, 1602.0, 1541.2, 1445.7, 1320.3, 1256.7, 1219.1, 1171.8, 978.0, 832.3, 758.1 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{23}NO_5Cl$: $[M+Cl]^-$, 440.1259. Found: *m/z* 440.1276.

The enantiomeric excess of **6o** was determined by HPLC analysis after benzoylation.

(*S*)-1-(4-(2-(4-methoxyphenyl)-2-oxoethoxy)phenyl)-3-oxo-3-(phenylamino)propyl

4-Bromobenzoate (16).



White solid. $[\alpha]_D^{20}$ –250.7 (*c* 0.04, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 8.56 (m, 1H), 7.93 (dd, *J* = 9.0, 1.5 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0, Hz, 2H), 6.39 (d, *J* = 7.0 Hz, 1H), 5.17 (s, 2H), 3.84 (s, 3H), 3.10 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.86 (dd, *J* = 15.0, 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 192.7, 167.2, 164.6, 164.0, 158.0, 138.0, 132.5, 131.6, 131.1, 130.4, 129.0, 128.7, 128.0, 127.8, 127.4, 124.0, 119.9, 114.9, 114.0, 73.3, 70.5, 55.4, 44.3. Mp. 129.0–130.0 °C. TLC: R_f 0.43 (hexane/EtOAc = 1:1). IR (KBr) 3342.8, 2965.7, 2932.9, 2361.9, 1717.7, 1684.9, 1656.9, 1602.0, 1513.2, 1441.9, 1267.3, 1217.1, 1171.8, 1117.8, 1104.3, 1007.9, 977.0, 829.4, 757.1, 695.4, 597.0, 545.9 cm^{-1}. HRMS (ESI) Calcd for $C_{31}H_{26}BrNO_6Cl$: $[M+Cl]^-$, 622.0627. Found: *m/z* 622.0650. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 5.7/1, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 68.2 mn, t_{major} = 79.7 mn.

References and Notes

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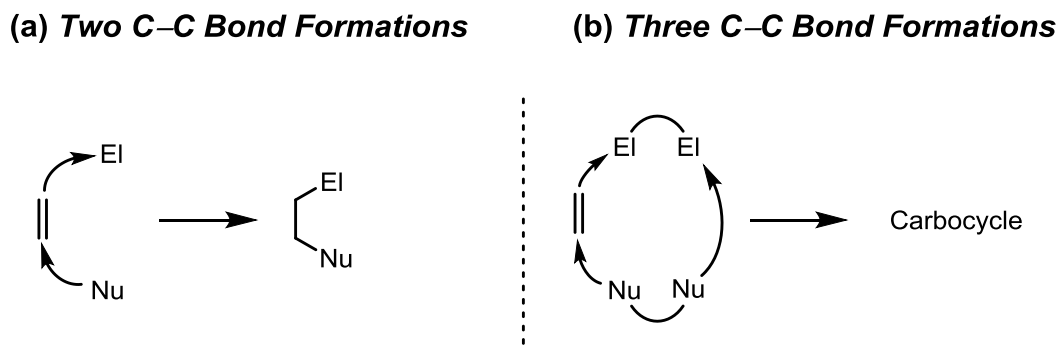
Chapter 4

Functionalized Cyclopentane Synthesis by Tandem Reaction of Allenones, Diketones, and Bis(iodozincio)methane

The tandem reaction using allenones, diketones, and bis(iodozincio)methane has been developed. The first step of this reaction involves conjugated addition of bis(iodozincio)methane to allenones to generate 1,3-dianion species, which consist of zinc enolate and allyl zinc. In the presence of 1,2-diketones, this reactive intermediate underwent double nucleophilic addition to provide the highly functionalized cyclopentane compounds bearing diol, olefin, and carbonyl group .

Introduction

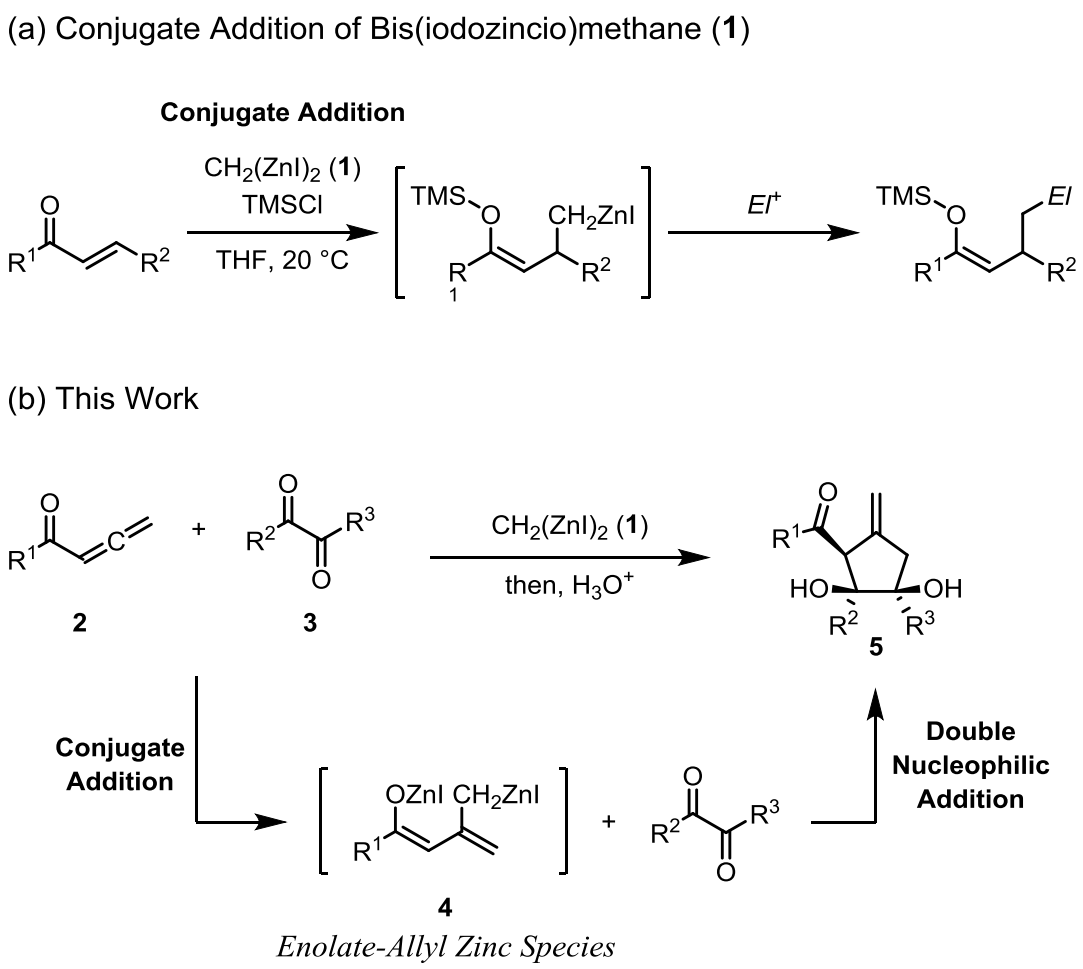
Tandem reactions enable a use of highly reactive intermediate without isolation for subsequent C-C bond formation reactions.[1] Especially, conjugate addition has attracted great attention because this reaction gives enolate derivatives, which are one of the most useful *C*-nucleophiles in organic synthesis. For example, the conjugate addition of organozinc reagents to α,β-unsaturated carbonyl compounds, followed by electrophilic traps have been established as highly chemo-, regio- and stereoselective tandem reactions.[2] This strategy could be applied in the total synthesis including prostaglandin derivatives.[3] As shown in Scheme 1, if a dianionic synthon along with a dielectrophilic partner is used in a tandem reaction, a carbocycle would be obtained. This additional C–C bond formation would further enhance the utility of tandem reactions, but the difficulty of selective synthesis of desired product would dramatically increase in such a system because many kinds of nucleophiles and electrophiles should exist in situ. Thus, the appropriate design of substrates, reagents, and catalyst should be required to achieve this goal.



Scheme 1. Tandem Reaction of Multi-Components.

Bis(iodozincio)methane (**1**),[4] which has two C–Zn bonds at the same carbon, works as a dianion equivalent. This dianionic reagent enabled the unique transformations. For example, the reaction of enones and *gem*-dizinc **1** exclusively afforded 1,4-adducts without copper catalyst

(Scheme 2 (a)).[5] The DFT calculation revealed that the pathway of 1,4-addition was kinetically more favorable than that of 1,2-addition in this reaction.[6] The author envision if an allenone is used instead of enone as Michael acceptor, enolate-allyl zinc species would be generated as shown in Scheme 2 (b). This 1,3-dianionic species is expected to exhibit extremely high reactivity, which could be utilized for tandem reaction if other electrophiles exist. In the presence of 1,2-diketones, the generated enolate-allyl zinc species would rapidly undergo double nucleophilic addition to provide the highly functionalized five-membered carbocycles bearing diol, olefin, and carbonyl group.



Scheme 2. Tandem Reaction of Multi-components.

Development of a new method for the preparation of five-membered carbon ring with high

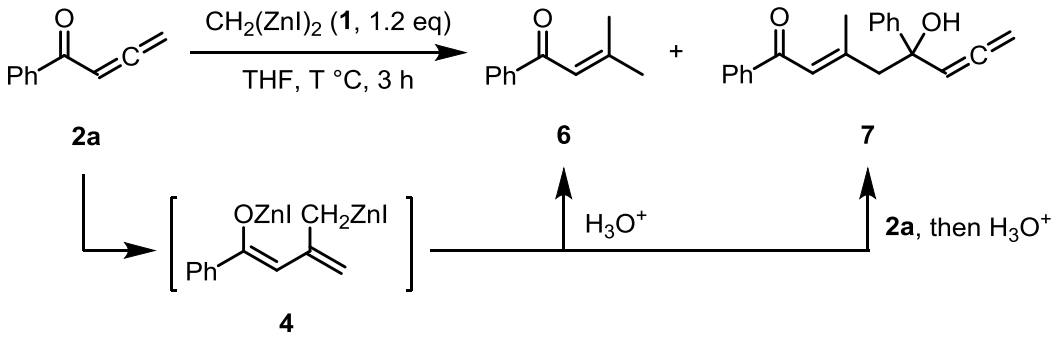
selectivity is sill of great value because they are found as one of the most ubiquitous carbocyclic motifs in natural organic compounds.[7] Especially, multi-component assembling for construction of cyclopentane ring has attracted great attention from the viewpoint of divergent synthesis. Actually, a significant effort has been devoted to [3+2] cycloaddition catalyzed by transition metal complex[8] or organocatalyst[9]. Moreover, some examples of nucleophilic [3+2] cycloaddition utilizing dianion equivalents and dielectrophiles have been also reported.[10] Although three component reactions for the synthesis of five-membered carbocycles would be more desirable with respect to efficiency and diversity, there are few examples except for Pauson-Khand reaction, which is a well-known example of [2+2+1] cocyclization.[11] Herein, the author have developed three component assembling of allenones, diketones, and bis(iodozincio)methane for the synthesis of functionalized cyclopentane by means of tandem reaction.

Results and Discussion

The author began our study with investigation of reaction of 1-phenylbuta-2,3-dien-1-one (**2a**) and **1** in THF (Table 1). He performed the reaction of **1** and **2a** in THF at −60 °C to give the compound **7** generated from the intermediate **4** and **2a**. The formation of the protonated product **6** cannot be observed and 70% of allenone **2a** was recovered. When the reaction was conducted at –40 °C, **7** was exclusively obtained in 92% yield. As the reaction temperature increased to 25 or 60 °C, complex mixture was obtained. These results suggested that the formed enolate-allyl zinc species were so reactive that the stock of this intermediate in situ cannot be possible. Thus, the author next investigated the reaction of **1** and **2a** in the presence of diketone **3a** (Table 2). As 1,2-diketones are known to have high electrophilicity compared to ketones, the author envision that the 1,3 dizinc species **4** more preferentially react with diketone than allenone **2a**. To our delight, addition of *gem*-dizinc **1** to a mixture of allenone **2a** and diketone **3a** in THF over 5 min at –40 °C followed by stirring for 20 min afforded the desired

product **5aa** in 35% yield as a single diastereomer.[12] The chemical yield was increased to 64% when the reaction was performed at –10 °C. However, the formation of the byproduct **7** couldn't be suppressed in all reaction conditions shown in Table 2. This side reaction hampered the complete conversion of diketone **3a** because allenone was completely consumed by this side reaction. Thus, he next investigated the reaction procedure to prevent this side reaction.

Table 1. Preparation of Enolate-Allyl Zinc Species **4**.[a]

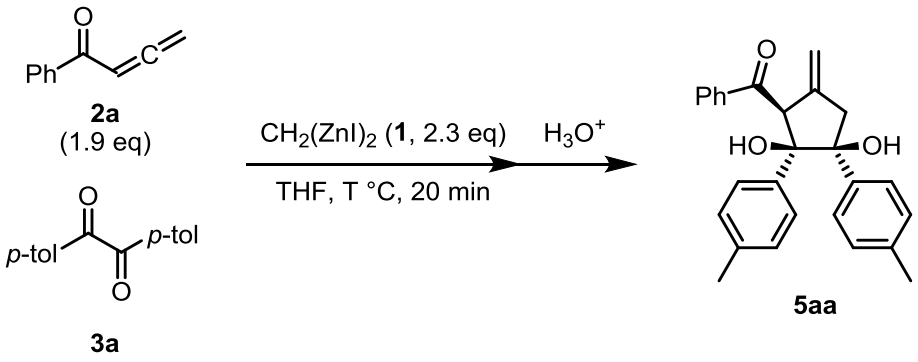


Enolate-Allyl Zinc Species

entry	T (°C)	Yield of **2** (%)[b]	Yield of **3** (%)[b]	Recovery of **1** (%)[b]
1	–60	<1	28	70
2	–40	<1	92	0
3	25	<1	0	0
4	60	<1	0	0

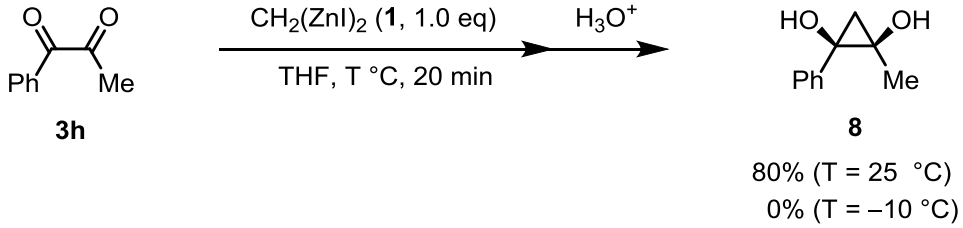
[a] Reactions were carried out using *gem*-dizinc **1** (0.2 mmol) and allenone **2a** (0.2 mmol) in THF (4.0 mL). [b] Yields of **6** and **7** and recovery of **2a** were determined by ^{1}H NMR using dibromomethane as an internal standard.

Table 2. Investigation of Reaction Conditions.[a]



entry	T (°C)	Yield of **5aa** (%)[b]	Recovery of **3a** (%)[b]
1	–40	26	74
2	–30	35	60
3	–20	61	39
4	–10	64	36
5	0	62	38

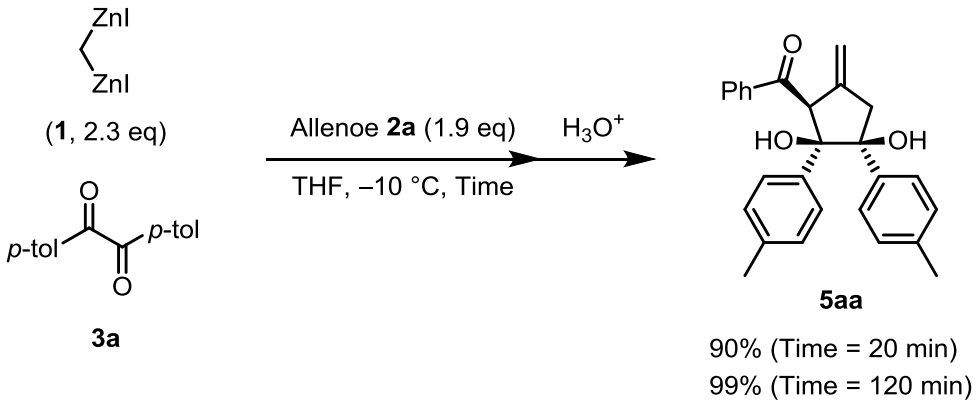
[a] Reactions were carried out using *gem*-dizinc **1** (0.3 mmol), allenone **2a** (0.25 mmol), and diketone **3a** (0.13 mmol) in THF (4.0 mL). [b] Yields were determined by ^{1}H NMR using dibromomethane as an internal standard.



Scheme 3. Cyclopropanation of Diketone **3h** with Bis(iodozincio)methane (**1**).

As shown in Scheme 3, the reaction of diketone **3h** with *gem*-dizinc **1** proceeded at ambient temperature to give the cyclopropane diols **8**.[13] However, the cyclopropanation didn't proceed at –10 °C. In contrast, the conjugate addition of *gem*-dizinc **1** to allenone **2a** can proceed even under –60 °C (Table 1, entry 1). Considering these results, the following reaction procedure would be effective in order to prevent the formation of **7**: a solution of **2a** in THF was slowly

added to a mixture of **3a** and **1** over 1 h at –60 °C followed by stirring for 20 min. This procedure can make a situation in which diketone **3a** is always excess compared to allenone **2a** by slow addition of **2a**. The formal control of stoichiometry would suppress the side reaction of **4** with **2a**. Actually, a significant improvement of chemical yield to 90% was observed as shown in Scheme 4. Moreover, the prolonged reaction time gave the desired product in quantitative yield.

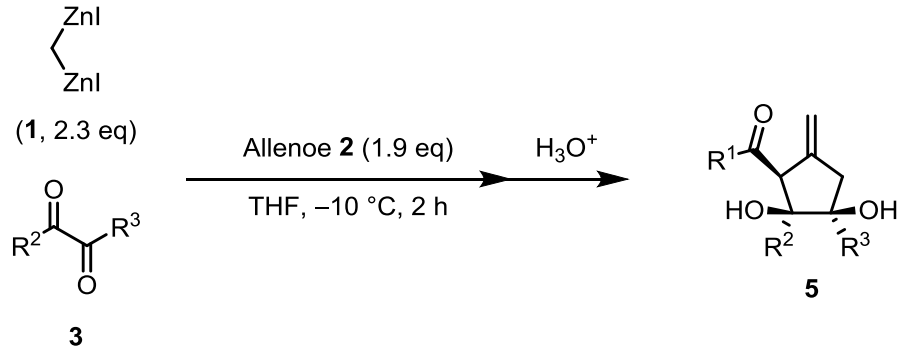


Scheme 4. Slow Addition of Allenone **2a** to a Mixture of Diketone **3a** and Bis(iodozincio)methane (**1**).

With the optimized reaction condition in hand, the author investigated the scope of allenones and diketones. All products shown in Table 3 were obtained as a single diastereomer. When allenone bearing electron donating group on phenyl ring was used, the product (**5ba**) was obtained in good yield. In addition, the allenone substrates tolerated halogen substituents such as chloro and bromo groups on the phenyl group (**5ca**, **5da**). This system also tolerated naphtyl group and phenyl group substituted allenone at para position of phenyl group to give the corresponding products in good to excellent yield (**5ea**, **5fa**). Alkyl substituted allenone could be also employed in this reaction (**5ga**). Diketone bearing electron donating group on para position of phenyl group gave the corresponding products in moderate to good yield (**5ab**-**5ac**). Heteroaryl substituted and alkyl substituted diketone also gave the products (**5ad**-**5af**), although

reaction of these substrates required lower temperature.

Table 3. Substrate Scope of Allenones and Diketones.[a]



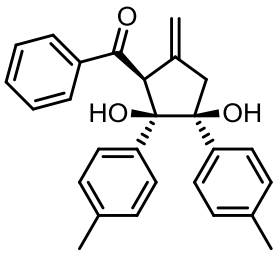
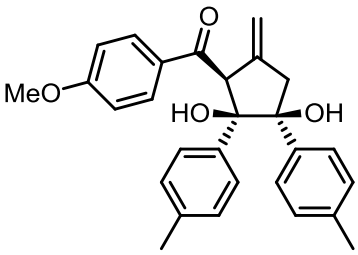
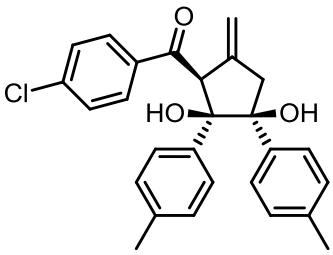
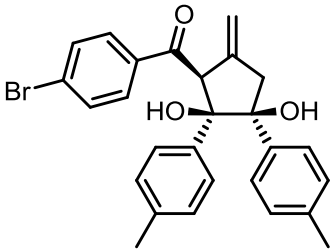
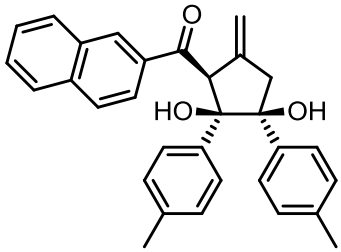
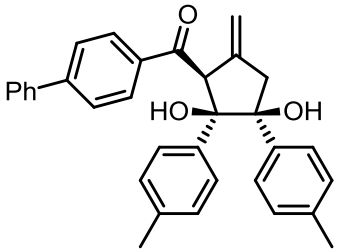
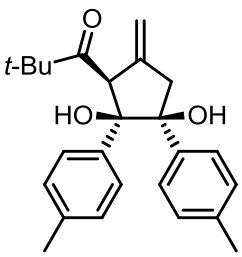
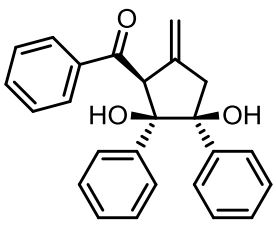
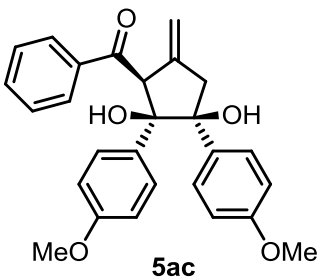
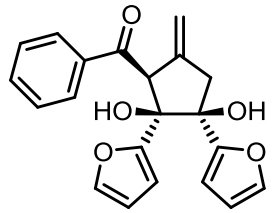
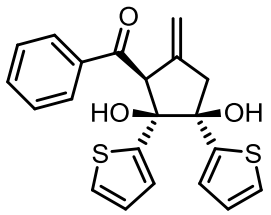
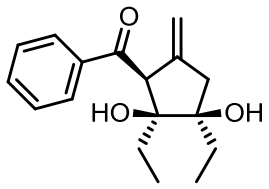
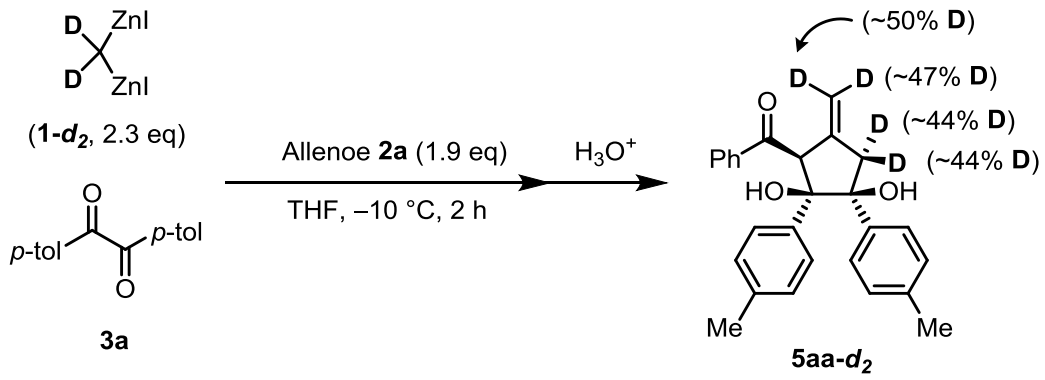
Product.[b]
 **5aa** 99%
 **5ba** 97%
 **5ca** 85%
 **5da** 77%
 **5ea** 94%
 **5fa** 85%
 **5ga** 85%
 **5ab** 85%
 **5ac** 85%

Table 3. (Continued)

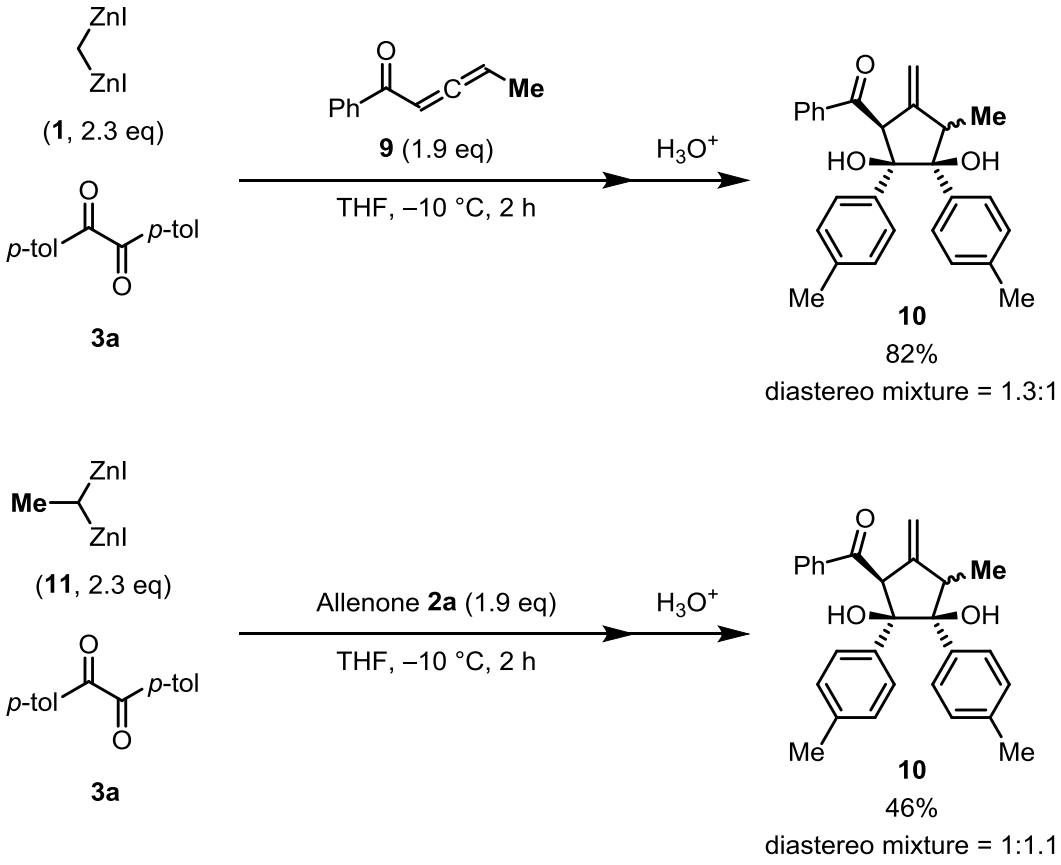
		
5ad	**5ae**	**5af**
95%[c]	95%[c]	30%[c]

[a] Reactions were carried out using *gem*-dizinc **1** (0.3 mmol), allenone **2** (0.25 mmol), and diketone **3** (0.13 mmol) in THF (4.0 mL). [b] Isolated yields. [c] Reaction was performed at –40 °C.

To gain the preliminary mechanistic data on three component tandem reaction, he examine the reaction of allenone **2a**, diketone **3a**, and deuterated *gem*-dizinc **1**-d_2. As shown in Scheme 5, the product **5a**-d_2 was deuterated at exomethylene C–H and β-methylene C–H in equal portion. This result suggested that the isomerization of allylzinc in the formed 1,3-dizinc species was very fast compared to the rate of reaction with diketone. Thus, the deuterium scrambling was observed in this reaction using deuterated *gem*-dizinc **1**-d_2. He next investigated the reaction using methyl substituted allenone **9** as shown in Scheme 6. When **9** was used in the tandem reaction, perfectly substituted cyclopentane compound **10** was obtained in good yield with low diastereoselectivity. In addition, using methyl substituted *gem*-dizinc **11** in this reaction gave same compound **10**. These results suggested that more substituted allyl zinc species preferred to exist in situ than less substituted allyl zinc species because reactions of ally zinc with a carbonyl group are well known to proceed through chair-like transition state.[14] Thus, more substituted carbon of this thermodynamically favorable intermediate attacked a carbonyl group of diketone to provide the perfectly substituted cyclopentane compound **10**.



Scheme 5. Three Component Tandem Reaction Using Deuterated *gem*-Dizinc **1**-d_2.



Scheme 6. Reaction Using Methyl Substituted Allenone **9** or *gem*-Dizinc **11**.

Conclusion

In summary, the author have developed functionalized cyclopentane synthesis by the tandem reaction of allenones, diketones, and bis(iodozincio)methane based on three consecutive nucleophilic additions. Michale addition of *gem*-dizinc to allenone generated enolate-allyl zinc species, which reacted with diketone in completely diastereoselective double nucleophilic addition. The product was decorated by diol, olefin, and carbonyl group. A variety of allenones and diketones was utilized in this reaction.

Experimental Section

Materials.

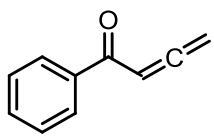
Unless otherwise noted, commercially available reagents were used without purification. All diketones listed in Chapter 4 were commercially available. Bis(iodozincio)methane (**1**) and 1,1-bis(iodozincio)ethane (**11**) were prepared by the method described in Chapter 2. Allenones **2** were prepared according to the reported procedure.[15]

General Procedure for the tandem reaction of allenones, diketones, and bis(iodozincio)methane

To a solution of diketone **3** (0.133 mmol) in THF (2.0 mL) and dizinc **1** (0.3 mmol, 0.30 M in THF), a solution of allenone **2** (0.25 mmol) was added dropwise at –10 °C over 1 hour under Ar. Then, the reaction mixture was stirred for 2 hours at –10 °C, and poured into saturated NH_4Claq (10 mL). The mixture was extracted with ethyl acetate and the combined organic layers were washed with brine and dried over Na_2SO_4. Purification by silica gel column chromatography (hexane / ethyl acetate) gave the the corresponding compound **5**.

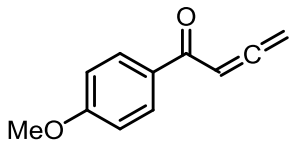
Characterization Data

1-Phenylbuta-2,3-dien-1-one (1a): CAS RN [69626-39-7].



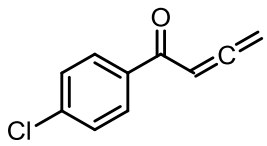
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.90 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.56 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.46 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 2H), 6.45 (t, *J* = 6.5 Hz, 1H), 5.27 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 217.1, 191.1, 137.4, 132.8, 128.7, 128.4, 93.2, 79.3.

1-(4-Methoxyphenyl)buta-2,3-dien-1-one (1b): CAS RN [196952-70-2].



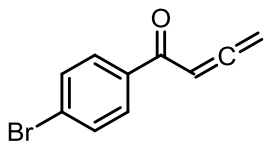
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.93 (ddd, *J* = 9.5, 2.5, 2.5 Hz, 2H), 6.93 (ddd, *J* = 9.5, 2.5, 2.5 Hz, 2H), 6.45 (t, *J* = 6.5 Hz, 1H), 5.25 (d, *J* = 6.5 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 216.5, 189.1, 163.4, 131.0, 130.3, 113.6, 92.8, 79.1, 55.5.

1-(4-Chlorophenyl)buta-2,3-dien-1-one (1c): CAS RN [196953-02-3].



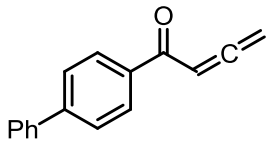
White solid. ^{1}H NMR ($CDCl_3$) δ 7.84 (ddd, *J* = 9.0, 2.5, 2.0 Hz, 2H), 7.43 (ddd, *J* = 9.5, 2.5, 2.0 Hz, 2H), 6.39 (t, *J* = 6.5 Hz, 1H), 5.28 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 217.2, 189.9, 139.2, 135.7, 130.1, 128.7, 93.2, 79.5.

1-(4-Bromophenyl)buta-2,3-dien-1-one (1d): CAS RN [378186-96-0].



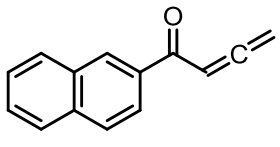
Red solid. δ 7.76 (ddd, *J* = 9.0, 2.0, 2.0 Hz, 2H), 7.59 (ddd, *J* = 9.0, 2.0, 2.0 Hz, 2H), 6.38 (t, *J* = 6.5 Hz, 1H), 5.50 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 217.2, 190.1, 136.1, 131.7, 130.2, 127.9, 93.2, 79.5.

1-((1,1'-Biphenyl)-4-yl)buta-2,3-dien-1-one (1e): CAS RN [1500108-88-2].



Orange solid. ^{1}H NMR ($CDCl_3$) δ 8.00 (ddd, *J* = 8.5, 2.0, 2.0 Hz, 2H), 7.68 (ddd, *J* = 8.5, 2.0, 1.5 Hz, 2H), 7.63 (m, 2H), 7.48 (m, 2H), 7.41 (m, 1H), 6.50 (t, *J* = 6.5 Hz, 1H), 5.30 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 217.0, 145.6, 139.8, 136.1, 129.3, 128.9, 128.8, 128.2, 127.3, 127.0, 93.2, 79.4.

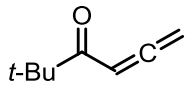
1-(Naphthalen-2-yl)buta-2,3-dien-1-one (1f).



Orange solid. ^{1}H NMR ($CDCl_3$) δ 8.44 (d, *J* = 1.0 Hz, 1H), 7.98 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.89 (t, *J* = 8.5 Hz, 2H), 7.61 (ddd, *J* = 8.5, 7.0, 1.0 Hz, 1H), 7.58 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H),

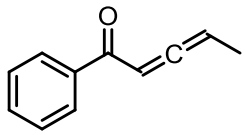
6.60 (t, J = 6.5 Hz, 1H), 5.30 (d, J = 6.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 217.1, 190.8, 135.4, 134.7, 132.3, 130.3, 129.5, 128.4, 128.3, 127.8, 126.8, 124.5, 93.3, 79.4. Mp. 66.2.–67.0 °C. TLC: R_f 0.36 (hexane/EtOAc = 5:1). IR (KBr) 3055.4, 2978.2, 1955.9, 1922.2, 1746.6, 1650.2, 1643.4, 1466.9, 1413.9, 1353.1, 1337.7, 1276.0, 1238.4, 1214.2, 1190.1, 1143.8, 1123.6, 1091.8, 1078.3, 1018.5, 987.6, 954.8, 943.2, 871.9, 854.5, 833.3, 794.7, 777.4, 765.8 cm^{-1}. HRMS (ESI) Calcd for $C_{14}H_{10}OK$: $[M+K]^+$, 195.0801. Found: *m/z* 195.0804.

2,2-Dimethylhexa-4,5-dien-3-one (1h): CAS RN [27552-18-7].



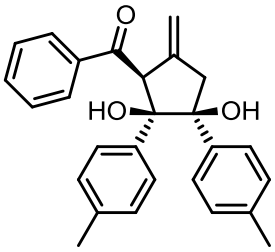
Yellow liguid. ^{1}H NMR ($CDCl_3$) δ 6.13 (t, J = 6.5 Hz, 1H), 5.17 (d, J = 6.5 Hz, 2H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 215.4, 204.1, 90.7, 79.0, 44.2, 26.4.

1-Phenylpenta-2,3-dien-1-one (1h): CAS RN [99845-86-0].



Yellow liguid. ^{1}H NMR ($CDCl_3$) δ 7.87 (dd, J = 8.0, 1.0 Hz, 2H), 7.54 (tt, J = 7.5, 1.5 Hz, 1H), 7.44 (dd, J = 7.5, 7.5 Hz, 2H), 6.32 (dq, J = 6.0, 3.0 Hz, 1H), 5.59 (dq, J = 7.0, 6.0 Hz, 1H), 1.81 (dd, J = 7.5, 3.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 214.5, 192.2, 137.6, 132.6, 128.6, 128.2, 93.4, 89.8, 12.9.

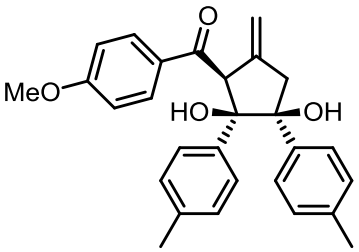
((1*S,2*R**,3*S**)-2,3-Dihydroxy-5-methylene-2,3-di-*p*-tolylcyclopentyl)(phenyl)methanone (5aa)**.



White solid. ^{1}H NMR ($CDCl_3$) δ 7.93 (dd, J = 8.0, 1.5 Hz, 2H), 7.62 (tt, J = 7.5, 1.5 Hz, 1H), 7.50 (dd, J = 8.0, 7.5 Hz, 2H), 6.98 (m, 4H), 6.86 (m, 4H), 6.12 (s, 1H), 5.28 (dd, J = 5.0, 2.5 Hz, 1H), 5.25 (d, J = 2.0 Hz, 1H), 4.82 (dd, J = 5.0, 2.5 Hz, 1H), 4.06 (s, 1H), 3.44 (ddd, J = 17.5, 3.0, 2.0 Hz, 1H), 3.29 (ddd, J = 17.5, 5.5, 2.5 Hz, 1H), 2.29 (s, 3H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 203.2, 147.5, 138.5, 137.7, 136.9, 136.8, 136.7, 134.3, 129.0, 129.0, 128.1, 128.0, 126.5, 126.2, 110.8, 86.3, 84.1, 53.9, 47.6, 21.0, 20.9. Mp. 129.2.–130.0 °C. TLC: R_f 0.53 (hexane/EtOAc = 3:1). IR (KBr) 3480.7, 3300.4, 2923.3, 1657.9, 1648.2, 1593.3, 1515.2, 1445.7, 1368.6,

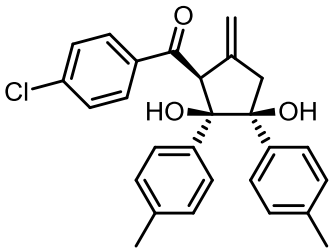
1344.4, 1199.8, 1188.2, 1110.1, 1094.7, 978.9, 943.2, 890.2, 837.1, 815.9, 750.3, 696.3 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{26}O_3Na$: $[M+Na]^+$, 421.1774. Found: *m/z* 421.1763.

((1*S,2*R**,3*S**)-2,3-Dihydroxy-5-methylene-2,3-di-*p*-tolylcyclopentyl)(4-methoxyphenyl)methanone** (**5ba**).



Yellow solid. ^1H NMR ($CDCl_3$) δ 7.93 (dt, *J* = 9.5, 2.5 Hz, 2H), 7.03 (m, 6H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.40. (s, 1H), 5.28 (dd, *J* = 5.0, 2.5, 1H), 5.20 (d, *J* = 2.0 Hz, 1H), 4.84 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.10 (s, 1H), 3.89 (s, 3H), 3.44 (dd, *J* = 17.0, 1.0 Hz, 1H), 3.30 (ddd, *J* = 17.5, 5.0, 2.5 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 201.4, 164.4, 147.6, 138.6, 137.0, 136.7, 136.5, 131.5, 130.7, 128.1, 127.9, 126.5, 126.2, 114.1, 110.5, 86.2, 84.1, 55.6, 53.3, 47.6, 21.0, 20.9. Mp. 128.2.–129.0 °C. TLC: R_f 0.58 (hexane/EtOAc = 2:1). IR (KBr) 3548.2, 3372.7, 3026.4, 2921.3, 1745.7, 1648.2, 1599.1, 1570.1, 1511.3, 1422.6, 1384.0, 1336.7, 1267.3, 1238.4, 1206.5, 1172.8, 1099.5, 1029.1, 988.6, 950.0, 899.8, 837.1, 815.9, 726.2 cm^{-1}. HRMS (ESI) Calcd for $C_{28}H_{28}O_4Na$: $[M+Na]^+$, 451.1880. Found: *m/z* 451.1869.

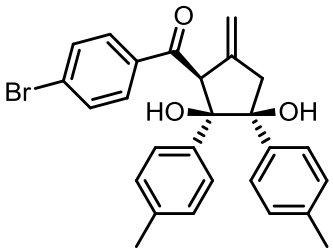
((1*S,2*R**,3*S**)-2,3-Dihydroxy-5-methylene-2,3-di-*p*-tolylcyclopentyl)(4-chlorophenyl)methanone** (**5ca**).



Yellow solid. ^1H NMR ($CDCl_3$) δ 7.89 (dd, *J* = 6.5, 2.0 Hz, 2H), 7.46 (dd, *J* = 6.5, 2.0 Hz, 2H), 6.96 (s, 4H), 6.85 (s, 4H), 5.92 (s, 1H), 5.29 (dd, *J* = 5.0, 2.0 Hz, 1H), 5.18 (d, *J* = 2.5 Hz, 1H), 4.80 (q, *J* = 2.5 Hz, 1H), 4.03 (s, 1H), 3.44 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.27 (ddd, *J* = 17.5, 5.0, 2.0 Hz, 1H), 2.28 (s, 3H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 202.0, 147.3, 140.9, 138.3, 136.9, 136.8, 136.8, 136.0, 130.4, 129.3, 128.1, 128.0, 126.5, 126.1, 111.0, 86.3, 84.2, 54.3, 47.4, 21.0, 20.9. Mp. 110.5.–111.2 °C. TLC: R_f 0.63 (hexane/EtOAc = 3:1). IR (KBr) 3452.7, 2922.3, 1670.4, 1587.5, 1515.2, 1401.3, 1386.9,

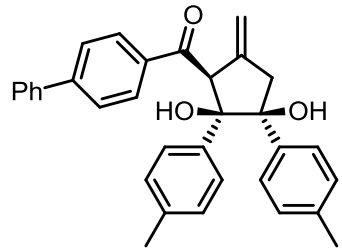
1347.3, 1205.6, 1180.5, 1095.6, 1055.1, 1012.7, 951.9, 889.2, 817.9, 765.8 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{25}Cl_2O_3$: $[M+Cl]^+$, 467.1175. Found: *m/z* 467.1182.

((1*S,2*R**,3*S**)-2,3-Dihydroxy-5-methylene-2,3-di-*p*-tolylcyclopentyl)(4-bromophenyl)methanone** (**5da**).



White solid. ^{1}H NMR ($CDCl_3$) δ 7.77 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.63 (dd, *J* = 9.0, 2.0 Hz, 2H), 6.95 (m, 4H), 6.84 (m, 4H), 5.89 (s, 1H), 5.29 (d, *J* = 2.5 Hz, 1H), 5.16 (d, *J* = 2.0 Hz, 1H), 4.80 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.01 (s, 1H), 3.43 (d, *J* = 17.5 Hz, 1H), 3.26 (ddd, *J* = 17.5, 5.0, 2.5 Hz, 1H), 2.28 (s, 3H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 202.2, 147.2, 138.2, 136.9, 136.8, 136.8, 136.4, 132.3, 130.4, 129.8, 128.1, 128.0, 126.5, 126.1, 111.1, 86.3, 84.2, 54.3, 47.4, 21.0, 21.0. Mp. 127.0.–127.8 °C. TLC: R_f 0.47 (hexane/EtOAc = 3:1). IR (KBr) 3449.8, 2921.3, 1670.4, 1653.1, 1582.7, 1514.2, 1396.5, 1387.8, 1352.2, 1261.5, 1205.6, 1184.3, 1097.5, 1072.5, 1009.8, 815.9, 727.2 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{25}BrO_3Na$: $[M+Na]^+$, 499.0879. Found: *m/z* 499.0870.

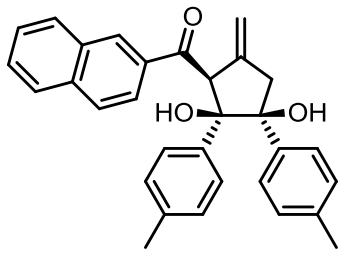
((1*S,2*R**,3*S**)-2,3-Dihydroxy-5-methylene-2,3-di-*p*-tolylcyclopentyl)(1,1'-biphenyl)-4-yl)methanone** (**5ea**).



White solid. ^{1}H NMR ($CDCl_3$) δ 8.01 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.72 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.63 (m, 2H), 7.49 (m, 2H), 7.43 (m, 1H), 6.99 (m, 4H), 6.88 (m, 4H), 6.18 (s, 1H), 5.31 (dd, *J* = 5.0, 2.5 Hz, 1H), 5.29 (d, *J* = 2.5 Hz, 1H), 4.89 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.09 (s, 1H), 3.46 (dd, *J* = 17.5, 0.5 Hz, 1H), 3.31 (ddd, *J* = 17.5, 5.0, 2.5 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 202.7, 147.5, 146.9, 139.4, 138.5, 136.9, 136.8, 136.7, 136.3, 129.6, 129.0, 128.5, 128.1, 128.0, 127.6, 127.3, 126.5, 126.2, 110.9, 86.3, 84.2, 54.0, 47.6, 21.0, 21.0. Mp. 84.2.–85.1 °C. TLC: R_f 0.49 (hexane/EtOAc = 3:1). IR (KBr) 3404.5, 3031.3, 2968.6, 2933.9, 2360.0, 2317.6, 1654.0, 1602.9, 1559.5, 1516.1, 1406.2,

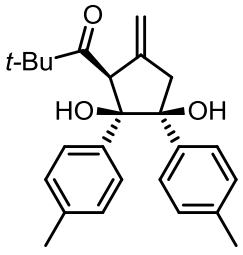
1378.2, 1332.9, 1207.5, 1186.3, 1099.5, 1006.9, 816.9, 769.6, 726.2, 696.3 cm^{-1}. HRMS (ESI) Calcd for $C_{33}H_{31}O_3$: $[M+H]^+$, 475.2268. Found: *m/z* 475.2264.

((1*S,2*R**,3*S**)-2,3-Dihydroxy-5-methylene-2,3-di-*p*-tolylcyclopentyl)(naphthalen-2-yl)methanone** (**5fa**).



White solid. ^1H NMR ($CDCl_3$) δ 8.44 (s, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.98 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.65 (td, *J* = 7.5, 1.5 Hz, 1H), 7.59 (td, *J* = 7.5, 1.0 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.23 (s, 1H), 5.41 (d, *J* = 2.5 Hz, 1H), 5.31 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.88 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.12 (s, 1H), 3.49 (d, *J* = 17.5 Hz, 1H), 3.33 (ddd, *J* = 17.5, 5.0, 2.5 Hz, 1H), 2.31 (s, 3H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 203.1, 147.6, 138.5, 136.9, 136.8, 136.7, 136.0, 135.1, 132.4, 131.5, 130.0, 129.3, 128.9, 128.1, 128.0, 127.8, 127.0, 126.6, 126.2, 124.0, 110.9, 86.4, 84.2, 54.0, 47.6, 21.1, 21.0. Mp. 76.2.–77.0 °C. TLC: R_f 0.57 (hexane/EtOAc = 3:1). IR (KBr) 3524.1, 3411.3, 3027.4, 2924.2, 2361.9, 2341.7, 1662.7, 1654.0, 1647.3, 1624.1, 1513.2, 1375.3, 1362.8, 1323.2, 1183.4, 1125.5, 1097.5, 985.7, 822.7, 741.7 cm^{-1}. HRMS (ESI) Calcd for $C_{31}H_{28}O_3Na$: $[M+Na]^+$, 471.1931. Found: *m/z* 471.1921.

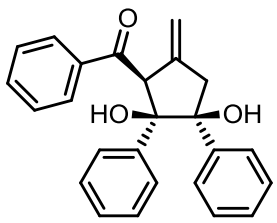
1-((1*S,2*R**,3*S**)-2,3-Dihydroxy-5-methylene-2,3-di-*p*-tolylcyclopentyl)-2,2-dimethylpropan-1-one** (**5ga**).



White solid. ^1H NMR ($CDCl_3$) δ 6.88 (m, 8H), 5.32 (dd, *J* = 4.0, 2.5 Hz, 1H), 5.03 (s, 1H), 4.97 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.85 (m, 1H), 4.79 (s, 1H), 3.45 (dd, *J* = 17.5, 1.0 Hz, 1H), 2.93 (ddd, *J* = 17.5, 4.0, 2.0 Hz, 1H), 2.25 (s, 6H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 220.8, 148.6, 138.7, 136.8, 136.6, 136.5, 127.9, 127.9, 126.2, 126.1, 112.5, 86.6, 85.2, 59.3, 45.8, 45.3, 25.7, 21.0, 21.0. Mp. 124.7.–125.0 °C. TLC: R_f 0.42 (hexane/EtOAc = 10:1). IR (KBr) 3495.2, 3379.4, 2971.5, 1693.6, 1654.0, 1515.2, 1473.7, 1429.3, 1386.9, 1316.5, 1251.9, 1185.3, 1086.9, 1073.4, 1036.8,

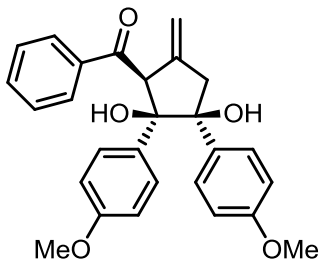
909.5, 878.6, 823.6, 756.1 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{30}O_3Na$: $[M+Na]^+$, 401.2087. Found: *m/z* 401.2077.

((1*S,2*R**,3*S**)-2,3-Dihydroxy-5-methylene-2,3-diphenylcyclopentyl)(phenyl)methanone** (**5ab**).



White solid. ^{1}H NMR ($CDCl_3$) δ 7.95 (dd, *J* = 9.0, 1.0 Hz, 2H), 7.63 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.16 (m, 3H), 7.10 (m, 3H), 7.04 (t, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 7.5 Hz, 2H), 6.20 (s, 1H), 5.31 (s, 2H), 4.85 (d, *J* = 2.0 Hz, 1H), 4.16 (s, 1H), 3.50 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.32 (dq, *J* = 17.5, 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 203.1, 147.2, 141.4, 139.8, 137.6, 134.4, 129.0, 129.0, 127.4, 127.3, 127.3, 127.2, 126.5, 126.2, 111.0, 86.3, 84.3, 53.8, 47.4. Mp. 35.2.–36.0 °C. TLC: R_f 0.53 (hexane/EtOAc = 3:1). IR (KBr) 3417.0, 3060.2, 2929.0, 1663.7, 1653.1, 1595.2, 1579.8, 1491.0, 1448.6, 1379.2, 1339.6, 1304.9, 1203.6, 1069.6, 984.7, 947.1, 868.1, 816.9, 764.8, 695.4 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{22}O_3Cl$: $[M+Cl]^-$, 405.1252. Found: *m/z* 405.1258.

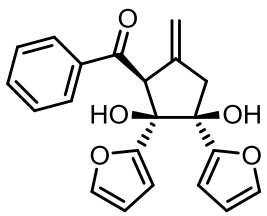
((1*S,2*R**,3*S**)-2,3-Dihydroxy-2,3-bis(4-methoxyphenyl)-5-methylenecyclopentyl)(phenyl)methanone** (**5ac**).



Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.92 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.62 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.50 (tt, *J* = 8.0, 1.5 Hz, 2H), 7.01 (dt, *J* = 9.0, 3.0 Hz, 2H), 6.90 (dt, *J* = 9.0, 3.0 Hz, 2H), 6.70 (dt, *J* = 9.5, 3.0 Hz, 2H), 6.59 (d, *J* = 9.0 Hz, 2H), 6.09 (s, 1H), 5.27 (dd, *J* = 4.5, 2.5 Hz, 1H), 5.20 (d, *J* = 2.0 Hz, 1H), 4.81 (dd, *J* = 2.5, 2.5 Hz, 1H), 4.03 (s, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.42 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.28 (ddd, *J* = 17.5, 5.5, 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 203.3, 158.7, 158.6, 147.3, 137.6, 134.3, 133.6, 132.1, 129.0, 129.0, 127.9, 127.5, 112.7, 112.6, 110.9, 86.1, 84.0, 55.2, 55.1, 53.8, 47.4. Mp. 52.4.–52.8 °C. TLC: R_f 0.33 (hexane/EtOAc = 3:1). IR (KBr) 3413.2, 2956.0, 2933.9, 2836.5, 1663.7, 1653.1,

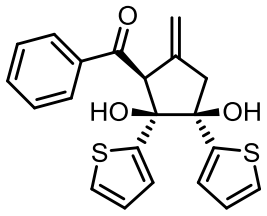
1610.6, 1596.2, 1513.2, 1448.6, 1374.3, 1339.6, 1252.8, 1204.6, 1179.5, 1096.6, 1035.8, 837.1, 694.4 cm^{-1}. HRMS (ESI) Calcd for $C_{27}H_{26}O_5Na$: $[M+Na]^+$, 453.1672. Found: *m/z* 453.1665.

((1*S,2*S**,3*R**)-2,3-Di(furan-2-yl)-2,3-dihydroxy-5-methylenecyclopentyl)(phenyl)methanone (5ad).**



Yellow solid. ^1H NMR ($CDCl_3$) δ 7.99 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.64 (td, *J* = 8.0, 1.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.30 (m, 1H), 7.09. (m, 1H), 6.29 (dd, *J* = 3.5, 0.5 Hz, 1H), 6.27 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.21 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.20 (s, 1H), 6.18 (dd, *J* = 3.0, 1.0 Hz, 1H), 5.28 (d, *J* = 2.5, 1H), 5.18 (dd, *J* = 5.5, 2.0 Hz, 1H), 4.74 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.05 (s, 1H), 3.40 (ddd, *J* = 17.5, 3.0, 2.0 Hz, 1H), 3.13 (ddd, *J* = 17.0, 5.0, 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 203.0, 154.2, 153.4, 145.8, 142.0, 141.7, 137.3, 134.4, 129.2, 129.0, 111.1, 110.4, 110.2, 107.8, 107.2, 83.0, 81.3, 53.1, 45.1. Mp. 105.5.–106.2 °C. TLC: R_f 0.46 (hexane/EtOAc = 3:1). IR (KBr) 3553.0, 3341.8, 3118.1, 2926.1, 1655.0, 1502.6, 1450.5, 1381.1, 1343.5, 1273.1, 1235.5, 1215.2, 1168.9, 1140.9, 1123.6, 1072.5, 1015.6, 1008.8, 994.4, 918.2, 894.0, 865.1, 796.6, 758.1, 734.9, 693.4 cm^{-1}. HRMS (ESI) Calcd for $C_{21}H_{18}O_5Na$: $[M+Na]^+$, 373.1046. Found: *m/z* 373.1039.

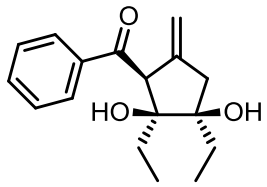
((1*S,2*S**,3*R**)-2,3-Dihydroxy-5-methylene-2,3-di(thiophen-2-yl)cyclopentyl)(phenyl)methanone (5ae).**



Yellow solid. ^1H NMR ($CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.66 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.53 (dd, *J* = 8.0, 7.5 Hz, 2H), 7.15 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.10 (dd, *J* = 5.0, 1.5 Hz, 1H), 6.95 (m, 2H), 6.76 (dd, *J* = 5.0, 4.0 Hz, 1H), 6.66 (s, 1H), 6.54 (dd, *J* = 4.0, 1.5 Hz, 1H), 5.30 (d, *J* = 2.5 Hz, 1H), 5.26 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.83 (dd, *J* = 5.5, 2.5 Hz, 1H), 4.28 (s, 1H), 3.44 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.35 (ddd, *J* = 17.5, 5.5, 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 202.8, 146.7, 145.4, 144.7, 137.4, 134.6, 129.1, 129.1, 126.4, 126.0, 125.7, 125.2, 124.2, 123.7, 111.8, 85.2, 83.7, 54.5, 48.0. Mp. 140.0.–140.5 °C. TLC: R_f 0.42 (hexane/EtOAc = 3:1). IR (KBr)

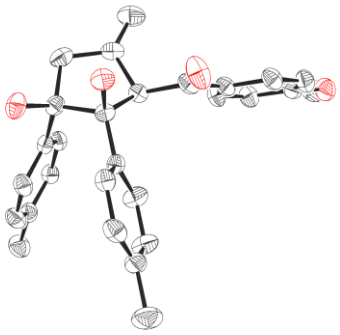
3529.9, 3396.8, 1662.7, 1654.0, 1592.3, 1446.7, 1374.3, 1349.3, 1255.7, 1232.6, 1208.5, 1192.1, 1105.3, 1047.4, 859.3, 716.6, 692.5 cm^{-1}. HRMS (ESI) Calcd for $C_{21}H_{18}O_3S_2Na$: $[M+Na]^+$, 406.0623. Found: *m/z* 406.0619.

((1*S,2*S**,3*R**)-2,3-Diethyl-2,3-dihydroxy-5-methylenecyclopentyl)(phenyl)methanone** (**5af**).



White solid. ^1H NMR ($CDCl_3$) δ 8.00 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.64 (tt, *J* = 7.5, 1.5 Hz, 2H), 7.53 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 2H), 5.14 (s, 1H), 5.02 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.66 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.53 (s, 1H), 3.87 (d, *J* = 2.0 Hz, 1H), 2.74 (d, *J* = 2.0 Hz, 2H), 1.77 (dq, *J* = 14.0, 7.0 Hz, 1H), 1.68 (dq, *J* = 14.0, 7.0 Hz, 1H), 1.51 (dq, *J* = 14.0, 7.0 Hz, 1H), 1.42 (ddq, *J* = 14.0, 7.0, 2.0 Hz, 1H), 1.05 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 204.9, 147.4, 137.8, 134.1, 129.1, 129.0, 111.1, 85.0, 82.5, 54.8, 43.8, 28.3, 26.7, 8.8, 8.3. Mp. 43.2.–43.8 °C. TLC: R_f 0.50 (hexane/EtOAc = 3:1). IR (KBr) 3417.0, 3283.0, 2976.3, 2960.9, 1659.8, 1645.4, 1596.2, 1579.8, 1447.6, 1332.9, 1303.9, 1291.4, 1232.6, 1203.6, 994.4, 887.3, 781.2, 695.4 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{22}O_3Cl$: $[M+Cl]^-$, 309.1252. Found: *m/z* 309.1252.

ORTEP Drawing of **5ba**



Identification code	**5ba**
Empirical formula	$C_{28}H_{28}O_4$
Formula weight	428.20
Temperature	273 K
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 10.1508(13) Å
	b = 13.469(2) Å
	c = 17.384(2) Å
Volume	2376.6(5) $Å^3$
Z	4
Density (calculated)	1.198 g/cm^3
Absorption coefficient	0.789 cm^{-1}
F(000)	912
Crystal size	0.320 x 0.210 x 0.200 mm^3
2θmax	55.0°
Reflections collected	25204
Final R indices [I>2sigma(I)]	5454
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	0.880
R indices (all data)	R1 = 0.0506, wR2 = 0.1146

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12. The relative configuration of product **5ba** was determined by X-ray structure anaylsis.
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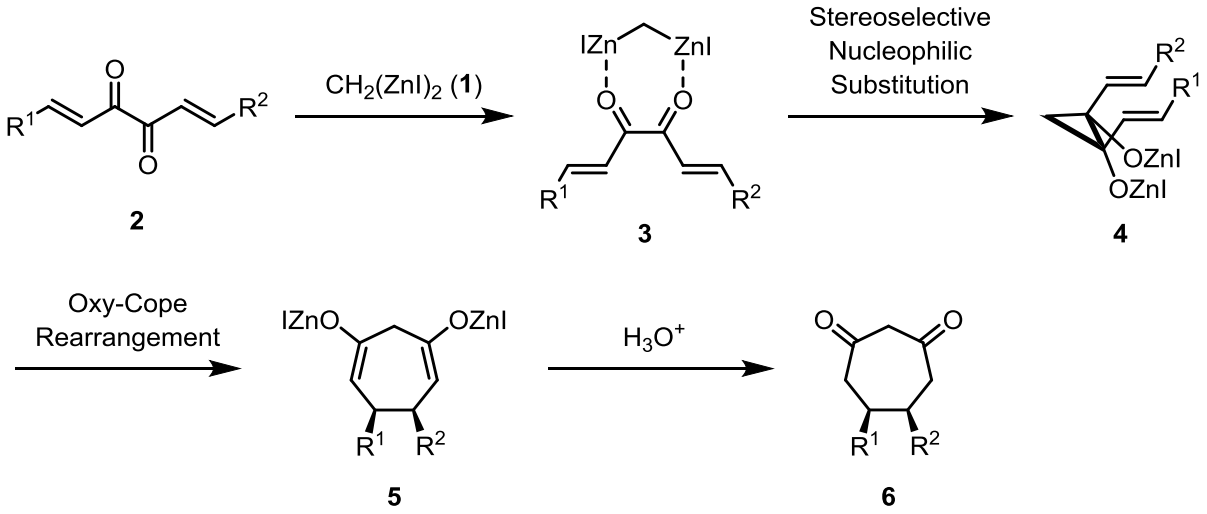
Chapter 5

Preparation of Cycloheptane Ring by Nucleophilic Cyclopropanation of 1,2-Diketones with Bis(iodozincio)methane

The nucleophilic cyclopropanation of hexa-1,5-diene-3,4-diones with bis(iodozincio)methane afforded the zinc alkoxides of *cis*-dialkenylcyclopropane-1,2-diols stereoselectively. The subsequent Oxy-Cope rearrangement afforded the corresponding zinc alkoxides of 5,6-dialkylcyclohepta-3,7-diene-1,3-diols.

Introduction

The Cope rearrangement of *cis*-divinylcyclopropanes has been recognized as an efficient route to synthesize cycloheptane rings. The disadvantageous entropic factor for a seven-membered ring construction is overcome by the close proximity of both ends caused by the rigid configuration of cyclopropane.[1] The difficulty in the stereoselective preparation of the *cis*-isomer of the substrate, however, often makes the transformation less valuable. Although some practical methods have been developed for the preparation of the *cis*-isomers,[2] most of the methods afforded the *trans*-isomers, which required a temperature of >100 °C to perform the Cope rearrangement.[3] Thus, a direct route to synthesize *cis*-isomers stereoselectively is desirable in order to construct cycloheptane rings easily.



Scheme 1. Synthesis of Cycloheptane Ring **5** by Nucleophilic Cyclopropanation of 1,2-Diketone **2**.

Bis(iodozincio)methane (**1**),[4] which have two C–Zn bonds at the same carbon, works as a dianion equivalent. Matsubara reported that the nucleophilic cyclopropanation of 1,2-diketones afforded *cis*-cyclopropane-1,2-diols stereoselectively.[5] The mechanism of the reaction was elucidated by a computational method; the *cis*-selectivity was attributed to the face-to-face

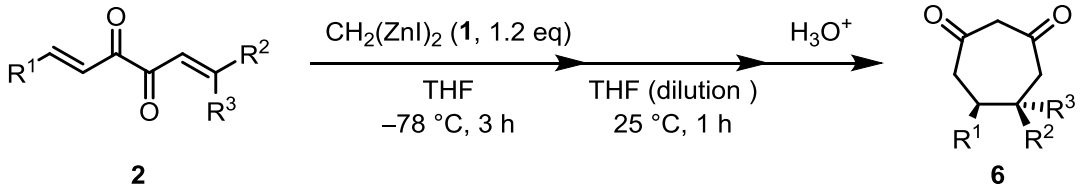
coordination of **1** with the diketones.[6] The author envisioned that the reaction of 1,6-dialkylhexa-1,5-diene-3,4-diones **2** with **1** would afford the Zn alkoxides of *cis*-divinylcyclopropane-1,2-diols **4**, *via* face-to-face coordination **3**, thus facilitating the oxy-Cope rearrangement of **4** to **5**, with additional acceleration by the alkoxide groups (Scheme 1).[7]

Results and Discussion

The reaction of (1*E*,5*E*)-1,6-diphenylhexa-1,5-diene-3,4-dione (R^1, R^2 = Ph, R^3 = H, **2a**) with dizinc **1** at −20 °C, however, afforded a complex mixture, even though it contained a small amount of the desired cycloheptane-1,3-dione **6a** after the hydrolysis. The main byproduct was the adduct of an enolate **5a** with the substrate **2a**. This result indicates that the first reaction, *i.e.*, the cyclopropanation of **2a** with **1** should be completed before the start of Cope rearrangement to prevent side reactions of the rearranged product **5** with substrate **2**. For this purpose, the author investigated the reaction of diketone **2** with **1** at the lower temperatures, which do not allow Cope-rearrangement, for an appropriate period, until the complete conversion of **2**; the resulting mixture was warmed up to promote the subsequent Cope-rearrangement. In fact, the reaction of **2a** with **1** for 3 h at −78 °C, followed by warming up the resulting mixture to 25 °C afforded the seven-membered ring **6a** in 78% yield.[8] Moreover, instead of the simple heating to 25 °C, the addition of THF (25 °C) to the reaction mixture afforded **6a** in 84% yield, because the dilution suppressed the intermolecular side reactions without affecting the rate of the intramolecular rearrangement reaction. Some examples of the preparation of cycloheptane-1,3-diones are shown in Table 1. Various cycloheptane-1,3-diones substituted with two *cis*-aryl groups **6** were prepared and isolated in good yields (Table 1, entries 1–4). The presence of an electron-withdrawing group on the benzene ring resulted in a low yield (entry 5). The presence of a bulky group such as 1-naphthyl also resulted in a low yield (entry 7). The presence of alkyl groups as the substituents (R^1, R^2, and R^3) did not hinder the reaction (Table 1, entries 8–11).

These transformations were stereospecific. As shown in entries 8 and 9, the *cis*- and *trans*-isomers were obtained specifically depending on the *E*,*Z*-configuration of the substrate.

Table 1. Preparation of Cycloheptane-1,3-diones **6**.[a]

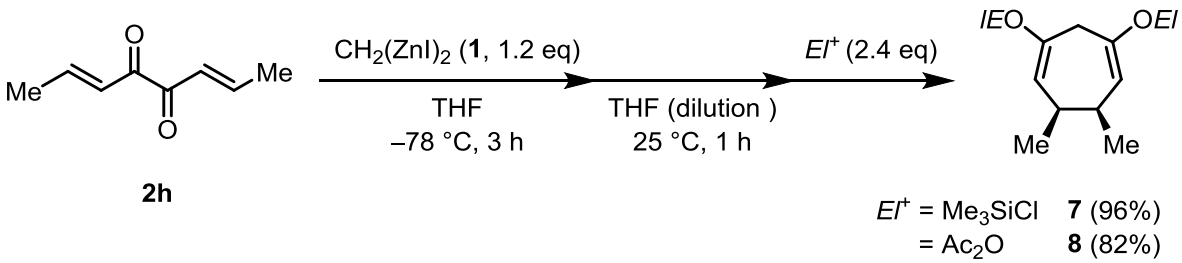


2 **6**

entry	Substrate	R^1	R^2	R^3	Yield of **6** (%)[b,c]
1	**2a**	Ph	Ph	H	84 (**6a**)
2	**2b**	4-MeC_6H_4	4-MeC_6H_4	H	93 (**6b**)
3	**2c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	98 (**6c**)
4	**2d**	4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	H	96 (**6d**)
5	**2e**	4-FC_6H_4	4-FC_6H_4	H	47 (**6e**)
6	**2f**	2-Furyl	2-Furyl	H	78 (**6f**)
7	**2g**	1-Naph	1-Naph	H	41 (**6g**)
8	**2h**	Me	Me	H	99 (**6h**)
9	**2i**	Me	H	Me	65 (**6i**)
10	**2j**	Me	Ph	H	88 (**6j**)
11	**2k**	Me	Me	Me	86 (**6k**)

[a] Reactions were carried out using *gem*-dizinc **1** (1.2 mmol) and diketone **2a** (1.0 mmol) in THF (9.4 mL). [b] Isolated yields. [c] The diastereomer was not observed.

The Zn-enolate intermediate **5** in Scheme 1 was able to be trapped with chlorotrimethylsilane (TMSCl) or acetic anhydride (Ac_2O). As shown in Scheme 2, after the treatment of **2h** with dizinc **1** at −78 °C for 3 h and at 25 °C for 1 h with additional THF, TMSCl was added. The corresponding silyl enol ether **7** was obtained in 96% isolated yield. Instead of TMSCl, the addition of Ac_2O afforded the corresponding enol acetate **8** in 82% isolated yield.



Scheme 2. Trapping of Zinc Enolate Intermediate from **2h** with Electrophiles.

This [6 + 1] transformation contains two reactions, that is, the nucleophilic cyclopropanation of 1,2-diketone and the oxy-Cope rearrangement of *cis*-1,2-divinylcyclopropane-1,2-diol. As the activation energy for the first step is smaller than the second one, the first reaction can be completed before the second reaction proceeds at −78 °C. Otherwise, the formed zinc enolate **5** reacts with the diketone **2**. Therefore, careful temperature control made the entire transformation proceed reasonably to obtain the 7-membered product in good yields. In other words, the two reactions were separated by the reaction temperature.

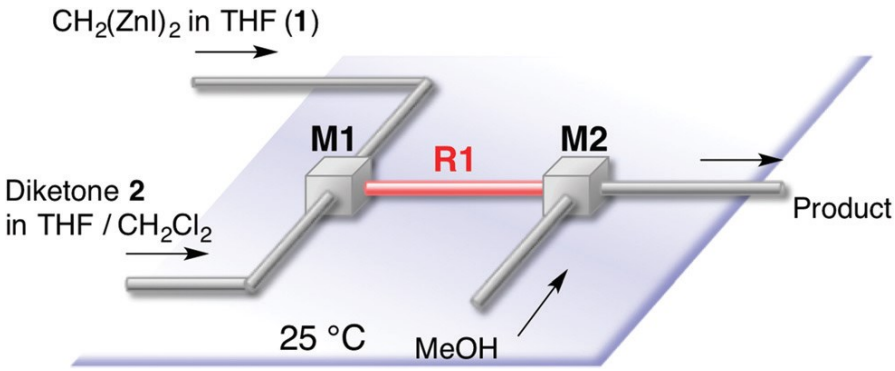
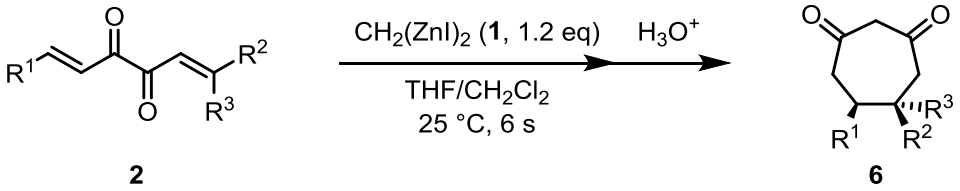


Figure 1. Microflow System for the Preparation of Cycloheptane-1,3-dione **6**.

Instead of temperature control, it is possible to separate the two reactions with space. The microflow system (space integration)[9] may improve the problem arising from a premature start of the second reaction, because it can supply a minimum amount of the substrate to be consumed at the micromixer spontaneously.[10] Thus, as shown in Fig. 1, the author constructed a microflow

system consisting of two T-shaped SUS micromixers (**M1** and **M2**, Φ = 0.5 mm) and SUS microtube reactors (**R1**, Φ = 1.0 mm).[11]

Table 2. Preparation of Cycloheptane-1,3-diones **6** Using a Microflow System.[a]



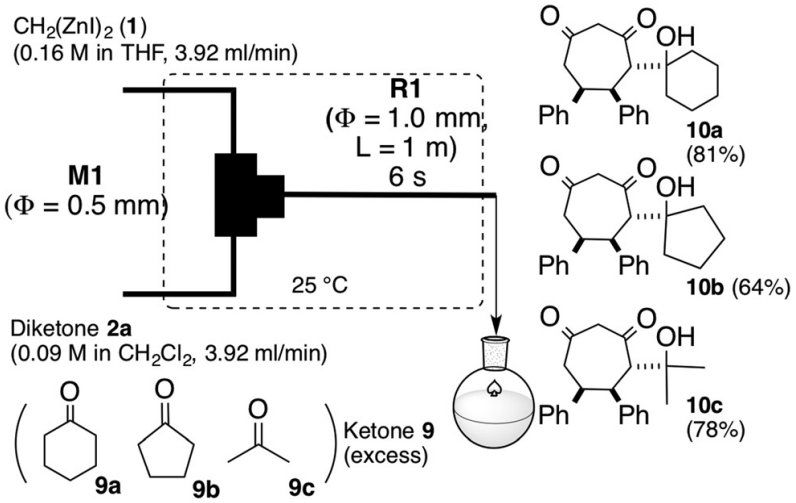
2 **6**

entry	Substrate	R^1	R^2	R^3	Yield of **6** (%)[c,d]
1	**2a**	Ph	Ph	H	>99 (**6a**)
2	**2b**	4-MeC_6H_4	4-MeC_6H_4	H	>99 (**6b**)
3	**2c**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	92 (**6c**)
4	**2d**	4-*t*-BuC_6H_4	4-*t*-BuC_6H_4	H	81 (**6d**)
5[b]	**2e**	4-FC_6H_4	4-FC_6H_4	H	82 (**6e**)
6[b]	**2f**	2-Furyl	2-Furyl	H	77 (**6f**)
7	**2h**	Me	Me	H	70 (**6h**)

[a] Reaction condition: *gem*-dizinc **1** (0.16 M in THF, 3.92 mL/min), **2** (0.16 M in CH_2Cl_2, 3.92 mL/min), and MeOH (neat, 7.25 mL/min). Temperature in M1 and R1 (25 °C). Residence time in R1 (6 s). [b] THF was used as the solvent for the solution of **2** instead of CH_2Cl_2. [c] Isolated yields. [d] The diastereomer was not observed.

A THF solution of **1** (0.16 M, 3.92 mL/min) and a THF or CH_2Cl_2 solution of 1,2-diketone (0.09 M, 3.92 mL/min) were introduced by a syringe pump; after passage through reactor **R1**, the enolate **5** and the excess amount of **1** were quenched with methanol in **M2**. The residence time was optimized by varying the length of the microtube reactor (see the ESI†). In the flow system, a residence time of 6 seconds (1 m length, Φ = 1.0 mm, SUS microtube reactor (**R1**)) afforded the products in good yields continuously. In this case, the residence time of the reaction mixture of **1** and **2** in **R1** was 6 s. The period was calculated from the flow rate (3.92 × 2 mL/min) and the inner volume of **R1**. The results are summarized in Table 2.

As shown in Table 2, the products were obtained in reasonable yields at 25 °C for 6 s continuously. Except entries 5 and 6, dichloromethane was used as the solvent to prepare the solution of diketones **2**, because the corresponding diketones except **2e** and **2f** were not very soluble in THF. Notably, the microflow system allowed us to use dichloromethane as a cosolvent for the reactions using a fairly basic dizinc reagent **1**. Moreover, dichloromethane is difficult to use as a cosolvent in a batch reaction, because the monomeric structure of dizinc **1** in THF is changed into the polymethylenezinc form through the Schlenk equilibrium by the addition of any other less polar solvent such as dichloromethane. The polymeric structure often loses nucleophilicity.[12]



Scheme 3. Reaction of Zinc Enolate Intermediate **5a** with Ketones **9**.

In the microflow system shown in Fig. 1, Zn-enolate **5** and an excess amount of dizinc **1** was protonated with methanol in **M2**. Subsequently, instead of protonation, the resulting reaction mixture *via* **R1** was introduced into a THF solution of ketones **9a**–**c** as shown in Scheme 3. Although dienolate **5** was treated with an excess amount of ketone, **5** reacted with only one molar equivalent of ketone to afford the corresponding aldol adducts **10a**–**c** diastereoselectively.[13]

Conclusion

In conclusion, the reaction of bis(iodozincio)methane (**1** with divinyl-1,2-diketones **2** afforded cycloheptane-1,3-diones **6** efficiently *via* a reactive *cis*-divinylcyclopropane derivative as the key intermediate. Bis(iodozincio)methane was found to be a unique reagent for performing a nucleophilic cyclopropanation reaction with *vicinal* electrophiles such as 1,2-diketone, and affords reactive cyclopropanol derivatives efficiently.[14] Although classical batch reactions required careful temperature control to suppress side-reactions of the product with the starting substrate, the microflow system removed the reactive product from the reaction site continuously, thus improving the yield of the desired product.

Experimental Section

Materials

Unless otherwise noted, commercially available reagents were used without purification.

General procedure for the synthesis of cycloheptane compounds 6 in a batch reactor

To a solution of diketone **2a** (1.0 mmol) in THF (1.0 mL), dizinc **1** (1.2 mmol, 0.35 M in THF) was added dropwise at −78 °C under Ar. After being stirred for 3 h at −78 °C, the mixture was diluted with THF (5 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 1 h, then poured into sat. NH_4Claq and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the corresponding cycloheptane compounds **6**.

General procedure for the synthesis of cycloheptane compounds 6 in a microreactor

Stainless steel (SUS304) T-shaped micromixer with an inner diameter of 0.5 mm was manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactor with an inner diameter of 1.0 mm was purchased from GL Sciences and was cut to the appropriate length (**R1** = 1 m). The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW) to construct the flow microreactor in the laboratory. The flow microreactor was dipped in the bath to control the temperature. Solutions were continuously introduced to the flow microreactor using syringe pumps, Harvard Model 11. After a steady state was reached, the product solution was collected for 90 s. When the collection time was longer, the product solution could be obtained in a preparative scale. As shown in Fig. 1, a flow microreactor consisting of two T-shaped micromixers (**M1** and **M2**, Φ = 0.5 mm) and one microtube reactor (**R1**, Φ = 1.0 mm) was used. To **M1**, bis(iodozincio)methane (**1**, 0.16 M solution in THF) was introduced by a syringe pump with a

rate of 3.92 mL min^{-1}. The syringe pump and **M1** were connected with a Teflon tube (Φ = 1.0 mm). To **M1**, a solution of **2** (0.09 M solution in dichloromethane for **2a**–**d**,**h** and in THF for **2e**,**f**) was introduced by a syringe pump with a rate of 3.92 mL min^{-1}. The syringe pump and **M1** were also connected with a Teflon tube (Φ = 1.0 mm). The mixture was passed through **R1** (Φ = 1.0 mm) and was mixed with MeOH (7.84 mL min^{-1}) in **M2**. The resulting mixture was poured into sat. NH_4Claq and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the cycloheptane derivatives **6**.

Instead of quenching, the product flow from **R1** was poured into a solution of a ketone (3.0 mmol) in THF (10 mL) at 25 °C. The addition from **R1** was continued for 3 min (the amount of the substrate was 1.06 mmol (0.09 M × 3.92 mL min^{-1} × 3 min)). After the addition, the resulting mixture was stirred for 30 min, then poured into sat. NH_4Claq and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the adduct **10**.

Procedure for synthesis of ((5R*,6S*)-5,6-dimethylcyclohepta-3,7-diene-1,3-diyl)bis(oxy)-bis(trimethylsilane) (7) and (5R*,6S*)-5,6-dimethylcyclohepta-3,7-diene-1,3-diyl diacetate (8)

To a solution of diketone **2a** (1.0 mmol) in THF (1.0 mL), dizinc **1** (1.2 mmol, 0.35 M in THF) was added dropwise at −78 °C under Ar. After being stirred for 3 h at −78 °C, the mixture was diluted with THF (10 mL, room temperature). The resulting mixture was stirred at 25 °C for 1 h. To the resulting mixture, chlorotrimethylsilane (2.4 mmol) was added at 0 °C. The resulting mixture was stirred for 1 h at 25 °C, then poured into sat. NH_4Claq and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the title compound **7**. Instead of treatment of the reaction mixture with chlorotrimethylsilane, an addition of acetic anhydride gave the product **8**.

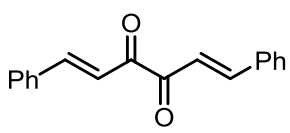
General procedure for the preparation of 1,2-diketones 2a-2g

To a solution of aldehyde (60.0 mmol) and 2,3-butanedione (15.0 mmol) in MeOH (20 mL), piperidine (3.0 mmol), and glacial acetic acid (3.0 mmol) were added sequentially. After the mixture was stirred under MeOH reflux for 6.5 h, MeOH was removed by evaporation. After the resulting mixture was cooled to 0 °C, it was filtered through glass filter G3. The residue was washed with ice-cold MeOH. The corresponding 1,2-diketones were obtained.

Procedure for the preparation of 1,2-diketones 2h-2k

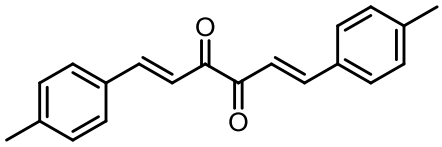
To a solution of dimethyl oxalate (47 mmol) in ether (100 mL), *N*,*N*'-dimethylethylene-1,2-diamine (47 mmol) was added. The resulting mixture was stirred for 12 h at 25 °C. The formed white powder was separated by filtration through glass filter G3. The residue was washed with ice–cooled ether. The obtained white powder was dried in vacuo. Without further purification, 1,4-dimethylpiperazine-2,3-dione (**11**, 42 mmol) was obtained in 90% yield (5.99 g). To a dispersion of **8** (5.0 mmol) in THF (7 mL), (*E*)-prop-1-en-1-ylmagnesium bromide (15 mmol, 0.7 M in THF) was added dropwise at 0 °C under Ar. The mixture was stirred for 30 min at 25 °C and for 2 h under THF reflux. The resulting mixture was poured into 3 M HClaq and extracted with EtOAc. The combined organic layers were washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give title compound **2h** .

(1*E*,5*E*)-1,6-Diphenylhexa-1,5-diene-3,4-dione (2a): CAS RN [126201-33-0].



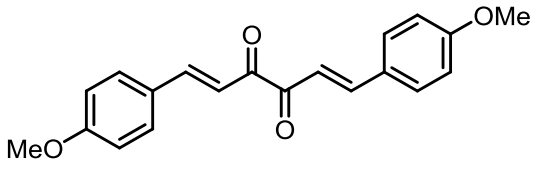
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.87 (d, J = 16.5 Hz, 2H), 7.69–7.64 (m, 4H), 7.48 (d, J = 16.5 Hz, 2H), 7.46–7.41 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 189.1, 147.8, 134.5, 131.3, 129.0, 129.0, 119.7.

(1*E*,5*E*)-1,6-Di-*p*-tolylhexa-1,5-diene-3,4-dione (2b): CAS RN [263249-11-2].



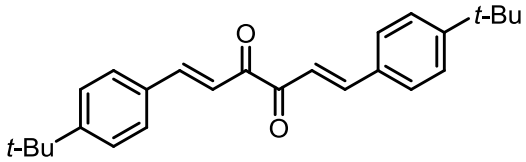
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.84 (d, *J* = 16.5 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 4H), 7.41 (d, *J* = 16.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 4H), 2.40 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 189.5, 147.9, 142.1, 131.8, 129.8, 129.0, 118.9, 21.6.

(1*E*,5*E*)-1,6-Bis(4-methoxyphenyl)hexa-1,5-diene-3,4-dione (2c): CAS RN [263249-10-1].



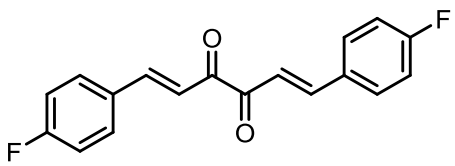
Orange solid. ^{1}H NMR ($CDCl_3$) δ 7.82 (d, *J* = 16.0 Hz, 2H), 7.62 (dt, *J* = 9.0, 2.5 Hz, 4H), 7.33 (d, *J* = 16.0 Hz, 2H), 6.94 (dt, *J* = 9.0, 2.5 Hz, 4H), 3.86 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 189.6, 162.4, 147.5, 130.9, 127.3, 117.7, 114.5, 55.5.

(1*E*,5*E*)-1,6-Bis(4-*tert*-butylphenyl)hexa-1,5-diene-3,4-dione (2d).



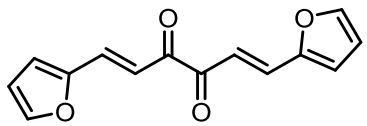
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.85 (d, *J* = 16.0 Hz, 2H), 7.62–7.58 (m, 4H), 7.46–7.43 (m, 4H), 7.43 (d, *J* = 16.0 Hz, 2H), 1.34 (s, 18H). ^{13}C NMR ($CDCl_3$) δ 189.5, 155.2, 147.8, 131.8, 128.9, 126.1, 119.1, 35.1, 31.1. Mp. 164.8–166.2 °C. IR (KBr): 2960, 1669, 1592, 1560, 993, 822, 746, 646 cm^{-1}. HRMS (EI) Calcd for $C_{26}H_{30}O_2$: $[M]^+$, 374.2246. Found: *m/z* 374.2248.

(1*E*,5*E*)-1,6-Bis(4-fluorophenyl)hexa-1,5-diene-3,4-dione (2e).



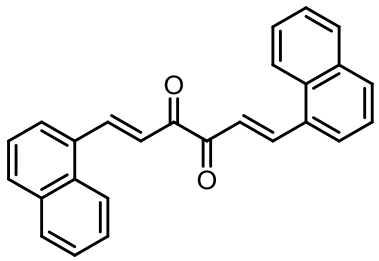
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.84 (d, *J* = 16.5 Hz, 2H), 7.68–7.64 (m, 4H), 7.43 (d, *J* = 16.5 Hz, 2H), 7.15–7.10 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 188.6, 164.6 (d, *J* = 253.4 Hz), 146.4, 131.0 (d, *J* = 8.7 Hz), 130.7, 119.2, 116.3 (d, *J* = 22.1 Hz). Mp. 184.7–187.0 °C. IR (KBr): 1675, 1617, 1599, 1589, 1507, 1245, 1161, 995, 815, 695, 523, 440 cm^{-1}. HRMS (EI) Calcd for $C_{18}H_{12}F_2O_2$: $[M]^+$, 298.0805. Found: *m/z* 298.0805.

(1*E*,5*E*)-1,6-Di(furan-2-yl)hexa-1,5-diene-3,4-dione (2f): CAS RN [1190209-38-1].



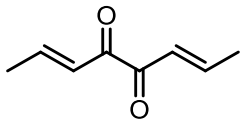
Brawn solid. ^{1}H NMR ($CDCl_3$) δ 7.61 (d, *J* = 15.5 Hz, 2H), 7.57 (ddd, *J* = 1.5, 0.5, 0.5 Hz, 2H), 7.31 (d, *J* = 15.5 Hz, 2H), 6.80 (ddd, *J* = 3.5, 0.5, 0.5 Hz, 2H), 6.53 (dd, *J* = 3.5, 1.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 188.6, 151.5, 146.0, 133.0, 117.6, 117.4, 113.0.

(1*E*,5*E*)-1,6-Di(naphthalen-1-yl)hexa-1,5-diene-3,4-dione (2g): CAS RN [1192343-59-1].



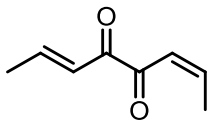
Orange solid. ^{1}H NMR ($CDCl_3$) δ 8.82 (d, *J* = 16.0 Hz, 2H), 8.29 (d, *J* = 8.5 Hz, 2H), 8.01 (d, *J* = 6.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.93–7.89 (m, 2H), 7.67 (d, *J* = 16.0 Hz, 2H), 7.65–7.61 (m, 2H), 7.59–7.53 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 188.8, 144.4, 133.8, 131.9, 131.8, 131.6, 128.9, 127.3, 126.4, 125.8, 125.5, 123.2, 121.9.

(2*E*,6*E*)-Octa-2,6-diene-4,5-dione (2h): CAS RN [55409-19-3].



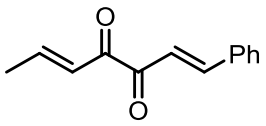
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.09 (dq, *J* = 7.0, 19.5 Hz, 2H), 6.61 (dq, *J* = 16.0, 1.5 Hz, 2H), 1.98 (dd, *J* = 7.0, 1.5 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 190.5, 149.5, 126.5, 19.0.

(2*Z*,6*E*)-Octa-2,6-diene-4,5-dione (2i).



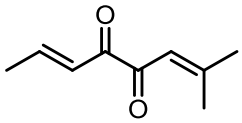
Orange liquid. ^{1}H NMR ($CDCl_3$) δ 7.15 (dq, *J* = 16.0, 7.0 Hz, 1H), 6.82 (dq, *J* = 11.5, 1.5 Hz, 1H), 6.77 (dq, *J* = 16.0, 2.0 Hz, 1H), 6.60 (dq, *J* = 15.5, 7.5 Hz, 1H), 2.21 (dd, *J* = 7.5, 1.5 Hz, 3H), 1.99 (dd, *J* = 7.0, 2.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 190.2, 188.9, 149.4, 149.0, 125.1, 122.0, 19.0, 16.6. IR (neat): 2983, 2941, 1717, 1447. 1377, 1260, 1046, 971 cm^{-1}. HRMS (EI) Calcd for $C_8H_{10}O_2$: $[M]^+$, 138.0681. Found: *m/z* 138.0681.

(1*E*,5*E*)-1-Phenylhepta-1,5-diene-3,4-dione (2j): CAS RN [55409-19-3].



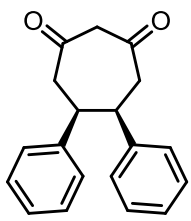
Orange solid. ^{1}H NMR ($CDCl_3$) δ 7.78 (d, *J* = 16.0 Hz, 1H), 7.64–7.61 (m, 2H), 7.46–7.39 (m, 3H), 7.33 (d, *J* = 16.0 Hz, 1H), 7.19 (dq, *J* = 15.5, 6.5 Hz, 1H), 6.77 (dq, *J* = 15.5, 1.5 Hz, 1H), 2.01 (dd, *J* = 6.5, 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 189.8, 189.6, 149.6, 147.7, 134.3, 131.3, 129.0, 128.9, 120.1, 19.1. Mp. 68.5–71.8 °C. IR (KBr): 2968, 2936, 1689, 1597, 1449, 1206, 974, 698 cm^{-1}. HRMS (EI) Calcd for $C_{13}H_{12}O_2$: $[M]^+$, 200.0837. Found: *m/z* 200.0842.

(*E*)-2-Methylocta-2,6-diene-4,5-dione (2k).



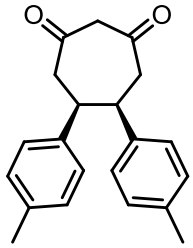
Orange liquid. ^{1}H NMR ($CDCl_3$) δ 7.13 (dq, *J* = 16.0, 7.0 Hz, 1H), 6.78 (dq, *J* = 16.0, 1.5 Hz, 1H), 6.72 (qq, *J* = 1.5, 1.0 Hz, 1H), 2.26 (d, *J* = 1.0 Hz, 3H), 2.01 (d, *J* = 1.5 Hz, 3H), 1.98 (dd, *J* = 7.0, 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 189.7, 189.2, 163.1, 148.6, 125.3, 118.1, 28.5, 21.6, 19.0. IR (neat): 2977, 2941, 2915, 1674, 1619, 1442, 1377, 1312, 1010, 972, 743 cm^{-1}. HRMS (EI) Calcd for $C_9H_{12}O_2$: $[M]^+$, 152.0837. Found: *m/z* 152.0836.

(5*R,6*S**)-5,6-Diphenylcycloheptane-1,3-dione (6a)**: CAS RN [222629-92-7].



White solid. ^{1}H NMR ($CDCl_3$) δ 7.18–7.10 (m, 6H), 6.74–6.69 (m, 4H), 3.95 (d, *J* = 17.5 Hz, 1H), 3.74–3.67 (m, 2H), 3.57 (d, *J* = 17.5 Hz, 1H), 3.22 (dd, *J* = 15.5, 11.0 Hz, 2H), 2.79 (dd, *J* = 15.5, 5.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 204.5, 139.3, 128.2, 128.1, 127.1, 58.2, 46.2, 45.8.

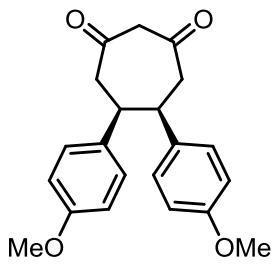
(5*R,6*S**)-5,6-Di-*p*-tolylcycloheptane-1,3-dione (6b).**



Yellow solid. ^{1}H NMR ($CDCl_3$) δ 6.45 (d, *J* = 8.0 Hz, 4H), 6.62 (d, *J* = 8.0 Hz, 4H), 3.95 (d, *J* = 17.0 Hz, 1H), 3.69－3.62 (m, 2H), 3.55 (d, *J* = 17.0 Hz, 1H), 3.17 (dd, *J* = 15.5, 11.0 Hz, 2H), 2.76 (dd, *J* = 15.0, 5.0 Hz, 2H), 2.27 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 204.7, 136.6, 136.3, 128.8, 58.3, 46.1, 45.8, 20.9. Mp.

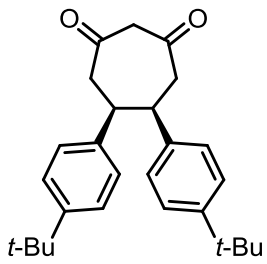
129.2–131.3 °C. IR (KBr): 3024, 2954, 1715, 1513, 1248, 1196, 1019, 806, 480 cm^{-1}. HRMS (EI) Calcd for $C_{21}H_{22}O_2$: $[M]^+$, 306.1620. Found: *m/z* 306.1625.

(5*R,6*S**)-5,6-Bis(4-methoxyphenyl)cycloheptane-1,3-dione (6c).**



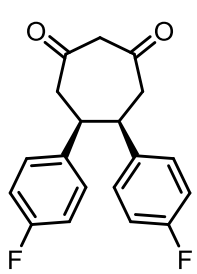
Yellow solid. ^1H NMR ($CDCl_3$) δ 6.71–6.67 (m, 4H), 6.66–6.62 (m, 4H), 3.93 (d, *J* = 17.0 Hz, 1H), 3.75 (s, 6H), 3.65–3.59 (m, 1H), 3.54 (d, *J* = 17.0 Hz, 1H), 3.14 (d, *J* = 15.0, 11.0 Hz, 2H), 2.75 (dd, *J* = 15.0, 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 204.7, 158.4, 131.4, 129.2, 113.4, 58.2, 55.1, 46.1, 45.5. Mp. 105.1–106.2 °C. IR (KBr): 2958, 1697, 1611, 1511, 1250, 1178, 1028, 839, 779, 541 cm^{-1}. HRMS (EI) Calcd for $C_{21}H_{22}O_4$: $[M]^+$, 338.1518. Found: *m/z* 338.1521.

(5*R,6*S**)-5,6-Bis(4-*tert*-butylphenyl)cycloheptane-1,3-dione (6d).**



White solid. ^1H NMR ($CDCl_3$) δ 7.13–7.09 (m, 4H), 6.64–6.60 (m, 4H), 3.95 (d, *J* = 17.0 Hz, 1H), 3.69–3.63 (m, 2H), 3.56 (d, *J* = 17.0 Hz, 1H), 3.19 (dd, *J* = 15.0, 11.0 Hz, 2H), 2.78 (dd, *J* = 15.0, 4.5 Hz, 2H), 1.25 (s, 18H). ^{13}C NMR ($CDCl_3$) δ 204.7, 150.0, 136.4, 127.8, 124.8, 58.4, 45.9, 45.7, 34.3, 31.3. Mp. 125.1–126.8 °C. IR (KBr): 2961, 2360, 1730, 1700, 1509, 853 cm^{-1}. HRMS (EI) Calcd for $C_{27}H_{34}O_2$: $[M]^+$, 390.2559. Found: *m/z* 390.2552.

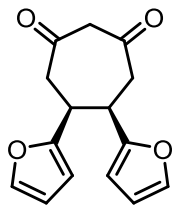
(5*R,6*S**)-5,6-Bis(4-fluorophenyl)cycloheptane-1,3-dione (6e).**



White solid. ^1H NMR ($CDCl_3$) δ 6.88–6.83 (m, 4H), 6.71–6.66 (m, 4H), 3.92 (d, *J* = 17.0 Hz, 1H), 3.70–3.63 (m, 2H), 3.57 (d, *J* = 17.0 Hz, 1H), 3.14 (dd, *J* = 15.0, 11.0 Hz, 2H), 2.77 (dd, *J* = 15.0, 5.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 204.0, 161.9 (d, *J* = 246.6 Hz), 134.8, 129.7 (d, *J* = 8.2 Hz), 115.4 (d, *J* = 21.1 Hz), 58.1, 45.8, 45.5. Mp. 165.7–169.8 °C. IR (KBr): 1722, 1696, 1603, 1511, 1224, 1159, 843, 812, 789, 514 cm^{-1}. HRMS (EI) Calcd for $C_{19}H_{16}F_2O_2$: $[M]^+$, 314.1118.

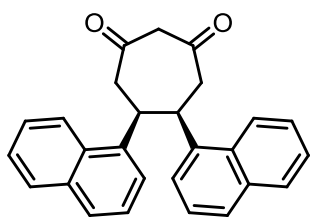
Found: *m/z* 314.1115.

(5*R,6*S**)-5,6-Di(furan-2-yl)cycloheptane-1,3-dione (6f).**



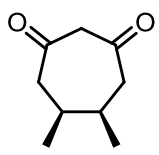
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.31 (dd, *J* = 2.0, 1.0 Hz, 2H), 6.23 (dd, *J* = 3.0, 2.0 Hz, 2H), 5.84 (ddd, *J* = 3.0, 1.0, 1.0 Hz, 2H), 3.93–3.88 (m, 2H), 3.89 (d, *J* = 15.0 Hz, 1H), 3.72 (d, *J* = 15.0 Hz, 1H), 3.05 (dd, *J* = 15.0, 9.5 Hz, 2H), 2.91 (dd, *J* = 15.0, 4.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 201.8, 153.4, 141.9, 110.2, 106.9, 59.9, 45.5, 38.9. Mp. 85.5–87.6 °C. IR (KBr): 3150, 3119, 1719, 1503, 1206, 1006, 942, 748 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{14}O_4$: $[M]^+$, 258.0892. Found: *m/z* 258.0891.

(5*R,6*S**)-5,6-Di(naphthalen-1-yl)cycloheptane-1,3-dione (6g).**



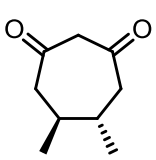
White solid. ^{1}H NMR ($CDCl_3$) δ 7.69–7.65 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.33–7.29 (m, 2H), 7.11–7.03 (m, 4H), 6.80–6.75 (m, 2H), 4.88–4.81 (m, 2H), 4.15 (d, *J* = 17.5 Hz, 1H), 3.73 (d, *J* = 17.5 Hz, 1H), 3.52 (dd, *J* = 15.5, 11.5 Hz, 2H), 2.89 (dd, *J* = 15.5, 5.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 205.0, 135.0, 133.5, 131.9, 128.7, 127.6, 125.9, 125.3, 124.5, 124.5, 121.9, 58.5, 46.3, 38.2. Mp. 67.5–69.8 °C. IR (KBr): 3050, 2926, 2364, 2343, 1696, 1598, 1507, 1396, 1259, 778 cm^{-1}. HRMS (EI) Calcd for $C_{27}H_{22}O_2$: $[M]^+$, 378.1620. Found: *m/z* 378.1621.

(5*R,6*S**)-5,6-Dimethylcycloheptane-1,3-dione (6h).**



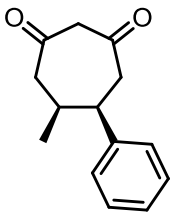
Colorless liquid. ^{1}H NMR ($CDCl_3$) δ 3.62 (d, *J* = 15.5 Hz, 1H), 3.35 (d, *J* = 15.5 Hz, 1H), 2.51 (dd, *J* = 14.0, 4.5 Hz, 2H), 2.47 (dd, *J* = 14.0, 8.5 Hz, 2H), 2.33–2.24 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 204.4, 59.7, 48.7, 34.9, 16.5. IR (neat): 2964, 2364, 1701, 1254, 1199, 1099 cm^{-1}. HRMS (EI) Calcd for $C_9H_{14}O_2$: $[M]^+$, 154.0994. Found: *m/z* 154.0998.

(5*S,6*S**)-5,6-Dimethylcycloheptane-1,3-dione (6i).**



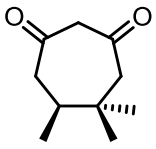
Colorless liquid. ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 2H), 2.59 (dd, *J* = 14.0, 3.0 Hz, 2H), 2.44 (dd, *J* = 14.0, 8.5 Hz, 2H), 1.87–1.77 (m, 2H), 1.09 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 205.4, 59.1, 50.0, 38.0, 20.7. IR (neat): 2963, 2360, 1698, 1611, 1459, 1388, 1252 cm^{-1}. HRMS (EI) Calcd for $C_9H_{14}O_2$: $[M]^+$, 154.0994. Found: *m/z* 154.0990.

(5*S,6*R**)-5-Methyl-6-phenylcycloheptane-1,3-dione (6j).**



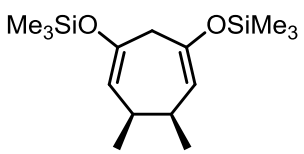
Colorless liquid. ^{1}H NMR ($CDCl_3$) δ 7.35–7.31 (m, 2H), 7.28–7.23 (m, 1H), 7.15–7.11 (m, 2H), 3.72 (d, *J* = 17.0 Hz, 1H), 3.51 (ddd, *J* = 12.5, 4.0, 4.0 Hz, 1H), 3.49 (d, *J* = 17.0 Hz, 1H), 3.17 (dd, *J* = 14.0, 12.5 Hz, 1H), 2.75 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.72 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.56 (dd, *J* = 13.5, 9.0 Hz, 1H), 2.52–2.44 (m, 1H), 0.81 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 204.9, 204.3, 141.6, 128.6, 127.6, 127.0, 59.0, 49.9, 45.9, 45.9, 44.3, 35.5. IR (neat): 2963, 2360, 1716, 1695, 1452, 1387, 1257, 1202, 1149, 744, 703 cm^{-1}. HRMS (EI) Calcd for $C_{14}H_{16}O_2$: $[M]^+$, 216.1150. Found: *m/z* 216.1145.

5,5,6-Trimethylcycloheptane-1,3-dione (6i).



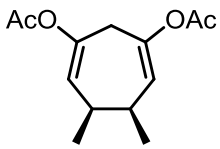
Colorless liquid. ^{1}H NMR ($CDCl_3$) δ 3.47 (d, *J* = 17.5 Hz, 1H), 3.33 (d, *J* = 17.5 Hz, 1H), 2.60 (dd, *J* = 16.0, 11.5 Hz, 1H), 2.51 (d, *J* = 12.0 Hz, 1H), 2.44 (dd, *J* = 16.0, 3.0 Hz, 1H), 2.32 (d, *J* = 12.0 Hz, 1H), 2.03 (ddq, *J* = 11.5, 7.0, 3.0 Hz, 1H), 1.09 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 206.3, 204.3, 58.5, 56.3, 47.7, 39.7, 37.3, 28.5, 22.3, 16.5. IR (neat): 2966, 2362, 1695, 1469, 1395, 1304, 1267, 1196, 1135 cm^{-1}. HRMS (EI) Calcd for $C_{10}H_{16}O_2$: $[M]^+$, 168.1150. Found: *m/z* 168.1147.

((5R*,6S*)-5,6-Dimethylcyclohepta-3,7-diene-1,3-diyl)bis(oxy)bis(trimethylsilane) (7).



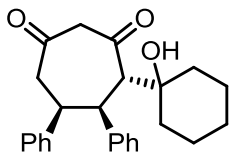
Colorless liquid. ^{1}H NMR ($CDCl_3$) δ 4.76 (dd, *J* = 6.0, 2.0 Hz, 2H), 3.28 (dtt, *J* = 19.5, 2.0, 2.0 Hz, 1H), 2.44 (d, *J* = 19.5 Hz, 1H), 2.42–2.35 (m, 2H), 0.95 (d, *J* = 7.0 Hz, 6H), 0.18 (s, 18H). ^{13}C NMR ($CDCl_3$) δ 146.8, 113.7, 40.6, 34.6, 17.5, 0.2. IR (neat): 2961, 2874, 1669, 1253, 1198, 1173, 1147, 962, 846, 752 cm^{-1}. HRMS (EI) Calcd for $C_{15}H_{30}O_2Si_2$: $[M]^+$, 298.1784. Found: *m/z* 298.1782.

(5R*,6S*)-5,6-Dimethylcyclohepta-3,7-diene-1,3-diyl diacetate (8).



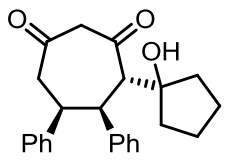
Colorless liquid. ^{1}H NMR ($CDCl_3$) δ 5.30 (dd, *J* = 6.5, 2.0 Hz, 2H), 3.74 (dtt, *J* = 19.5, 2.0, 2.0 Hz, 1H), 2.65–2.55 (m, 2H), 2.55 (d, *J* = 19.5 Hz, 1H), 2.01 (s, 6H), 1.04 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 169.5, 143.7, 123.0, 35.1, 34.2, 20.9, 16.7. IR (neat): 2967, 2876, 1755, 1693, 1370, 1225, 1134, 1092, 1061, 1020, 900 cm^{-1}. HRMS (EI) Calcd for $C_{13}H_{18}O_4$: $[M]^+$, 238.1205. Found: *m/z* 238.1215.

(4*S,5*S**,6*S**)-4-(1-Hydroxycyclohexyl)-5,6-diphenylcycloheptane-1,3-dione (10a).**



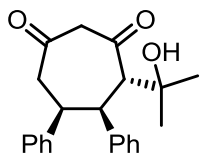
Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.11–7.19 (m, 6H), 6.70 (d, *J* = 6.5 Hz, 2H), 6.64–6.65 (m, 2H), 3.81 (m, 4H), 3.60 (d, *J* = 17.5 Hz, 1H), 3.37 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.11 (dd, *J* = 17.5, 15.0 Hz, 1H), 2.61 (dd, *J* = 17.5, 4.0 Hz 1H), 1.63–1.72 (m, 2H), 1.24–1.46 (m, 4H), 1.15 (d, *J* = 16.0 Hz, 1H), 0.98–1.07 (m, 2H), 0.47 (t, *J* = 11.5 Hz 1H). ^{13}C NMR ($CDCl_3$) δ 211.3, 205.3, 140.6, 137.7, 129.5, 128.0, 127.9, 127.8, 127.0, 126.8, 77.2, 73.8, 60.9, 49.3, 43.8, 43.8, 37.5, 35.9, 25.4, 21.8, 21.1. Mp. 175.2–175.8 °C. IR (KBr): 3510.6, 2960.9, 2938.7, 2852.8, 1692.6, 1495.9, 1457.3, 1398.5, 1380.1, 1359.9, 1282.7, 1175.7, 1156.4, 1139.0, 1076.3, 982.8, 845.8, 765.8, 708.9 cm^{-1}. HRMS (ESI) Calcd for $C_{25}H_{28}O_3Cl$: $[M+Cl]^-$, 411.1721. Found: *m/z* 411.1736.

(4*S,5*S**,6*S**)-4-(1-Hydroxycyclopentyl)-5,6-diphenylcycloheptane-1,3-dione (10b).**



Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.16–7.10 (m, 6H), 6.73 (d, *J* = 6.5 Hz, 2H), 6.66–6.64 (m, 2H), 3.89 (dd, *J* = 9.5, 4.0 Hz, 1H), 3.84–3.77 (m, 1H), 3.81 (d, *J* = 2.0 Hz, 1H), 3.59 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.46 (d, *J* = 2.5 Hz, 1H), 3.28 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.21 (ddd, *J* = 17.5, 15.5, 1.0 Hz, 1H), 2.64 (ddd, *J* = 17.5, 4.0, 1.0 Hz, 1H), 1.89–1.84 (m, 1H), 1.78–1.71 (m, 1H), 1.59–1.24 (m, 4H), 0.97–0.93 (m, 1H), 0.47–0.41 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 210.5, 205.6, 140.6, 137.6, 129.6, 128.0, 127.9, 127.8, 127.0, 127.0, 82.7, 77.2, 61.7, 59.5, 50.4, 43.9, 41.0, 38.3, 23.4, 22.3. Mp. 185.0–185.5 °C. IR (KBr): 3525.1, 2974.4, 2924.2, 2869.2, 1714.8, 1693.6, 1493.9, 1456.3, 1382.1, 1266.3, 1456.3, 1382.1, 1266.3, 1232.6, 1139.0, 1096.6, 1003.0, 767.7, 708.9 cm^{-1}. HRMS (ESI) Calcd for $C_{24}H_{26}O_3Cl$: $[M+Cl]^-$, 397.1565. Found: *m/z* 397.1579.

(4*S,5*S**,6*S**)-4-(2-Hydroxypropan-2-yl)-5,6-diphenylcycloheptane-1,3-dione (10c).**



Yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.18–7.11 (m, 6H), 6.67 (d, *J* = 7.0 Hz, 2H), 6.65–6.63 (m, 2H), 3.86–3.80 (m, 3H), 3.75 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.61 (dd, *J* = 18.0, 1.0 Hz, 1H), 3.35 (dd, *J* =9.0, 2.0 Hz, 1H), 3.14 (ddd, *J* =18.0, 14.0, 1.0 Hz, 1H), 2.62 (dd, *J* = 18.0, 3.5 Hz, 1H), 1.20 (s, 3H), 0.64 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 210.9, 205.3, 140.5, 137.7, 129.4, 128.0, 128.0, 127.9, 127.1, 126.9, 72.4, 61.2, 60.4, 50.2, 43.9, 43.8, 30.2, 28.5. Mp. 111.2–112.0 °C. IR (KBr): 3500.6, 2974.4, 1721.5, 1689.7, 1495.9, 1455.4, 1392.7, 1380.1, 1362.8, 1235.5, 1197.9, 1158.3, 1136.1, 1095.6, 1078.3, 958.7, 767.7, 704.1 cm^{-1}. HRMS (ESI) Calcd for $C_{22}H_{24}O_3Cl$: $[M+Cl]^-$, 371.1408. Found: *m/z* 371.1422.

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Publication List

All of present thesis have been or are to be published in the following journals.

Chapter 1 Preparation of an Arenylmethylzinc Reagent with Functional Groups by Chemoselective Cross-Coupling Reaction of Bis(iodozincio)methane with Iodoarenes

Yukako Shimada, Ryosuke Haraguchi, and Seijiro Matsubara

Synlett **2015**, *26*, 2395–2398.

Chapter 2 Chemo- and Regioselective Preparation of Zinc Enolate from Thiol Esters by Palladium Catalyzed Cross-Coupling Reaction

Ryosuke Haraguchi, Zenichi Ikeda, Akihiro Ooguri, and Seijiro Matsubara

Tetrahedron **2015**, *71*, 8830–8837.

Chapter 3 Catalytic Asymmetric Aldol-Type Reaction of Zinc Enolate Equivalent of Amides

Ryosuke Haraguchi and Seijiro Matsubara

Org. Lett. **2013**, *15*, 3378–3380.

Preparation of the Zinc Enolate Equivalent of Amides by Zinciomethylation of Isocyanates: Catalytic Asymmetric Reformatsky-Type Reaction

Ryosuke Haraguchi and Seijiro Matsubara

Synthesis **2014**, *46*, 2272–2282.

Chapter 4 Functionalized Cyclopentane Synthesis by Tandem Reaction of Allenones Diketones, and Bis(iodozincio)methane

Ryosuke Haraguchi and Seijiro Matsubara

Submitted for publication.

Chapter 5 Rapid Preparation of Cycloheptane Ring from 1,2-Diketone and Bis(iodozincio)methane via Oxy-Cope Rearrangement Using Microflow System

Ryosuke Haraguchi, Yoshiaki Takada, and Seijiro Matsubara

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Preparation of Cycloheptane Ring by Nucleophilic Cyclopropanation of 1,2-Diketones with Bis(iodozincio)methane

Ryosuke Haraguchi, Yoshiaki Takada, and Seijiro Matsubara

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