Studies on Carbometalation of Alkynes and Nucleophilic Substitution of Chlorosilanes with Organomagnesium and Organozinc Reagents

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2012

Contents

Abbreviations

Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aryl
Boc	tertiary-butoxycarbonyl
bp	boiling point
bs	broad singlet (spectral)
Bu	butyl
Bn	benzyl
c	cyclo
˚C	degrees Celsius
calcd	calculated
cat.	catalytic
cm	centimeter(s)
Co.	company
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
dba	dibenzylideneacetone
DME	dimethoxyethane
DPPE (dppe)	1,2-bis(diphenylphosphino)ethane
DPPM (dppm)	bis(diphenylphosphino)methane
DPPP (dppp)	1,3-bis(diphenylphosphino)propane
dr	diasteromeric ratio
E	*entgegen* (means “opposite”)
Ed(s).	editor(s)
ee	enantiomeric excess
EI	electron impact
eq(s)	equation(s)
equiv	equivalent(s)
Et	ethyl
g	gram(s)
GC	gas chromatography
gem	geminal
GPC	gel permeation chromatography
h	hour(s)
Hz	hertz (s^{-1})
HRMS	high-resolution mass spectrum
i	iso
i.e.	that is
IR	infrared (spectrum)
J	coupling constant (in NMR)
Ltd.	limited
m	multiplet (spectral), meter(s), milli
m	meta
M	molar (1 M = 1 mol dm^{-3})
Me	methyl
μL	microliter(s)
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mmHg	millimeter of mercury
mmol	millimole
mp	melting point
MPa	megapascal
n	normal
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
o	ortho
p	para
Ph	phenyl
pp.	page(s)
ppm	parts per million (in NMR)
Ph	phenyl
Pr	propyl
q	quartet (spectral)
quant.	quantitative
quint	quintet
ref(s)	reference(s)
r.r.	regioisomeric ratio
r.t.	room temperature (25 ± 3 ˚C)
s (*sec*)	secondary
s	singlet (spectral)
sept	septet (spectral)
t	triplet (spectral)
t (*tert*)	tertiary
TBDMS	tertiary-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran

Abbreviations

TLC	thin-layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Tol(tolyl)	methylphenyl
Ts	*p*-toluenesulfonyl
UV	ultraviolet
Vol.	volume
Z	*zusammen* (means “together”)

General Introduction

1. Introduction

Whereas transition metal-catalyzed synthetic reactions utilizing non-organometallic reagents have attracted siginificant attentions from organic chemists, classical organometallic reagents still play invaluable roles in modern organic chemistry. Among the organometallic reagents, organomagnesium and organozinc reagents have been widely employed for organic synthesis due to their versatile reactivity and availability. The author is interested in the chemistry of organomagnesium and organozinc reagents and has focused on reactions with these reagents to expand its potential in organic synthesis. The studies of the thesis were divided into two sections: 1) transition metal-catalyzed carbometalation of alkynes with organomagnesium and organozinc reagents, 2) metal-catalyzed nucleophilic substitution of chlorosilanes with organomagnesium reagents.

2. Transition Metal-Catalyzed Carbometalation of Alkynes (Chapters 1–4)

The regio- and stereoselective synthesis of multisubstituted alkenes is one of the major challenges in organic synthesis. The importance of multisubstituted alkenes is verified by the occurrence of the structures in natural products, materials, and drugs. Classical reactions such as Wittig, Horner–Wadsworth–Emmons, and McMurry reactions are widely applied to the synthesis of multisubstituted alkenes. However, controlling stereochemistry is not trivial, especially for the synthesis of tetrasubstituted alkene.

In contrast, carbometalation reaction of alkynes usually proceeds in a stereoselective fashion to provide multisubstituted alkenyl metals. The resulting alkenyl metals can be easily converted to a wide variety of multisubstituted alkenes. Additionally, regioselectivity is controllable by the tuning of sterics and electronics of the substrates. However, the scope of substrates and reagents is usually not wide. For example, carbometalation of simple aliphatic acetylene is relatively difficult and only few reports were published including

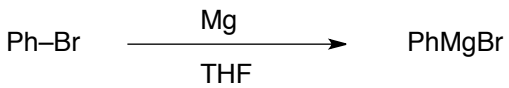
methylalumination,[1] carbostannylation,[2] carboboration,[3] and carbomagnesiation.[4] The fact drove the author to develop a more general carbometalation reaction of alkynes with organomagnesium and organozinc reagents.

In this section, the author wishes to start with presenting background of preparative methods of organomagnesium and organozinc reagents. Although there are vast amounts of the preparative methods, synthesis of stereodefined multisubstituted alkenyl metals is still difficult. Thus, the author then describes previous studies of carbomagnesiation and carbozincation reactions, which provided a direct route to stereodefined organomagnesium and organozinc reagents. Finally, he describes his works on carbomagnesiation and carbozincation of alkynes.

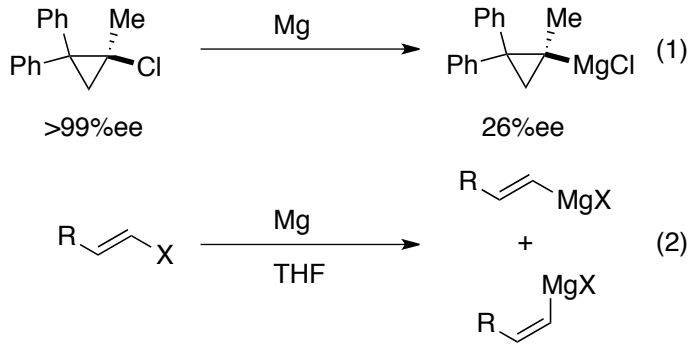
2-1. Preparations of Organomagnesium and Organozinc Reagents

The most popular method for preparing organomagnesium reagents still remains the classical Grignard method, starting from magnesium metal and organic halides (Scheme 1). Although the direct insertion method is versatile and efficient, there are two major drawbacks. One is functional group compatibility and the other is controlling the stereochemistry. Usually, Grignard's direct insertion of magnesium metal into carbon-halogen bonds is not applicable to the synthesis of functionalized organomagnesium reagents because the insertion does not take place at so low temperatures that functional groups are compatible with the resulting organomagnesium reagent. Additionally, isomerization may happen during the formation of organomagnesium reagents (Scheme 2).

Scheme 1. Organomagnesium Reagents from Magnesium Metal and Organic Halides

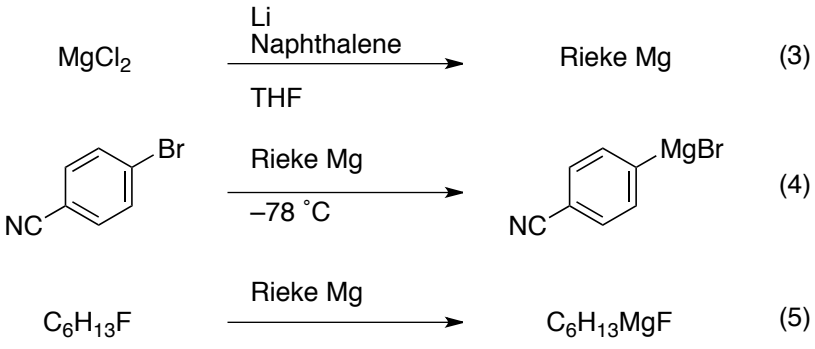


Scheme 2. Isomerization During the Formation of Organomagnesium Reagents



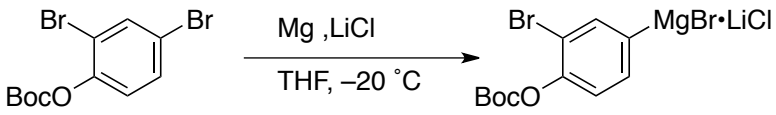
As a pioneering work for the synthesis of functionalized organomagnesium reagents, Rieke synthesized highly active magnesium metal by reducing magnesium chloride with lithium in the presence of naphthalene (Scheme 3, eq. 3). This activated magnesium powder (Rieke magnesium) is applicable to the preparation of functionalized organomagnesium reagents by the metal insertion reaction at –78 ˚C (Scheme 3, eq. 4).[5] It is noteworthy that the Rieke magnesium can insert to a commonly unreactive carbon–fluorine bond to generate alkylmagnesium fluoride (Scheme 3, eq. 5).[6]

Scheme 3. Highly Reactive Rieke Magnesium for the Preparation of Organomagnesium Reagents



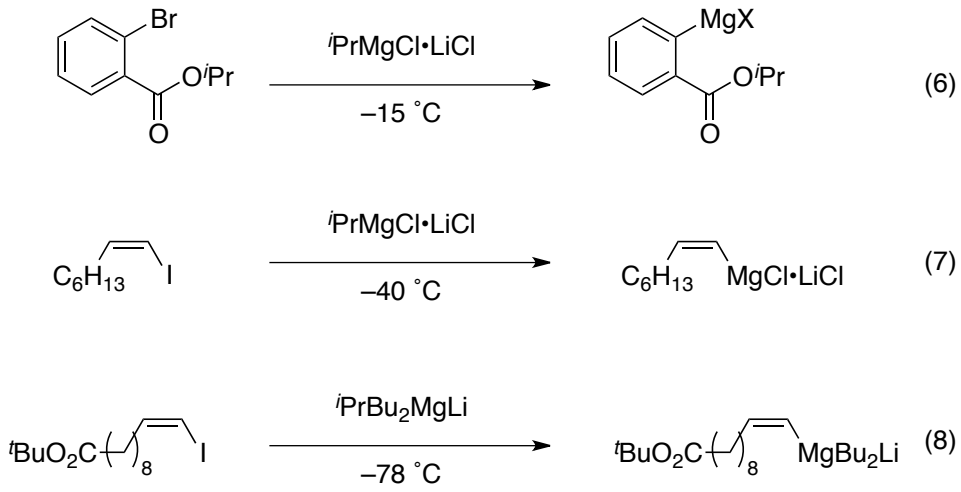
Recently, Knochel reported a direct magnesium insertion into aryl halides in the presence of lithium chloride.[7] The arylmagnesium reagents, which possessed a wide variety of functional groups such as nitrile, ester, and tosylate, were obtained under mild reaction conditions (Scheme 4).

Scheme 4. Synthesizing Functionalized Arylmagnesium Reagents in the Presence of LiCl



To overcome the problem on isomerization, halogen–metal exchange is employed as an efficient route to stereodefined organomagnesium reagents. Moreover, halogen-magnesium exchange methods can solve the problems on functional group compatibility. Knochel reported that functionalized aryl- or alkenylmagnesium reagents could be prepared from the corresponging aryl- or alkenyl halides by the halogen–metal exchange reaction with ^{i}PrMgCl•LiCl (Scheme 5, eq. 6).[8a] *E*/*Z* isomerization was rarely observed during the exchange (Scheme 5, eq. 7).[8b] Shinokubo and Oshima reported the halogen–magnesium exchange proceeded smoothly with wide substrate scope by employing lithium triorganomagnesate without loss of stereochemistry (Scheme 5, eq. 8).[9] Reactive functional groups such as ester, amide, and nitrile were also compatible with the exchange reaction.

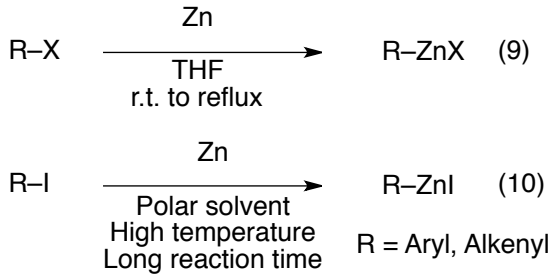
Scheme 5. Preparation by Halogen–Metal Exchange



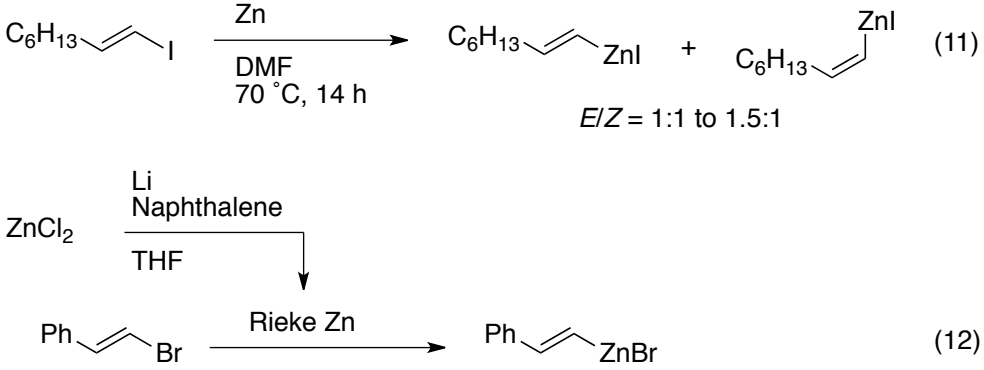
Preparation of organozinc reagents is similar to that of organomagnesium reagents. Mainly, organozinc halides are prepared by the direct insertion of zinc metal into organic halides (Scheme 6).[10] With alkyl halides (Br or I), the insertion reaction proceeds in THF at ambient to

elevated temperature (Scheme 6, eq. 9). In contrast to the reaction of alkyl iodides, the insertion of zinc metal is not trivial for sp^2 carbon–iodide bonds. The insertion reaction of alkenyl and aryl iodides may require higher temperature, longer reaction time, and/or employing a polar solvent (Scheme 6, eq. 10). The reaction of pure (*E*)-1-iodo-1-octene with zinc dust in DMF at 70 ˚C for 14 h provided a mixture of stereoisomers of octenylzinc iodides (Scheme 7, eq. 11).[11] Although Rieke reported the reaction of (*E*)-styryl bromide with Rieke zinc to provide (*E*)-styrylzinc bromide with retention of stereochemistry, there were no examples of the reaction of alkyl-substituted alkenyl halides (Scheme 7, eq. 12).[12]

Scheme 6. Organozinc Reagents from Zinc Metal

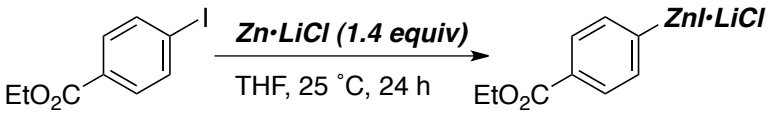


Scheme 7. Alkenylzinc Reagents from Zinc Metal

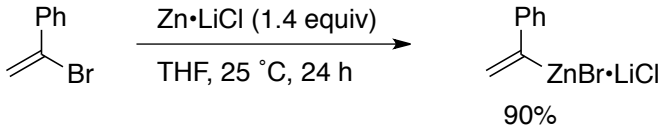


In 2006, Knochel reported the addition of lithium chloride accelerated the zinc insertion to organic halides (Scheme 8, eq. 13).[13] Importantly, commercially available zinc dust could be used for the reaction. However, the reaction of α-bromostyrene with zinc metal was the only example of the preparation of alkenylzinc reagent in the paper (Scheme 8, eq. 14).

Scheme 8. Knochel's Method for Synthesizing Organozinc Reagent in the Presence of LiCl



(13)

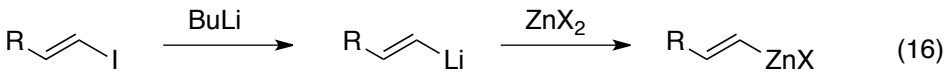


(14)

Usually, stereodefined alkenyllithium or magnesium can be prepared by halogen-metal exchange. Thus, alkenylzinc reagents are easily prepared from the corresponding organolithium and organomagnesium reagents by transmetalation (Scheme 9, eq. 15). However, due to the high reactivity of organolithium and organomagnesium reagents, functionalized organozinc reagents have been difficult to synthesize.[14]

Scheme 9. Transmetalation from Organolithium and Organomagnesium Reagents

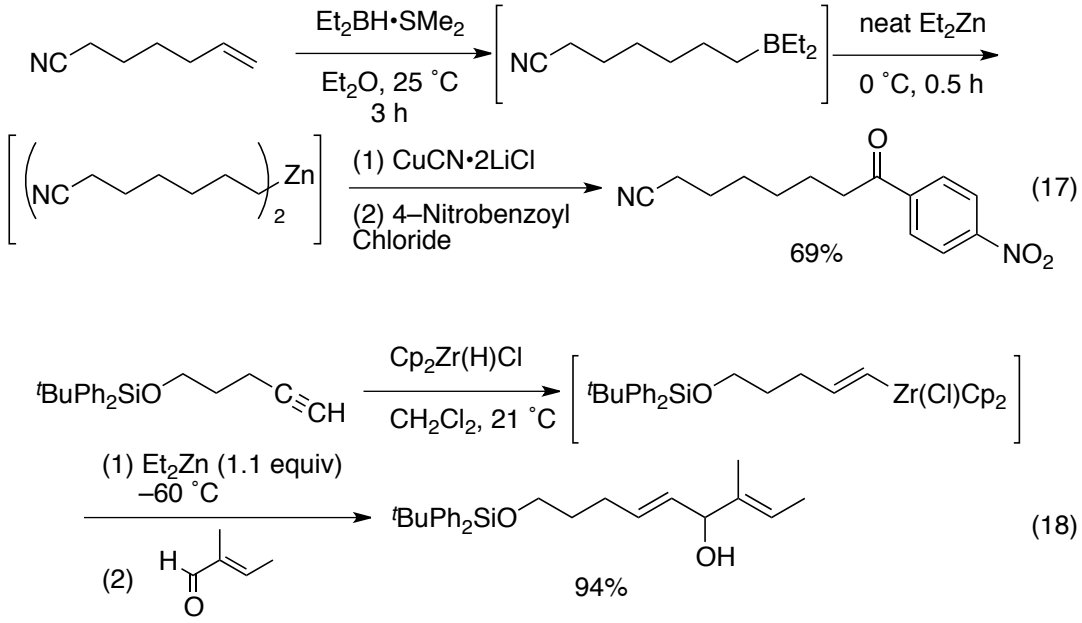
(15)



(16)

Preparation of organozinc reagents can be accomplished by transmetalation from boron and zirconium. Organoboron compounds are good precursors of primary organozinc reagent by boron–zinc exchange (Scheme 10, eq. 17).[15] Similarly, alkenylzirconium compounds, which prepared by hydrozirconiation of alkyne, can be converted to organozinc reagents by transmetalation (Scheme 10, eq. 18).[16]

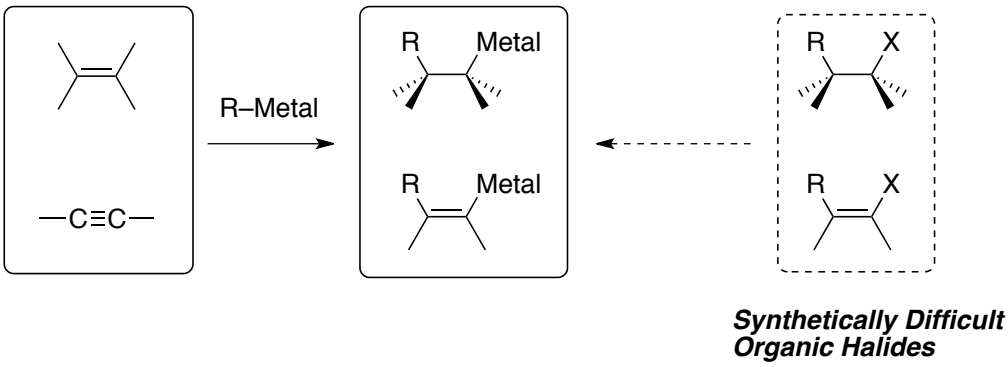
Scheme 10. Transmetalation from Organoboron and Organozirconium Compounds



2-2. Carbometalation Reactions with Organomagnesium and Organozinc Reagents

As the author mentioned above, preparation of stereodefined alkenylmetal is still difficult to achieve, especially for multisubstituted ones. Thus, he focused on carbometalation, the addition reaction of the C–Metal bond of organometallic reagents to carbon–carbon multiple bonds (Scheme 11). The reaction provides a direct route to complex organometallic compounds without a troublesome multistep synthesis of the corresponding organic halides as a precursor.

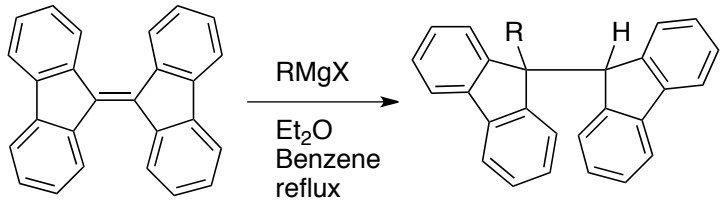
Scheme 11. Carbometalation of C–C Multiple Bonds



In general, carbon–carbon multiple bonds are unreactive with organomagnesium and

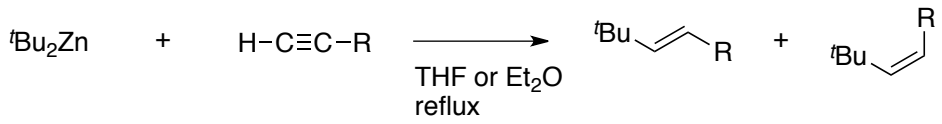
organozinc reagents, thus limited substrates and reagents could be employed for the uncatalyzed intermolecular carbometalation. Fuson and Porter reported carbomagnesiation of fulvalene derivatives with ^{t}BuMgCl and $PhCH_2MgCl$.[17] However, the reaction with other reagents such as MeMgI or PhMgBr failed (Scheme 12). Similarly, uncatalyzed intermolecular carbozincation reactions were reported but the reagents were restricted to $^t Bu_2Zn$ (Scheme 13).[18]

Scheme 12. Carbomagnesiation of Fulvalene Derivative



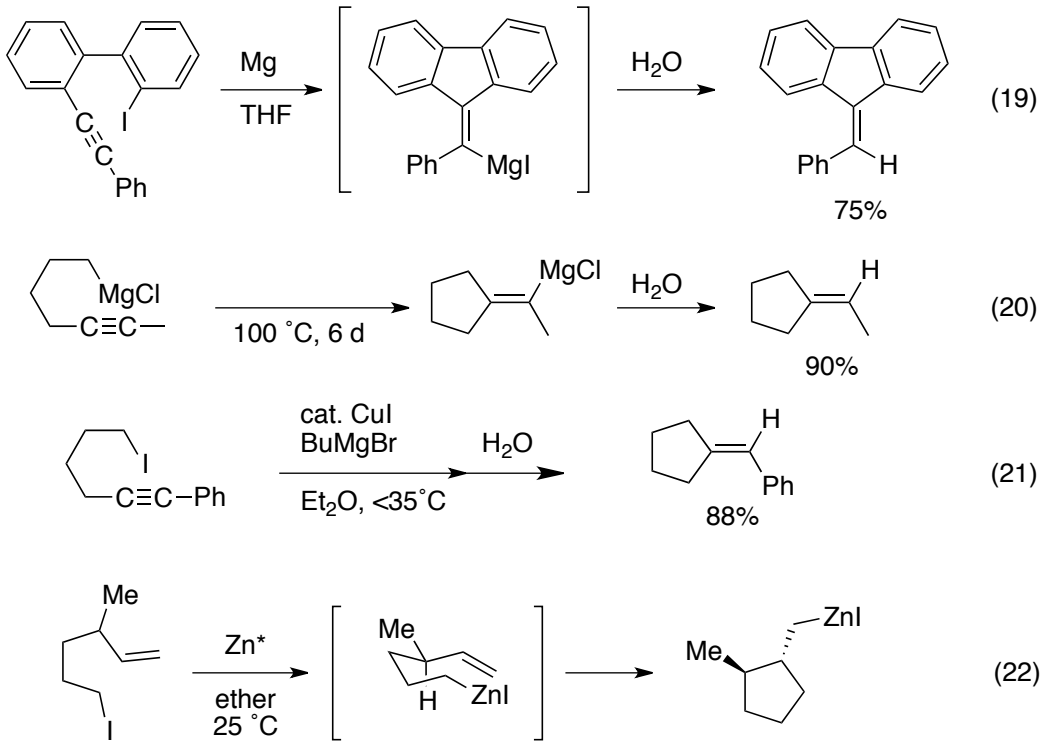
RMgX	Yield (%)
^{t}BuMgCl	68
$PhCH_2MgCl$	58
MeMgI	0
PhMgBr	0

Scheme 13. Carbozincation of Terminal Alkynes with $^t Bu_2Zn$



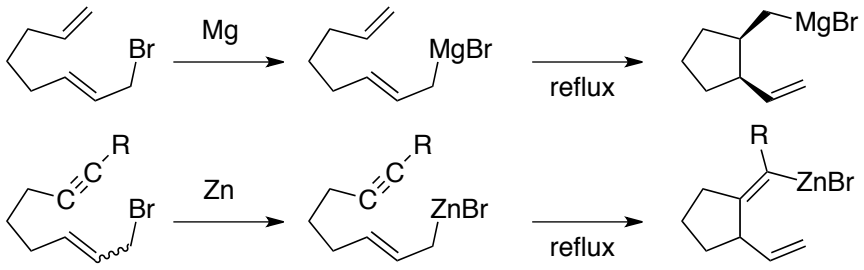
Although intermolecular carbometalations are difficult, intramolecular reactions proceed easier. The reaction of aryl iodide which possesses an alkyne moiety at the suitable position gave the ring-closed product efficiently (Scheme 14, eq. 19).[19] The intramolecular reactions of aliphatic alkynes were considerably slow and required high temperature, although they provided the products in high yields (Scheme 14, eq. 20).[20] Importantly, the addition of copper salts accelerated the intramolecular reaction (Scheme 14, eq. 21).[21] Compared to organomagnesium reagents, preparation of organozinc reagents is relatively difficult and therefore highly coordinating solvents are required for the preparation. Unfortunately, such solvents retard the intramolecular carbozincation reaction. This problem was solved by highly active Rieke zinc, which allowed the preparation of some organozinc reagents in ether. Therefore, treatment of alkyl iodide with Rieke zinc readily formed the corresponding cyclized product (Scheme 14, eq. 22).[22]

Scheme 14. Intramolecular Carbometalation

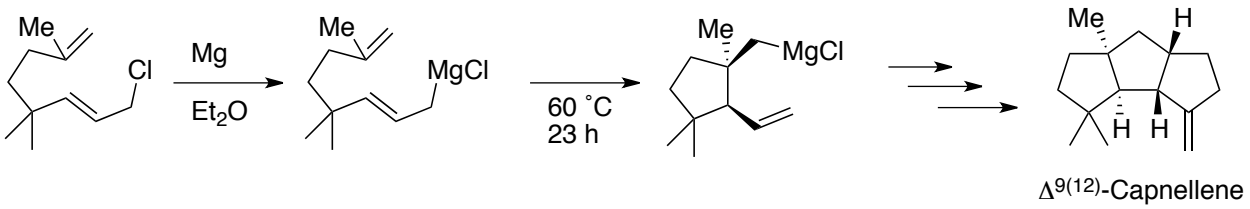


Additionally, intramolecular magnesium-ene[23a,b] and zinc-ene[23c] reactions were reported. These reactions were entropically favored and therefore the reaction proceeds with high efficiency and selectivity (Scheme 15). Oppolzer applied intramolecular magnesium-ene reaction to the synthesis of natural products (Scheme 16).[24]

Scheme 15. Magnesium- and Zinc-ene Reactions



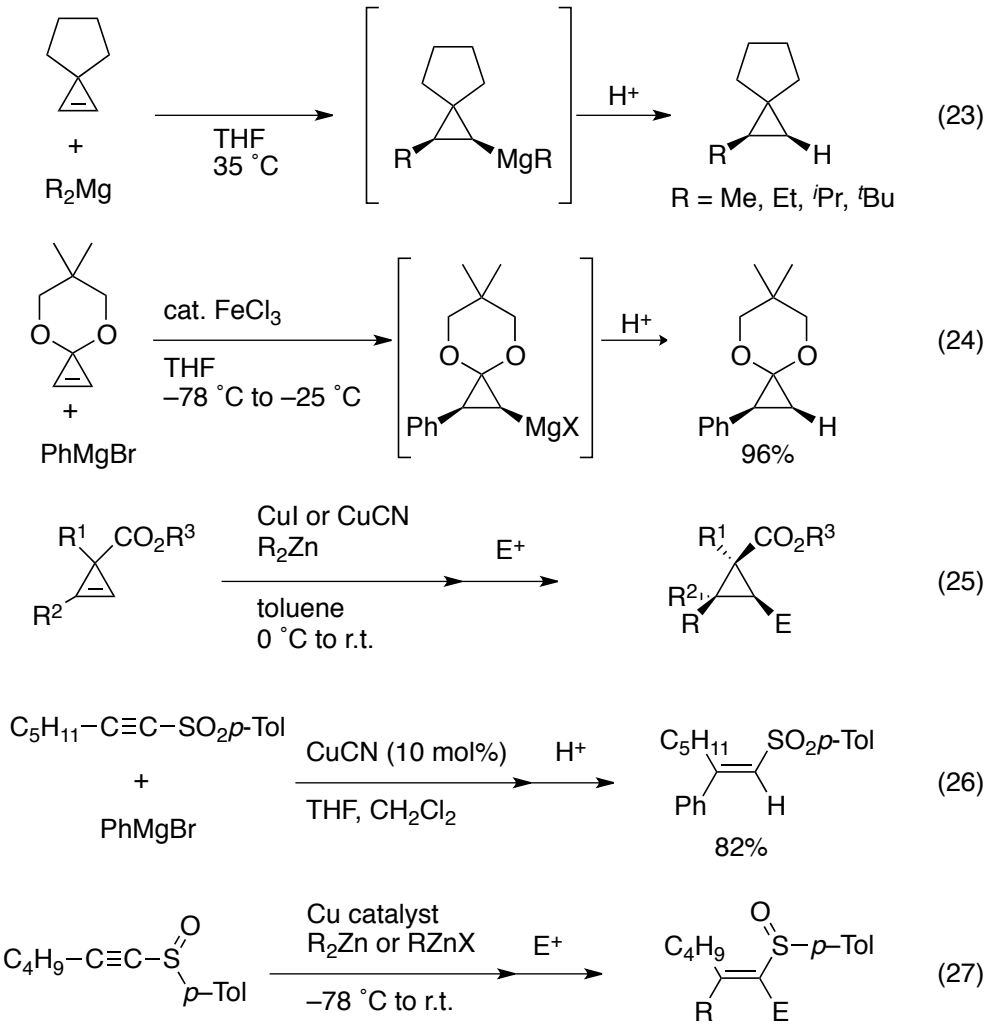
Scheme 16. Synthesis of $\Delta^{9(12)}$-Capnellene



$\Delta^{9(12)}$-Capnellene

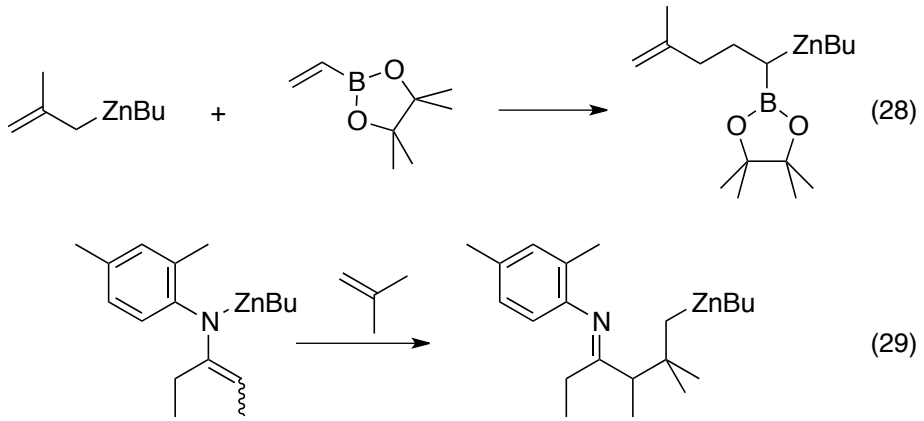
Increasing the reactivity of alkynes and alkenes is another strategy to achieve intermolecular carbometalation reactions. For example, strained alkenes are highly reactive toward carbometalation. The reactions of cyclopropenes took place without the aid of metal catalyst (Scheme 17, eq. 23).[25] Nakamura and coworker discovered that an addition of iron salt enhanced the carbometalation of cyclopropenone acetal (Scheme 17, eq. 24) and they applied the reaction to the enantioselective carbometalation reaction.[26] It is noteworthy that the reaction did not proceed at low temperature and gave a complex mixture at higher temperature (up to 65 ˚C) in the absence of the iron catalyst. Cyclopropenes bearing an ester group is a good substrate for the copper-catalyzed carbozincation reaction and provided the corresponding organozinc intermediates diastereoselectively (Scheme 17, eq. 25).[27] Not only strained alkenes but also electron-deficient alkynes are reactive. The reaction of alkynyl sulfones proceeded smoothly in the presence of a copper catalyst (Scheme 17, eq. 26).[28] The copper-catalyzed reaction of 1-alkynyl sulfoxides with organozinc reagents afforded vinylic sulfoxides with high stereoselectivity (Scheme 17, eq. 27).[29]

Scheme 17. Carbomagnesiation and Carbozincation of Activated Alkynes and Alkenes



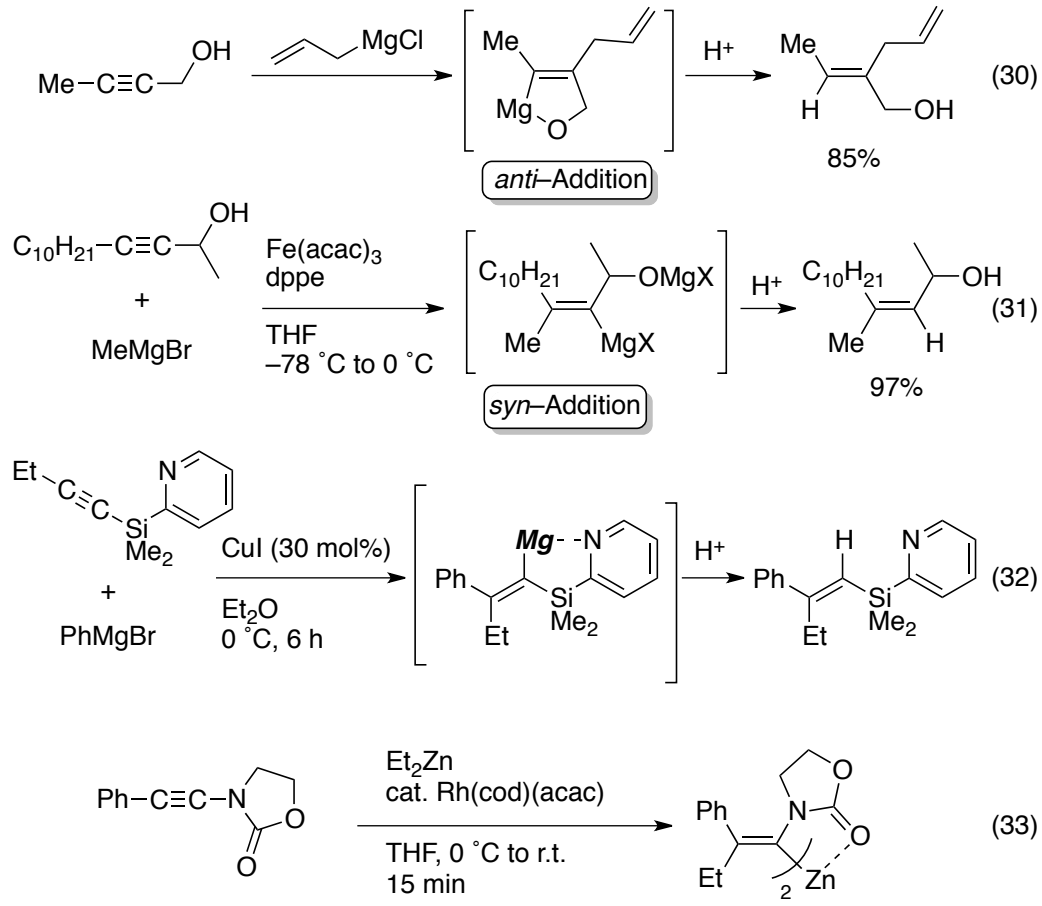
Allylic zinc reagents are generally reactive to weakly activated alkenes without the addtion of catalysts. Treatment of vinylboronate with methallylzinc reagent afforded the corresponding zinc intermediate (Scheme 18, eq. 28).[30] Zinc enamide, isoelectronic with an allylzinc reagent, reacted with unactivated carbon-carbon double bond (Scheme 18, eq. 29).[31]

Scheme 18. Organozinc Reagents by Carbozincation of Alkynes and Alkenes



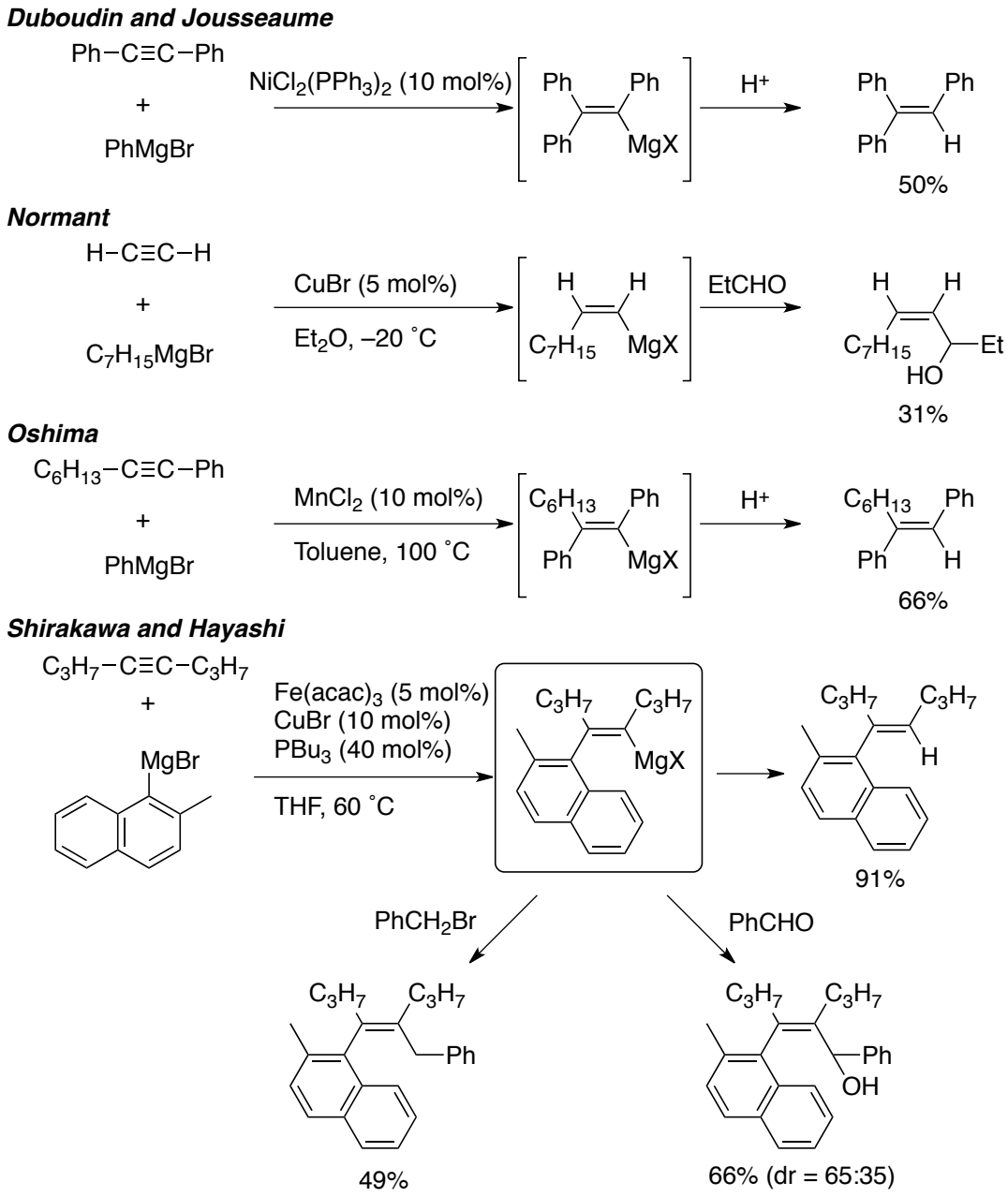
Introducing a directing group to substrates is also effective for the carbomagnesiation reaction. Treatment of propargyl alcohols with an allylic magnesium reagent provided the allylated product by *anti* addition (Scheme 19, eq. 30).[32] Interestingly, the *anti* stereoselectivity is opposite to the typically *syn*-selective carbomagnesiation. It is noteworthy that *syn*-carbometalation of propargyl alcohols was accomplished when iron was employed as a catalyst (Scheme 19, eq. 31).[33] Recently, Itami and Yoshida reported copper-catalyzed carbomagnesiation of alkynylsilanes bearing a metal-coordinating 2-pyridyl group on the silicon (Scheme 19, eq. 32).[34] In 2009, rhodium-catalyzed carbozincation of ynamides was reported by Lam, furnishing multisubstituted enamides (Scheme 19, eq. 33).[35]

Scheme 19. Carbomagnesiation of Alkynes Bearing a Directing Group



As mentioned above, the reaction of simple unactivated alkynes having no directing group is usually difficult. Several selected successful reactions under transition metal catalysis are shown in Scheme 20. In 1972, nickel-catalyzed carbomagnesiation of alkynes were reported.[36] Normant demonstrated that copper-catalyzed carbomagnesiation of acetylene.[37] In 1998, Oshima reported manganese-catalyzed arylmagnesiation reaction of alkynes.[38] The reaction proceeded smoothly with arylacetylenes, whereas the reaction of simple aliphatic alkyne failed. The first report on transition metal-catalyzed carbomagnesiation of dialkylacetylenes was disclosed by Shirakawa and Hayashi using an iron/copper cocatalyst system.[4] The carbomagnesiated intermediates were utilized for the synthesis of tetrasubstituted alkenes.

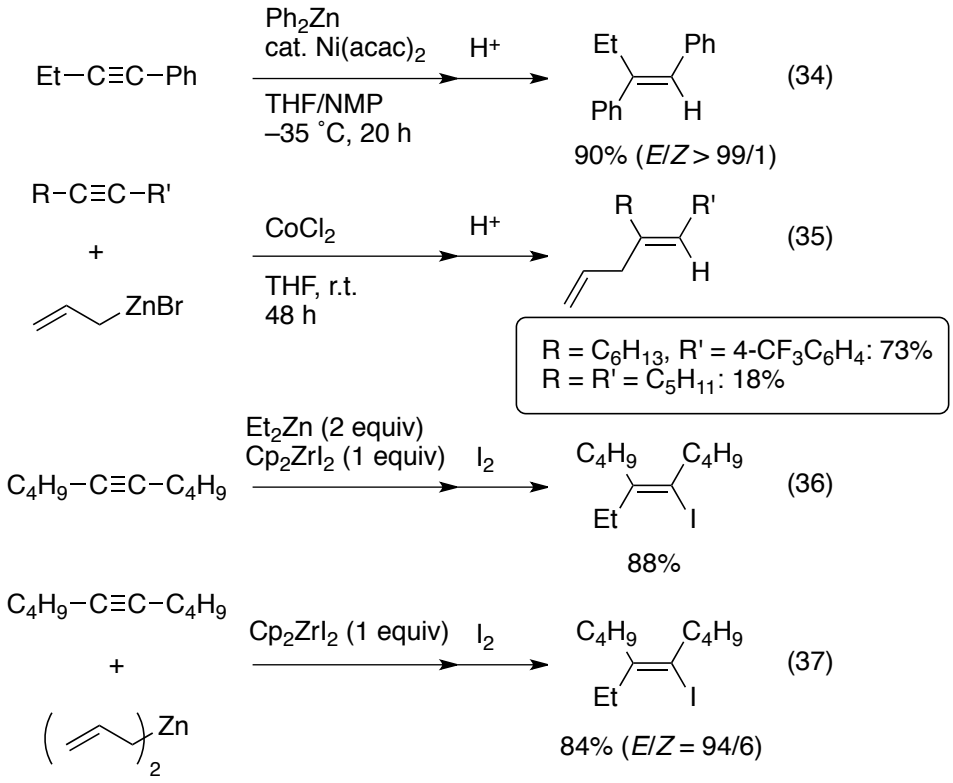
Scheme 20. Carbomagnesiation of Simple Alkynes



Knochel reported efficient carbozincation of simple arylacetylene with diorganozinc (Scheme 21, eq. 34).[39] However, reagents were limited to neat dialkylzinc or an ethereal solution of sublimed diarylzinc. Attempts to use Ph_2Zn prepared *in situ* from PhLi or PhMgBr and $ZnCl_2$ gave unsatisfactory results. Additionally, the reaction of simple dialkylacetylenes had not been reported in the paper. Yorimitsu and Oshima reported cobalt could catalyze

allylzincation of arylacetylenes.[40] Although the reaction with arylacetylenes proceeded smoothly, the reaction of simple aliphatic acetylene such as 6-dodecyne resulted in low yield (Scheme 21, eq. 35). Efficient ethyl-[41a] and allylzincation[41b] of unreactive dialkylacetylene were reported but 1 equiv of Zr was required (Scheme 21, eqs. 36 and 37).

Scheme 21. Carbozincation of Simple Alkynes

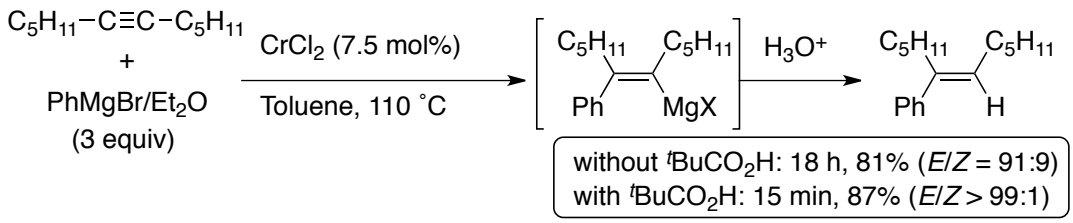


2-3. The Author's Works on Carbometalation of Alkynes

Chromium-Catalyzed Arylmagnesiation of Alkynes (Chapter 1)

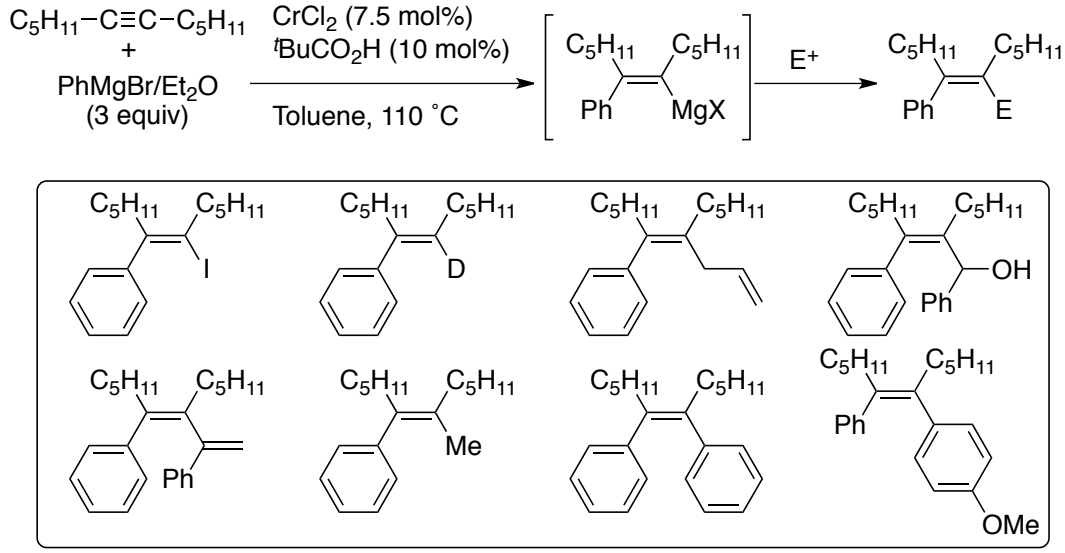
As described above, carbomagnesiation of simple alkynes is difficult to achieve. In Chapter 1, the author describes that chromium salts catalyzed arylmagnesiation reaction to afford alkenylmagnesium compounds regio- and stereoselectively. Treatment of 6-dodecyne with phenylmagnesium reagent in the presence of $CrCl_2$ in toluene at 110 °C for 18 h provided the arylated product in high yield (Scheme 22). Interestingly, the addition of pivalic acid accelerates the reaction, which completed within 15 min.

Scheme 22. Chromium-Catalyzed Phenylmagnesiation of 6-Hexyne



The resulting alkenylmagnesium reagents could react with various electrophiles to provide tetrasubstituted alkenes efficiently (Scheme 23).

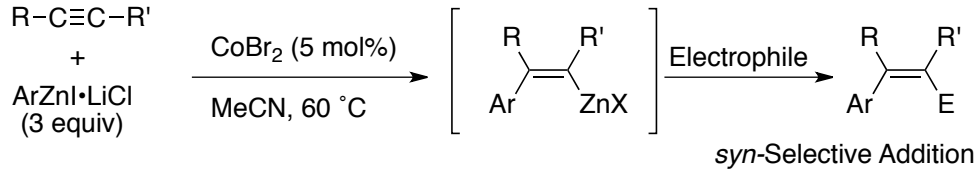
Scheme 23. Tetrasubstituted Alkenes by Trapping Various Electrophiles



Cobalt-Catalyzed Arylzincation of Alkynes (Chapter 2)

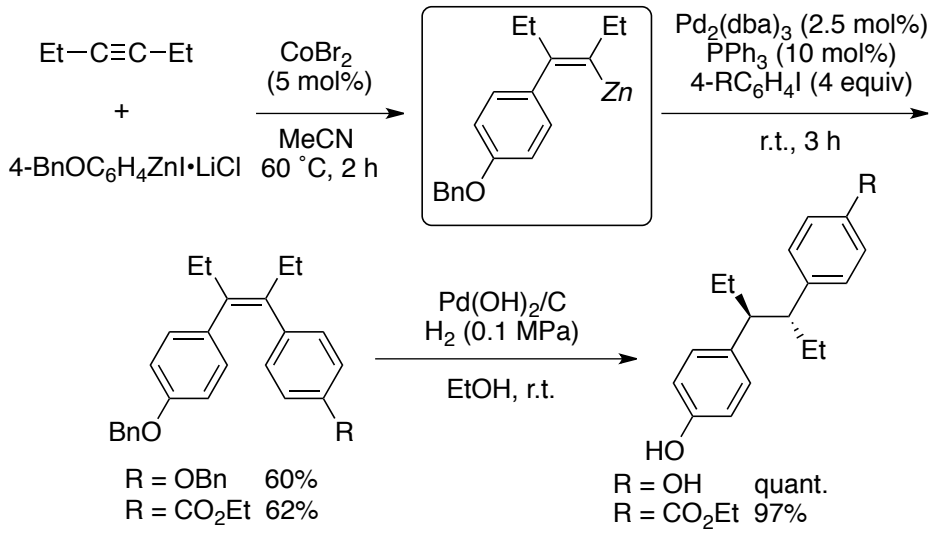
Although the arylmagnesiation was efficient for the synthesis of tri- and tetrasubstituted alkenes, functional group compatibility was low due to the inherent nucleophilicity of organomagnesium reagents. Thus, the author decided to study arylzincation. In Chapter 2, he discovered that cobalt bromide catalyzed arylzincation of various alkynes with high *E*/*Z* selectivity (Scheme 24).

Scheme 24. Cobalt-Catalyzed Arylzincation of Alkyne



The reaction proceeded with a wide range of alkynes and functionalized arylzinc reagents. The reaction was applicable to the stereoselective synthesis of a synthetic estrogen and its derivatives (Scheme 25).

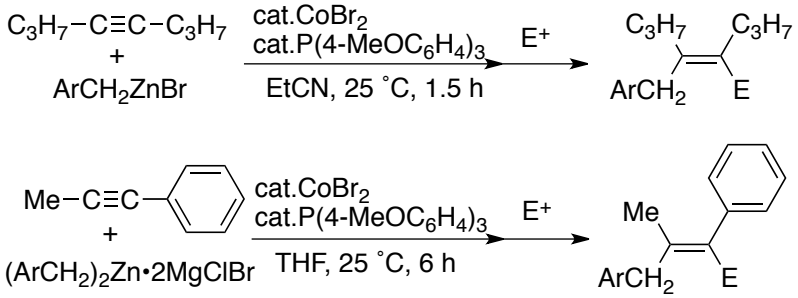
Scheme 25. Concise Synthesis of *meso*-Hexestrol and Its Derivative



Cobalt-Catalyzed Benzylzincation of Alkynes (Chapter 3)

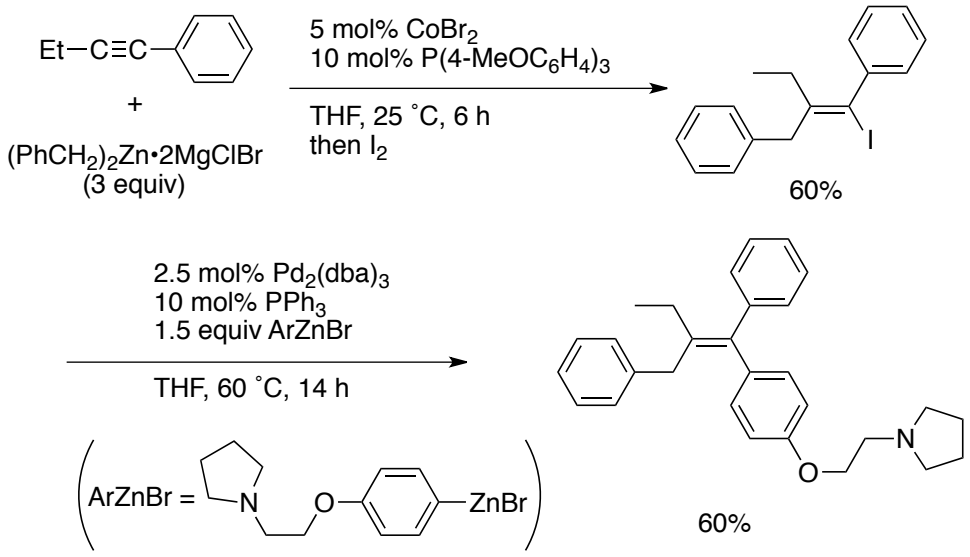
A cobalt catalyst is also effective for benzylzincation of alkynes. In Chapter 3, the author describes cobalt-catalyzed benzylzincation of aliphatic and aryl-substituted alkynes (Scheme 26).

Scheme 26. Cobalt-Catalyzed Benzylzincation of Alkynes



The author applied the benzylzincation reaction to synthesize an estrogen receptor antagonist. Benzylzincation of 1-phenyl-1-butyne followed by addition of iodine provided the corresponding vinyl iodide. The vinyl iodide was treated with arylzinc reagent to afford the estrogen receptor antagonist regio- and stereoselectively (Scheme 27).

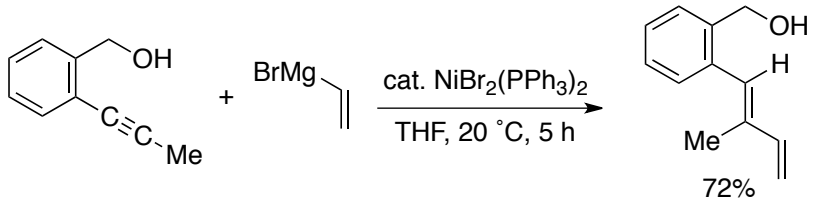
Scheme 27. Short Synthesis of an Estrogen Receptor Antagonist



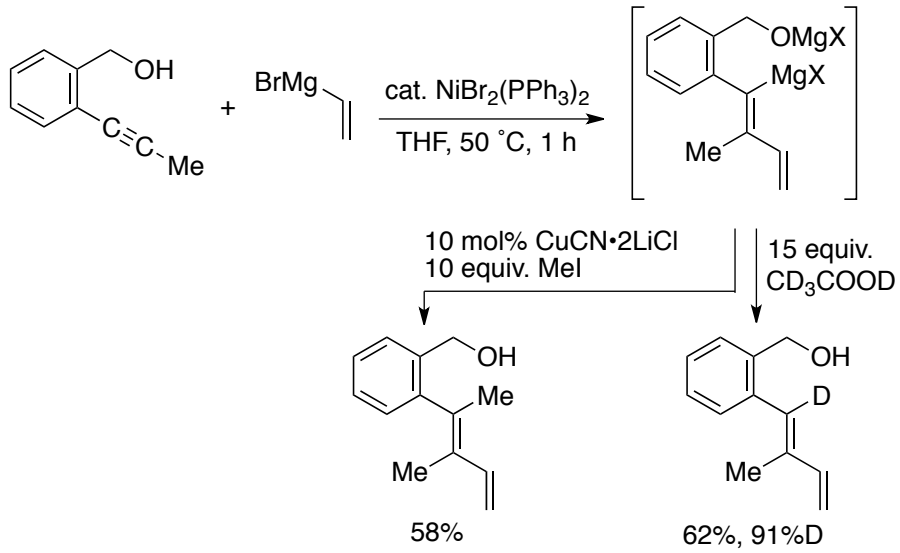
Nickel-Catalyzed Carbometalation Reactions of [2-(1-Propynyl)phenyl]methanol with 1-Alkenylmagnesium Reagents (Chapter 4)

While there are many examples of carbometalation reaction of aryl-, allyl-, alkynyl-, and alkylmetal reagents, 1-alkenylation reaction of alkyne has been rarely reported. In Chapter 4, the author presents nickel-catalyzed carbometalation reaction of alkynes with 1-alkenylmagnesium reagents. Treatment of [2-(1-propynyl)phenyl]methanol with vinylmagnesium bromide in the presence of $NiBr_2(PPh_3)_2$ in THF at 20 ˚C for 5 h provided the vinylated product in good yield (Scheme 28). The vinylmagnesium adduct could be trapped with CD_3COOD or iodomethane in the presence of CuCN•2LiCl (Scheme 29).

Scheme 28. Nickel-Catalyzed Vinylmagnesiation of Alkyne



Scheme 29. Trapping of the Resulting Alkenylmagnesium Intermediate with Electrophiles

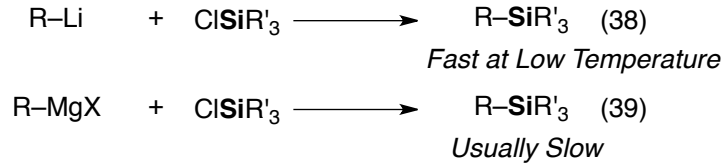


3. Nucleophilic Substitution of Chlorosilanes with Organomagnesium Reagents (Chapters 5 and 6)

The chemistry of organosilanes has been studied for long years since Friedel and Crafts reported the first synthesis of organosilanes from dialkylzinc and tetrachlorosilane in 1863.[42] Carbon–silicon bonds are generally stable, and thus organic silicon compounds are easily handled. In contrast to its stability, organosilanes are useful for various organic transformations through activation of substrates and/or C–Si bonds of the reagents.

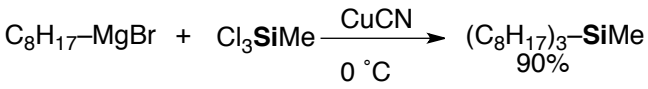
Although various preparative methods have been reported during the long history of organosilicon chemistry, the synthesis of organosilicon still heavily depends on the classical nucleophilic substitution of chlorosilanes with organolithium or organomagnesium reagents. In general, the reactions of chlorosilanes with organolithium reagents undergo smoothly at low temperatures (Scheme 30, eq. 38). However, the reaction with much less reactive, yet readily available organomagnesium reagents requires high temperatures and prolonged reaction times (Scheme 30, eq. 39).

Scheme 30. Nucleophilic Substitution of Chlorotriorganosilane



Although addition of cyanide or thiocyanide is known to accelerate the transmetalation reaction of chlorosilanes, the use of the toxic anions should be avoided (Scheme 31).[43] Thus, the author started his work for exploring efficient and lower toxic catalytic system.

Scheme 31. Nucleophilic Substitution of Chlorosilane in the Presence of Cyanide



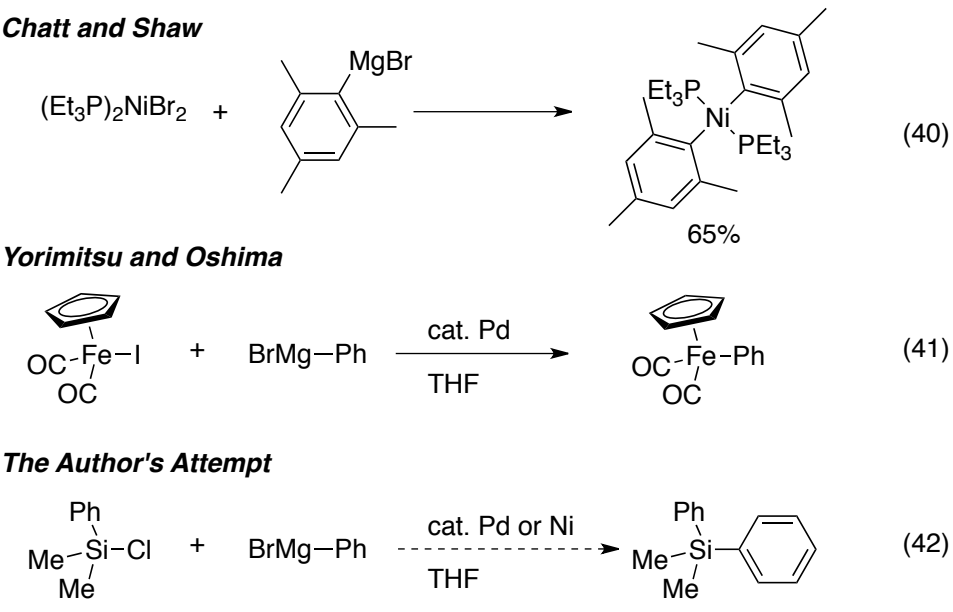
In this section, he describes his works of silver and zinc-catalyzed nucleophilic substitution reaction of chlorosilanes with organomagnesium reagents.

3-1. The Author's Works on Nucleophilic Substitution of Chlorosilanes

Silver-Catalyzed Transmetalation between Chlorosilanes and Aryl and Alkenyl Grignard Reagents for Synthesis of Tetraorganosilanes (Chapter 5)

Organomagnesium reagents react not only with organic electrophiles but also with metals to produce new carbon–metal bonds. In 1960, Chatt and Shaw reported that the reaction of $NiBr_2(PEt_3)_2$ with mesitylmagnesium bromide smoothly afforded the corresponding diorganonickel complex (Scheme 32, eq. 40).[44a] However, this is not the case with the reaction of $[CpFe(CO)_2I]$ with organomagnesium reagents, which required palladium catalyst to make carbon–iron bonds. Yorimitsu and Oshima proposed the reaction would proeed through oxidative addition of the Fe–I bond to palladium(0) (Scheme 32, eq. 41).[44b] The author's first attempt, the reaction of chlorosilanes with organomagnesium reagents in the presence of palladium or nickel catalyst, failed (Scheme 32, eq. 42).

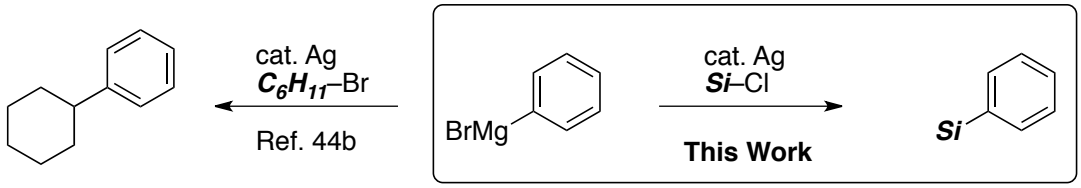
Scheme 32. Transmetalation from Organomagnesium Reagents



Silver-catalyzed coupling reaction with alkyl halides with organomagnesium reagents was reported in his laboratory.[45] The author envisioned that silver salts should catalyze the reactions

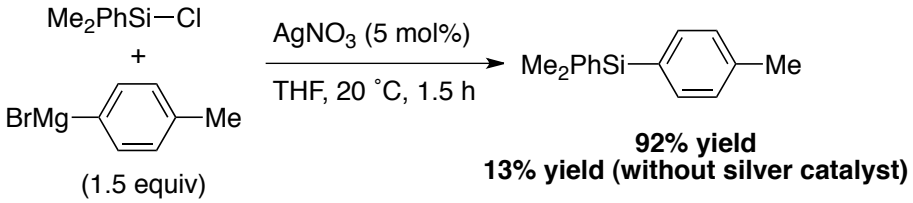
of chlorosilanes with organomagnesium reagents (Scheme 33). In Chapter 5, the author describes the transmetalation of chlorosilanes with organomagnesium reagents under silver catalysis and the mechanistic insights for the reaction.

Scheme 33. Silver-Catalyzed Reaction with Organomagnesium Reagents



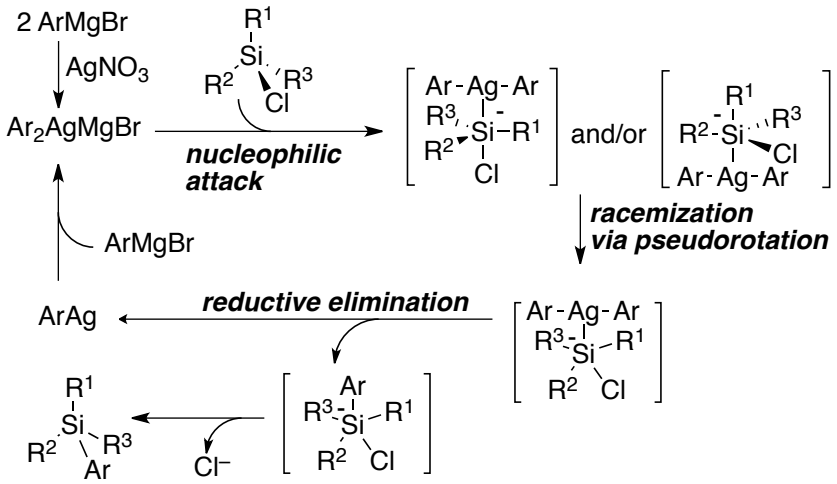
Treatment of chlorodimethylphenylsilane with 4-methylphenylmagnesium bromide in the presence of silver nitrate in THF at 20 ˚C for 1.5 h provided the corresponding tetraorganosilanes in 92% yield (Scheme 34). Notably, the arylated product was obtained in only 13% yield in the absence of silver nitrate.

Scheme 34. Silver-Catalyzed Nucleophilic Substitution of Chlorosilane



The author proposed the reaction mechanism shown in Scheme 35. The reaction would proceed with the formation of diarylargentate species, followed by nucleophilic attack of the argentate complex.

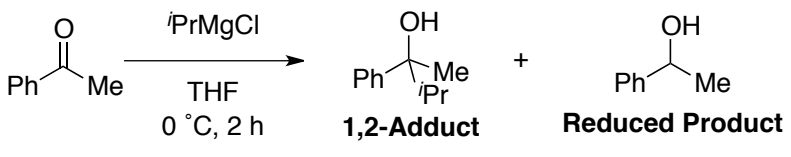
Scheme 35. Proposed Mechanism



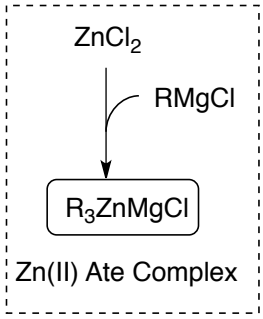
Zinc-Catalyzed Nucleophilic Substitution Reaction of Chlorosilanes with Organomagnesium Reagents (Chapter 6)

The author then tried to expand the chemistry of ate-complex with chlorosilanes. He envisioned that a zinc catalyst should be superior to transition metal catalysts due to its low toxicity, abundance, environmental friendliness, and low cost. Notably, Ishihara reported selective alkylation of ketones and aldimines with organomagnesium reagents catalyzed by zinc chloride via a formation of triorganozincate.[46] The resulting triorganozincate was more nucleophilic than the corresponding organomagnesium reagents (Scheme 36).

Scheme 36. Zinc-Catalyzed Alkylation of Ketones with Organomagnesium Reagent



Catalyst	1,2-Adduct (%)	Reduced Product (%)
with $ZnCl_2$	85	0
without $ZnCl_2$	31	11

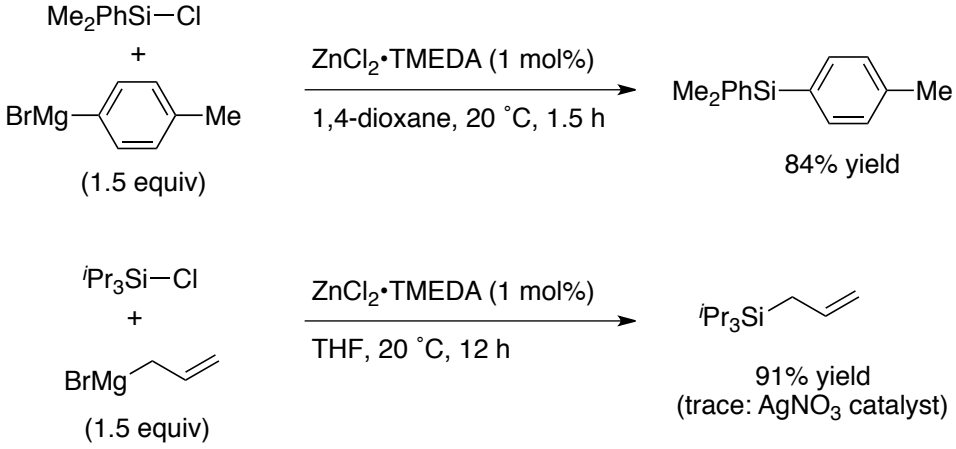


Finally, the author discovered that simple zinc salts also catalyzed the nucleophilic

substitution reaction of chlorosilanes with organomagnesium reagents. The studies on the zinc-catalyzed reaction revealed that the reaction was more versatile than the previous silver-catalyzed one.

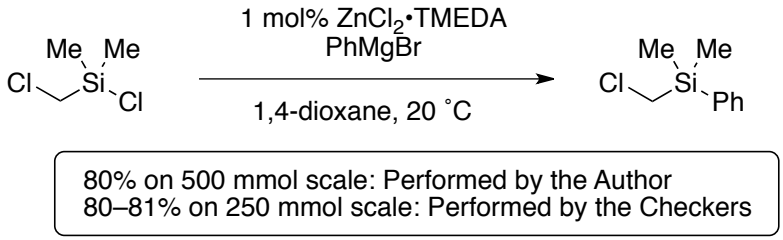
Treatment of chlorodimethylphenylsilane with 4-methylphenylmagnesium bromide in the presence of zinc chloride • *N*,*N*,*N'*,*N'*-tetramethylethylenediamine complex ($ZnCl_2$•TMEDA) in 1,4-dioxane at 20 ˚C for 1.5 h provided the corresponding tetraorganosilanes in 84% yield (Scheme 37). The scope of organomagnesium reagents in the silver-catalyzed reaction was limited to aryl- and bulky 1-alkenylmagnesium reagents because of the poor thermal stability of organosilver reagents. On the other hand, due to the high stability of organozinc reagents, not only arylmagnesium reagents but also allyl-, benzyl-, vinylmagnesium reagents were applicable to the reaction.

Scheme 37. Zinc-Catalyzed Nucleophilic Substitution of Chlorosilanes



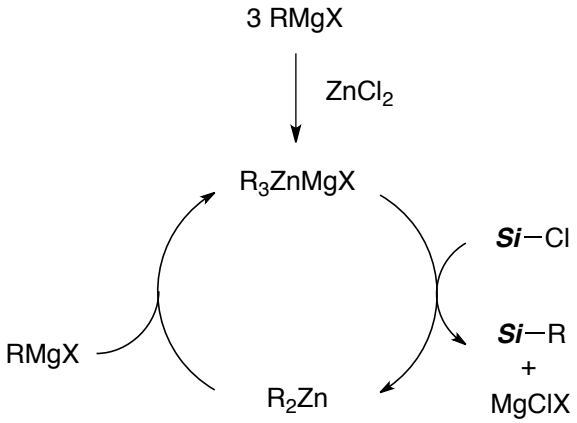
The procedures of the reaction were quite simple and easy, thus the reaction was proven to be scalable and significantly reliable (Scheme 38). The author performed the reaction of chloro(chloromethyl)dimethylsilane with phenylmagnesium bromide on a 500 mmol scale. The reaction proceeded smoothly to furnish the corresponding (chloromethyl)dimethylphenylsilane in 80% yield. Jane Panteleev and Mark Lautens, the checkers of the reaction, performed the reaction on a 250 mmol scale and obtained the product in 80–81% yield with high reproducibility. The results were published in *Organic Synthesis*.

Scheme 38. Large Scale Reaction



The active species of the reaction would be a zincate, which is produced *in situ* from zinc salt and organomagnesium reagent (Scheme 39).

Scheme 39. Plausible Mechanism



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Chapter 1

Chromium-Catalyzed Arylmagnesiation of Alkynes

Arylmagnesiation of unfunctionalized alkynes in the presence of catalytic amounts of chromium(II) chloride and pivalic acid proceeds with high stereoselectivity. The alkenylmagnesium intermediate reacts with various electrophiles to afford the corresponding tetrasubstituted olefins in good yields.

Chapter 1

Introduction

Carbometalation of alkynes is a straightforward method for the synthesis of multisubstituted olefins in organic synthesis.[1] To date, most studies of the process have focused on employing heteroatom-containing alkynes, such as homopropargyl ethers and propargyl alcohols as substrates.[2] As for the carbometalation of unfunctionalized alkynes, however, much less progress has been made.[3-5] The development of facile, efficient, and general methods for the carbometalation of unfunctionalized alkynes remains an important challenge. In Chapter 1, the author wishes to report that a simple chromium salt promotes arylmagnesiation of unfunctionalized alkynes with high efficiency.

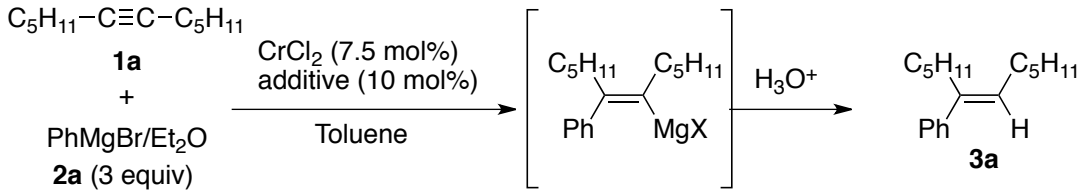
Results and Discussion

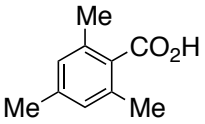
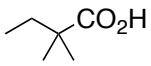
Treatment of 6-dodecyne (**1a**, 1.0 mmol) with phenylmagnesium bromide (**2a**, 3.0 mmol, 2 M diethyl ether solution) in toluene (3 mL) at 110 ˚C in the presence of chromium(II) chloride (0.075 mmol) for 18 h provided 6-phenyl-6-dodecene (**3a**) in an *E*/*Z* ratio of 91:9 in 81% yield (Table 1, entry 1). The author screened several transition metal catalysts, such as iron, cobalt, and nickel salts, none of which did show any catalytic activity under similar reaction conditions.[6] The choice of reaction solvent is crucial. The use of THF instead of toluene resulted in recovery of the starting material **1a**.

The author next explored several additives to improve the yield and the *E*/*Z* selectivity (Table 1). Surprisingly, the addition of a catalytic amount of protic additives led to higher yield, better stereoselectivity, and faster reaction rate.[7,8] Although the reaction required 18 h at 110 ˚C when no additive was employed, the processes with methanol went to completion within 2 h (entries 3 and 4). The acceleration effect was also observed with other alcoholic additives. The addition of phenol and *tert*-butyl alcohol gave a similar result with methanol (entry 4 vs. entries 5 and 6). Further investigation revealed that the use of carboxylic acids not only resulted

in faster reactions (0.25 h) but also increased the ratio of *E*/*Z* isomers to greater than 99:1 (entries 7–11). After the screening of carboxylic acids, pivalic acid showed the best result to provide (*E*)-6-phenyl-6-dodecene (**3a**) in 87% yield after 0.25 h (entry 10). The chromium salt/pivalic acid system proceeded even at 60 ˚C to afford the corresponding phenylated product **3a** in 75% yield albeit the reaction was slow (entry 13). This arylmagnesiation was readily scalable. Treatment of 10 mmol of 6-dodecyne (**1a**) with phenylmagnesium bromide (**2a**, 30 mmol) in the presence of chromium(II) chloride (0.75 mmol) and pivalic acid (1.0 mmol) in toluene (30 mL) in a similar manner provided **3a** in an *E*/*Z* ratio of >99:1 in 78% yield (entry 10 in the parentheses). It is worth noting that the additive-free process did not produce **3a** at all at 60 ˚C (entry 2 vs. 13).[9]

Table 1. Effect of Additives on the Chromium-Catalyzed Phenylmagnesiation of 6-Dodecyne[a]



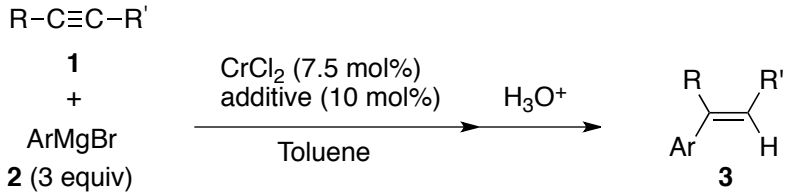
entry	additive	temp (˚C)	time (h)	yield (%)[b]	*E*/*Z*[c]
1	none	110	18	81	91:9
2	none	60	18	0	–
3	MeOH	110	1	62	ND[d]
4	MeOH	110	2	77	95:5
5	PhOH	110	2	77	95:5
6	^{t}BuOH	110	2	75	95:5
7	$MeCO_2H$	110	0.25	79	>99:1
8	$PhCO_2H$	110	0.25	81	>99:1
9		110	0.25	78	>99:1
10	**^{t}BuCO$_2$H**	**110**	**0.25**	**87 (78)[e]**	**>99:1**
11		110	0.25	84	>99:1
12	^{t}BuCO$_2$H	110	2	92	96/4
13	^{t}BuCO$_2$H	60	18	75	96:4

[a] Performed on a 1.0 mmol scale.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Not determined.
[e] Performed on a 10 mmol scale.

Various combinations of alkynes and aryl Grignard reagents were examined in the chromium/pivalic acid-catalyzed process (Table 2). All the reactions afforded the corresponding *E* adducts exclusively or predominantly, except for the reaction of 1-(trimethylsilyl)propyne (**1e**) (entry 9). Arylmagnesium reagents having a methyl substitution at the ortho, meta, or para position effected the arylmagnesiation, and all the reactions afforded

the corresponding *E* isomers exclusively (entries 1–3). 3-Methoxy- and 4-chlorophenylmagnesium bromides participated in the reaction (entries 4 and 5). The use of bulky *tert*-butyl substituted acetylene **1b** provided the corresponding product **3g** with complete regioselectivity (entry 6). However, the regioselectivity could not be controlled by much smaller 2-propyl substituent.[10] The regioselectivity was simply governed by the steric factor of the two substituents of the dialkylacetylene. The reactions of the phenyl-substituted alkynes afforded modest yields of the arylmagnesiation products (entries 7 and 8). Diphenylacetylene (**1f**) also reacted with phenylmagnesium bromide, giving triphenylethylene (**3k**) in 70% yield (entry 10). Unfortunately, the use of terminal alkynes resulted in failure.

Table 2. Chromium-Catalyzed Arylmagnesiation of Alkynes[a]



1b : R = C_6H_{13}, R' = ^{t}Bu
1c : R = C_6H_{13}, R' = Ph
1d : R = Me, R' = Ph
1e : R = Me, R' = TMS
1f : R = Ph, R' = Ph

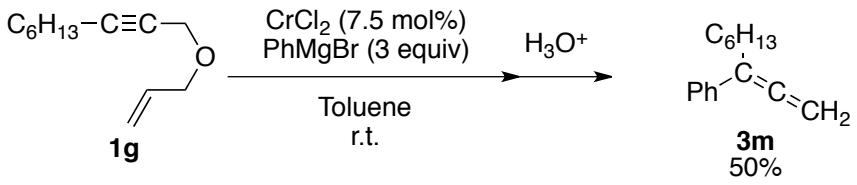
2b : Ar = 2-MeC_6H_4
2c : Ar = 3-MeC_6H_4
2d : Ar = 4-MeC_6H_4
2e : Ar = 4-ClC_6H_4
2f : Ar = 3-$MeOC_6H_4$

entry	1	2	3	temp (˚C)	time (h)	yield (%)[b]	*E*/*Z*[c]
1	**1a**	**2b**	**3b**	110	10	55	>99:1
2	**1a**	**2c**	**3c**	110	0.5	80	>99:1
3	**1a**	**2d**	**3d**	110	0.5	81	>99:1
4	**1a**	**2e**	**3e**	110	2	61	88:12
5[d]	**1a**	**2f**	**3f**	110	18	69	87:13
6[e]	**1b**	**2a**	**3g**	110	4	53	>99:1
7	**1c**	**2a**	**3h**	110	2	68[f]	92:8
8	**1d**	**2a**	**3i**	60	18	51[f]	95:5
9	**1e**	**2a**	**3j**	60	18	67	65:35
10	**1f**	**2a**	**3k**	60	0.5	70	–

[a] Performed on a 1.0 mmol scale.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.
[d] The reaction was carried out without ^{t}BuCO$_2$H.
[e] $CrCl_2$ (20 mol%) and ^{t}BuCO$_2$H (20 mol%) were used.
[f] A small amount of the corresponding regioisomer was observed (entry 7; 10% yield, entry 8; 1% yield).

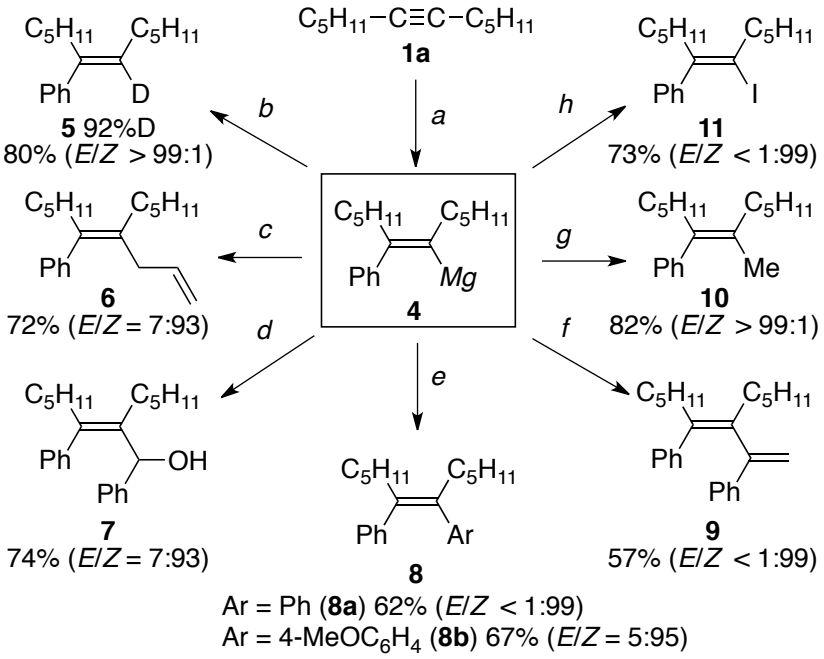
The reaction of propargyl ether **1g** provided 1-phenyl-1,2-octadiene **3m** in 50% by S_N2' reaction pathway (Scheme 1).

Scheme 1. Chromium-Catalyzed Reaction of Propargyl Ether



With the reliable carbomagnesiation reaction in hand, the author investigated the utility of the intermediary alkenylmagnesium compound **4** (Scheme 2). The intermediate reacted with various electrophiles, such as deuterium oxide, allyl bromide, benzaldehyde, iodomethane, or iodine, to give the corresponding tetrasubstituted alkenes with high stereoselectivity in good overall yield. As for trapping of **4** with allyl bromide or iodomethane, the addition of a catalytic amount of CuCN·2LiCl improved the yield of the corresponding products **6** and **10**. The alkenylmagnesium intermediate **4** was useful for palladium-catalyzed cross-coupling reactions of aryl iodides, such as iodobenzene and 4-iodoanisole, and the two aryl groups were introduced smoothly with high stereoselectivity. The conjugated diene **9** was also prepared from the arylmagnesiation product **4** via palladium-catalyzed cross-coupling reaction.

Scheme 2. Reactions of Various Electrophiles with Arylmagnesiation Intermediate **4**[a]



[a]Reagents and Conditions
a) $CrCl_2$ (7.5 mol%), $^tBuCO_2H$ (10 mol%), PhMgBr (3 equiv), toluene, 110 ˚C, 0.25 h
b) D_2O, 0 ˚C, 3 h
c) CuCN•2LiCl (10 mol%), CH_2=$CHCH_2Br$ (4 equiv), 0 ˚C, 3 h
d) PhCHO (4 equiv), 0 ˚C, 3 h
e) $Pd_2(dba)_3$ (2.5 mol%), P(*o*-tolyl)$_3$ (5 mol%), ArI (4 equiv), 25 ˚C, 3 h
f) $Pd_2(dba)_3$ (2.5 mol%), P(*o*-tolyl)$_3$ (5 mol%), PhC(Br)=CH_2 (4 equiv), 25 ˚C, 12 h
g) CuCN•2LiCl (10 mol%), MeI (4 equiv), 0 ˚C, 3 h
h) I_2 (4 equiv), 0 ˚C, 3 h

Conclusion

The arylmagnesiation of unfunctionalized alkynes has been achieved by using a chromium salt. Notably, the addition of a catalytic amount of pivalic acid dramatically enhanced the reactivity and stereoselectivity. The procedure is highly efficient to construct multisubstituted ethene units.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (300 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to $CHCl_3$ at 7.26 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Anhydrous $CrCl_2$ was purchased from Aldrich and was used under argon. Arylmagnesium bromide was prepared from magnesium metal and the corresponding bromoarene in diethyl ether. Diethyl ether was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. Toluene was dried over slices of sodium and used after distillation. All reactions were carried out under argon atmosphere.

Typical procedure for chromium/pivalic acid-catalyzed arylmagnesiation of alkynes: The reaction of 6-dodecyne with phenylmagnesium bromide (Table 1, entry 10) is representative. Anhydrous chromium(II) chloride (9.2 mg, 0.075 mmol) was placed in a 20-mL reaction flask. Toluene (3 mL), 6-dodecyne (**1a**, 166 mg, 1.0 mmol), phenylmagnesium bromide (**2a**, 2.0 M diethyl ether solution, 1.5 mL, 3.0 mmol), and pivalic acid (11 μL, 0.10 mmol) were sequentially added at 25 ˚C. The resulting mixture was heated at 110 ˚C for 15 min. After the mixture was cooled to room temperature, the reaction was quenched with water. The products were extracted with hexane three times. The combined organic layer was dried over Na_2SO_4 and concentrated. Silica gel column purification (hexane) of the crude product provided

(*E*)-6-phenyl-6-dodecyne (**3a**, 212 mg, 0.87 mmol) in 87% isolated yield.

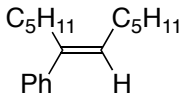
General procedure for the arylmagnesiation and the subsequent reaction with allyl bromide (Scheme 2): Anhydrous chromium(II) chloride (9.2 mg, 0.075 mmol) was placed in a 20-mL reaction flask. Toluene (3 mL), 6-dodecyne (**1a**, 166 mg, 1.0 mmol), phenylmagnesium bromide (**2a**, 2.0 M diethyl ether solution, 1.5 mL, 3.0 mmol), and pivalic acid (11 μL, 0.10 mmol) were sequentially added at 25 ˚C. The resulting mixture was heated at 110 ˚C for 15 min. After the mixture was cooled to 0 ˚C, allyl bromide (0.34 mL, 4.0 mmol) and CuCN·2LiCl (1.0 M in THF, 0.1 mL, 0.1 mmol) were added. After being stirred for 3 h at 0 ˚C, the reaction mixture was poured into saturated ammonium chloride solution. The products were extracted with hexane three times. The combined organic layer was dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (hexane) of the crude product provided the corresponding product **6** (205 mg, 0.72 mmol, *E*/*Z* = 7:93) in 72% isolated yield.

Characterization Data

The stereochemistry of the arylmagnesiation products was assigned by comparison with known compounds that have an analogous structure.

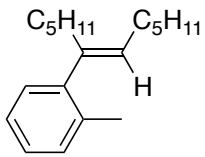
Compounds **3i**[11], **3j**[12], **3k**[13] and **3m**[14] are known compounds and showed the identical spectra with those in the literature.

(*E*)-6-Phenyl-6-dodecene (3a)



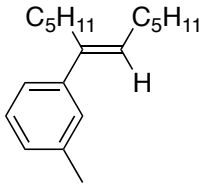
oil. IR (neat) 2926, 1444, 758, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H), 1.24–1.50 (m, 12H), 2.18 (q, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 5.64 (t, *J* = 7.2 Hz, 1H), 7.18–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.25, 14.28, 22.70, 22.81, 28.62, 28.73, 29.79, 29.88, 31.85, 32.03, 126.50, 126.51, 128.29, 129.36, 140.25, 143.73; Found: C, 88.45; H, 11.55%. Calcd for $C_{18}H_{28}$: C, 88.27; H, 11.70%.

(*E*)-6-(2-Methylphenyl)-6-dodecene (3b)



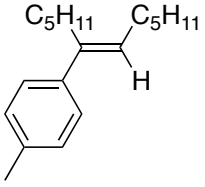
oil. IR (neat) 2926, 1459, 759, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (t, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 6.6 Hz, 3H), 1.25–1.41 (m, 12H), 2.16 (q, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 2.31 (t, *J* = 7.2 Hz, 2H), 5.22 (t, *J* = 7.2 Hz, 1H), 7.02–7.15 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.27, 14.31, 20.14, 22.76, 22.82, 28.09 28.21, 29.77, 31.82, 31.94, 32.20, 125.37, 126.41, 129.24, 130.02, 130.10, 135.48, 140.78, 144.93; Found: C, 88.09; H, 11.89%. Calcd for $C_{19}H_{30}$: C, 88.30; H, 11.70%.

(*E*)-6-(3-Methylphenyl)-6-dodecene (3c)



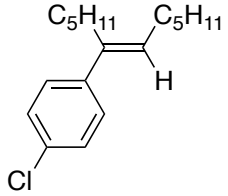
oil. IR (neat) 2926, 1602, 1460, 782, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H), 1.27–1.53 (m, 12H), 2.17 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 2.46 (t, *J* = 7.5 Hz, 2H), 5.62 (t, *J* = 7.5 Hz, 1H), 7.01–7.04 (m, 1H) 7.11–7.21 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.27, 14.29, 21.75, 22.73, 22.85, 28.68, 28.76, 29.85, 29.98, 31.89, 32.10, 123.66, 127.33 (Two signals merge.), 128.20, 129.17, 137.76, 140.42, 143.81; Found: C, 88.06; H, 11.56%. Calcd for $C_{19}H_{30}$: C, 88.30; H, 11.70%.

(*E*)-6-(4-Methylphenyl)-6-dodecene (3d)



oil. IR (neat) 2925, 1512, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H), 1.23–1.53 (m, 12H), 2.16 (q, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 2.45 (t, *J* = 7.2 Hz, 2H), 5.61 (t, *J* = 7.2 Hz, 1H), 7.08–7.11 (m, 2H) 7.22–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.28, 14.30, 21.23, 22.74, 22.85, 28.67, 28.74, 29.87, 29.91, 31.88, 32.10, 126.39, 128.64, 129.04, 136.13, 140.08, 140.85; Found: C, 88.23; H, 11.49%. Calcd for $C_{19}H_{30}$: C, 88.30; H, 11.70%.

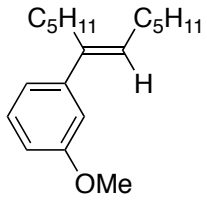
(*E*)-6-(4-Chlorophenyl)-6-dodecene (3e)



oil. IR (neat) 2928, 1490, 1092, 829, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 6.6 Hz, 3H),

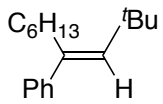
0.90 (t, *J* = 6.6 Hz, 3H), 1.26–1.43 (m, 12H), 2.17 (q, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 5.62 (t, *J* = 7.2 Hz, 1H), 7.04–7.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.24, 14.28, 22.72, 22.83, 28.52, 28.77, 29.75, 29.82, 31.87, 31.98, 127.84, 128.44, 129.96, 132.25, 139.31, 142.20; Found: C, 77.72; H, 10.04%. Calcd for $C_{18}H_{27}Cl$: C, 77.53; H, 9.76%.

(*E*)-6-(3-Methoxylphenyl)-6-dodecene (3f)



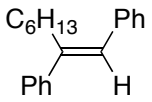
oil. IR (neat) 2927, 1577, 1465, 1285, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H), 1.24–1.46 (m, 12H), 2.17 (q, *J* = 7.2 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 5.65 (t, *J* = 7.2 Hz, 1H), 6.74–6.78 (m, 1H), 6.87–6.94 (m, 2H), 7.18–7.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.27, 14.29, 22.73, 22.84, 28.66, 28.74, 29.79, 30.00, 31.88, 32.08, 55.39, 111.69, 112.62, 119.17, 129.21, 129.49, 140.21, 145.40, 159.71. Found: C, 83.15; H, 11.28%. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02%.

(*E*)-2,2-Dimethyl-4-phenyl-3-decene (3g)



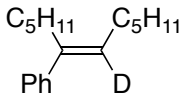
oil. IR (neat) 2957, 1465, 747, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, *J* = 6.0 Hz, 3H), 1.20 (s, 9H), 1.21–1.28 (m, 8H), 2.59 (t, *J* = 7.5 Hz, 2H), 5.55 (s, 1H), 7.18–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.21, 22.81, 29.06, 29.81, 30.65, 31.66, 31.87, 33.03, 126.45, 126.97, 128.18, 139.56, 140.69, 145.29. Found: C, 88.72; H, 11.76%. Calcd for $C_{18}H_{28}$: C, 88.45; H, 11.55%.

(*E*)-1,2-Diphenyl-1-octene (3h)



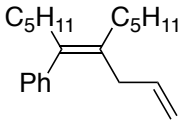
oil. IR (neat) 2926, 1598, 758, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, *J* = 6.9 Hz, 3H), 1.22–1.44 (m, 8H), 2.69 (t, *J* = 8.1 Hz, 2H), 6.69 (s, 1H), 7.16–7.58 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.23, 22.80, 28.90, 29.54, 30.43, 31.75, 126.69, 126.84, 127.32, 128.27, 128.44, 128.54, 128.99, 138.61, 143.41, 143.65; Found: C, 91.03; H, 9.06%. Calcd for $C_{20}H_{24}$: C, 90.85; H, 9.15%.

(*E*)-6-Deuterio-7-phenyl-6-dodecene (5, 92%D)



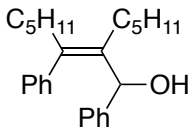
oil. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H), 1.24–1.50 (m, 12H), 2.17 (t, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 7.18–7.35 (m, 5H).

(*Z*)-4-Pentyl-5-phenyl-1,4-decadiene (6)



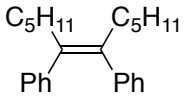
oil. IR (neat) 2926, 1636, 1459, 909, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (t, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 6.9 Hz, 3H), 1.22–1.47 (m, 12H), 2.14 (t, *J* = 7.5 Hz, 2H), 2.29–2.36 (m, 2H), 2.57 (d, *J* = 6.3 Hz, 2H), 4.88–4.95 (m, 2H), 5.68 (ddt, *J* = 16.8, 10.2, 6.3 Hz, 1H), 7.06–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.27, 14.31, 22.77, 22.86, 28.28, 28.77, 30.99, 32.06, 32.37, 34.37, 37.80, 115.12, 126.10, 128.02, 128.97, 133.58, 137.90, 137.97, 144.03; Found: C, 88.66; H, 11.34%. Calcd for $C_{21}H_{32}$: C, 88.36; H, 11.37%.

(*Z*)-2-Pentyl-1,3-diphenyl-2-octene-1-ol (7)



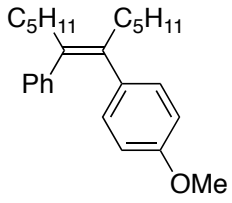
solid. IR (nujol) 3309, 2922, 1451, 997, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, *J* = 6.9 Hz, 3H), 0.84 (t, *J* = 6.9 Hz, 3H), 1.16–1.30 (m, 12H), 1.57 (d, *J* = 3.6 Hz, 1H), 1.95 (dt, *J* = 5.1, 13.5 Hz, 1H), 2.13 (dt, *J* = 5.1, 13.5 Hz, 1H), 2.30–2.39 (m, 2H), 5.34 (d, *J* = 3.3 Hz, 1H), 7.18–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.21, 14.24, 22.51, 22.73, 27.68, 27.81, 30.90, 32.19, 32.81, 34.68, 74.05, 125.92, 126.66, 129.87, 128.15, 128.42, 128.94, 137.42, 141.44, 142.78, 143.31; Found: C, 85.47; H, 9.62%. Calcd for $C_{25}H_{34}O$: C, 85.66; H, 9.78%.

(*Z*)-6,7-Diphenyl-6-dodecene (8a)



oil. IR (neat) 2858, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (m, *J* = 6.9 Hz, 6H), 1.26–1.34 (m, 12H), 2.52 (t, *J* = 7.5 Hz, 4H), 6.90–7.07 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.26, 22.76, 28.34, 32.04, 34.49, 125.53, 127.49, 129.97, 138.51, 143.74; Found: C, 89.94; H, 10.06%. Calcd for $C_{25}H_{32}$: C, 90.23; H, 10.18%.

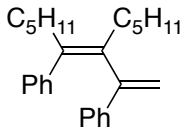
(*Z*)-6-(4-Methoxyphenyl)-7-phenyl-6-dodecene (8b)



oil. IR (neat) 2955, 1509, 1245, 831, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.88 (m, 6H), 1.22–1.29 (m, 12H), 2.47–2.51 (m, 4H), 3.69 (s, 3H), 6.57–6.60 (m, 2H), 6.82–7.08 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.27 (Two signals merge.), 22.75, 22.77, 28.37, 28.39, 32.06 (Two signals

merge.), 34.56 (Two signals merge.), 55.19, 112.95, 125.41, 127.55, 130.00, 130.93, 136.03, 137.90, 138.12, 143.98, 157.43; Found: C, 85.52; H, 9.81%. Calcd for $C_{25}H_{34}O$: C, 85.66; H, 9.78%.

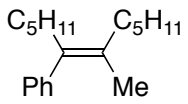
(*Z*)-3-Pentyl-2,4-diphenyl-1,3-nonadiene (9)



oil. IR (neat) 2927, 1491, 897, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84–0.89 (m, 6H), 1.26–1.38 (m, 12H), 2.20 (t, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 4.69 (d, *J* = 1.8 Hz, 1H), 5.26 (d, *J* = 1.8 Hz, 1H), 7.07–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.24, 14.29, 22.77 (Two signals merge), 28.24, 28.39, 31.87, 31.95, 32.10, 34.32, 115.83, 125.81, 126.93, 127.26, 127.59, 128.26, 128.69, 138.10, 139.78, 140.86, 143.95, 148.95. Found: C, 90.19; H, 9.96%. Calcd for $C_{26}H_{34}$: C, 90.11; H, 9.89%.

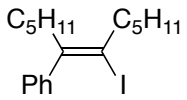
The stereochemical structure of **9** was determined tentatively by analogy with the stereochemistry of cross-coupling products **8a** and **8b**.

(*E*)-6-Methyl-7-phenyl-6-dodecene (10)



oil. IR (neat) 2926, 1440, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (t, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 6.9 Hz, 3H), 1.22–1.46 (m, 12H), 1.49 (s, 3H), 2.15 (t, *J* = 7.5 Hz, 2H), 2.28–2.32 (m, 2H), 7.05–7.09 (m, 2H) 7.16–7.32 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.24, 14.30, 20.05, 22.75, 22.90, 28.46 (Two signals merge.), 32.05, 32.25, 34.14 (Two signals merge.), 125.82, 127.99, 129.21, 131.59, 136.02, 144.62; Found: C, 88.05; H, 11.88%. Calcd for $C_{19}H_{30}$: C, 88.30; H, 11.70%.

(*Z*)-6-Iodo-7-phenyl-6-dodecene (11)



oil. IR (neat) 2926, 1458, 1119, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 6.9 Hz, 3H), 1.23–1.39 (m, 10H), 1.60–1.65 (m, 2H), 2.45 (t, *J* = 8.1 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H), 7.05–7.07 (m, 2H) 7.24–7.37 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.16, 14.25, 22.61, 22.80, 28.03, 29.66, 31.01, 31.68, 34.83, 41.35, 106.52, 127.02, 128.22, 128.46, 147.39, 147.82; Found: C, 58.63; H, 7.32%. Calcd for $C_{18}H_{27}I$: C, 58.38; H, 7.35%.

References and Notes

1. (a) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 4.4, pp 865–911. (b) Marek, I.; Normant, J. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 271–337. (c) Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed.* **1997**, *36*, 93–95.
2. For a review on metal-mediated carbometalation of alkynes and alkenes containing heteroatoms, see: (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899–5913. For a recent example on transition metal-catalyzed carbometalation of alkynes containing heteroatoms, see: (b) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050–15051.
3. The arylmetalation of unfunctionalized alkynes is very difficult to achieve: Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164–17165 and references cited therein.
4. For recent examples on transition metal-catalyzed carbometalation of unfunctionalized alkynes, see: (a) Shirakawa, E.; Yamasaki, K.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 10221–10222. (b) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2006**, *128*, 14438–14439.
5. (a) Nishikawa, T.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 4629–4630. (b) Nishikawa, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2795–2797. In these reports, the author described chromium-catalyzed annulation reactions of acetylenic compounds with methallylmagnesium chloride, probably initiated by carbometalation of alkyne units. However, the carbometalation processes suffered from limitations as to the scope of the alkynes and Grignard reagents. The alkynes available for use are limited to 1,6-diynes and 1,6-enynes. In other words, the intramolecular carbomagesiation of unfunctionalized alkynes did not proceed at all. Additionally, the author obtained promising results only with methallylmagnesium chloride of high nucleophilicity. (c) Molander, G. A.; Sommers, E.

M. *Tetrahedron Lett*. **2005**, *46*, 2345–2349.

6. The use of chromium(III) chloride afforded **3** in a yield similar to the chromium(II) chloride catalyst in the absence of pivalic acid. In the presence of pivalic acid, chromium(II) chloride was superior to other chromium salts.
7. The corresponding magnesium alkoxide or carboxylate might accelerate the reaction. Example of the acceleration of a carbometalation reaction by the addition of magnesium alkoxide: (a) Liu, X.; Fox, J. M. *J. Am. Chem. Soc*. **2006**, *128*, 5600–5601.
8. The examples of positive effects for the yield and enantioselectivity by the addition of alcohol or alkoxide, see: (a) Vogl, E. M.; Groger, G.; Shibasaki, M. *Angew. Chem., Int. Ed*. **1999**, *38*, 1570. (b) Funabashi, K.; Jackmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed*. **2003**, *42*, 5489–5492.
9. Interestingly, the reaction with $Cr(OAc)_3$ was slow and resulted in only 30% yield after 5 h in the absence of pivalic acid. The reason for the dramatic effect of the additives is not clear at this stage.
10. The reaction of 2-methyl-3-decyne provided the arylated products in 39% yield with 1/1 regioselectivity.
11. (a) Zhou, C.; Larock, R. C. *J. Org. Chem*. **2005**, *70*, 3765–3777. (b) Zhou, C.; Larock, R. C. *J. Org. Chem*. **2005**, *70*, 3765–3777. See also Ref. 3.
12. The products are commercially available from Aldrich.
13. Chou, S. S. P.; Kuo, H. L.; Wang, C. J.; Tsai, C. Y.; Sun, C. M. *J. Org. Chem*. **1989**, *54*, 868–872.
14. Varghese, J. P.; Knochel, P.; Marek, I. *Org. Lett*. **2000**, *2*, 2849–2852.

Chapter 2

Cobalt-Catalyzed Arylzincation of Alkynes

Cobalt(II) bromide catalyzes arylzincation of alkynes with arylzinc iodide•lithium chloride complexes in acetonitrile. The scope of the arylzincation is wide enough to use unfunctionalized alkynes, such as 6-dodecyne, as well as arylacetylenes. The inherent functional group compatibility of arylzinc reagents allows preparation of various functionalized styrene derivatives. The reaction is applicable to the efficient and stereoselective synthesis of a synthetic estrogen and its derivative.

Chapter 2

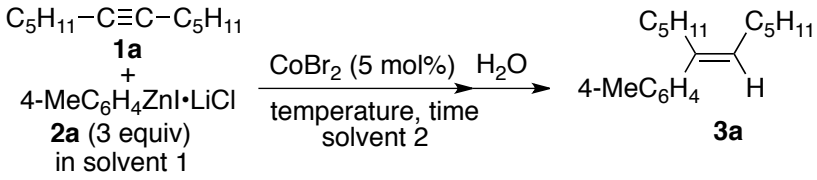
Introduction

Carbometalation of alkynes is a useful reaction to synthesize multisubstituted alkenes.[1] In particular, carbozincation is one of the most important reactions due to the high functional group compatibility of organozinc reagents. Although there are several reports on transition metal-catalyzed carbozincation of propynoate derivatives,[2] alkynyl sulfoxide,[3] phenylacetylenes,[4] or ynamides,[5] carbozincation of unfunctionalized alkynes such as dialkylacetylene remains an important challenge.[6] In Chapter 2, the author wishes to report that simple cobalt salts[7] can catalyze arylzincation of a wide range of alkynes including unfunctionalized ones.[8] In addition, the reaction offers a new route to the key structure of various synthetic estrogen derivatives.

Results and Discussion

The author's investigation began with treatment of 6-dodecyne (**1a**) with 4-methylphenylzinc iodide•lithium chloride complex (1 M in THF)[9] in toluene at 100 ˚C in the presence of cobalt bromide for 1 h. However, the reaction did not proceed (Table 1, entry 1). Interestingly, the addition of acetonitrile promoted the reaction to provide (*E*)-6-(4-methylphenyl)-6-dodecene (**3a**) stereoselectively in 22% yield (Table 1, entry 2). The addition of acetonitrile was also effective for the reaction in 1,4-dioxane or 1,2-dichloroethane as a solvent (Table 1, entries 3 and 4). The author then replaced THF solvent of the reagent with acetonitrile to improve the reaction by increasing a concentration of acetonitrile in the system. Gratifyingly, the reaction gave a better result that **3a** was obtained in 41% yield (Table 1, entry 5). Further investigation showed that the reaction could proceed at 60 ˚C to afford **3a** in 55% yield in the absence of toluene (Table 1, entry 6). The addition of propionitrile was less effective, and isobutyronitrile completely suppressed the reaction (Table 1, entries 7 and 8). Other polar solvents such as ethyl acetate are also ineffective (Table 1, entry 9).

Table 1. Solvent Effect of the Arylzincation Reaction

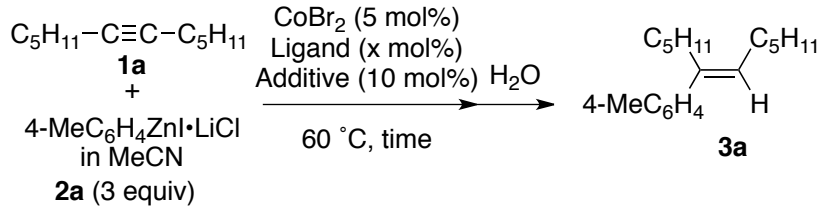


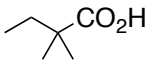
entry	solvent 1	solvent 2	temp (˚C)	time (h)	yield(%)[a]
1	THF	toluene	100[b]	1	–
2	THF	toluene/MeCN (3/1)	100[b]	1	22
3	THF	1,4-dioxane/MeCN (3/1)	100[b]	1	24
4	THF	$ClCH_2CH_2Cl$/MeCN (3/1)	100[b]	1	15
5	MeCN	toluene	100[b]	4	41
6	MeCN	–	60	4	55
7	EtCN	–	60	4	32
8	^{i}PrCN	–	60	4	–
9	$MeCO_2Et$	–	60	4	–

[a] Yields were determined by ^{1}H NMR.
[b] The reaction was performed in a sealed tube.

Subsequently, various phosphorus ligands and additives were assessed under the conditions shown in Table 1, entry 6 (Table 2). Among a series of bulky phosphine ligands, P^tBu_3 gave the highest yield[10] (entries 2–4). Other bidentate phosphine ligands, such as dppe and dppb retarded the reaction (entries 5 and 6). Unfortunately, no acceleration effect[11] was observed in the cobalt-catalyzed arylzincation reaction by the addition of alcohol or carboxylic acid (entries 7–9).

Table 2. Ligand and Additive Screening of the Arylzincation reaction



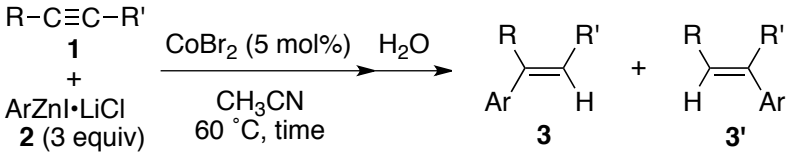
entry	Ligand (mol%)	Additive	time (h)	yield(%)[a]
1	none	–	4	55
2	P^{t}Bu$_3$ (10)	–	4	64[b]
3	PCy$_3$ (10)	–	4	59
4	P(*o*-Tol)$_3$ (10)	–	1[c]	56
5	dppe (5)	–	11	17
6	dppp (5)	–	11	17
7	P^{t}Bu$_3$ (10)	MeOH	1	38
8	P^{t}Bu$_3$ (10)		1	24
9	P^{t}Bu$_3$ (10)	^{t}BuOK	1	30

[a] Yields were determined by ^{1}H NMR.
[b] Isolated Yield.
[c] Starting Material disappeared at 1 h.

The scope of arylzinc reagents and alkynes was studied, and the results are summarized in Table 3. The reactions with phenyl- and 3-methylphenylzinc reagents proceeded smoothly to afford the corresponding products in high yields (entries 1 and 2). However, sterically hindered 2-methylphenylzinc reagent **2d** failed to react (entry 3). Arylzinc reagents bearing bromo and ethoxycarbonyl group were also applicable and provided the corresponding arylated products in 64 and 72% yields, respectively (entries 4 and 5). Whereas an arylzinc reagent having an electron-donating methoxy group reacted smoothly, a trifluoromethyl-substituted arylzinc reagent was less reactive (entries 6 and 7). Attempts to alkylate **1a** with hexylzinc iodide•lithium chloride under cobalt catalysis afforded (*Z*)-6-dodecene in less than 20% yields, and none of the corresponding hexylated product was observed.

The reaction of 2-octyne (**1b)** provided a 55:45 mixture of regioisomers (entry 8). 1-Phenyl-1-propyne reacted smoothly with high regioselectivity, whereas the reaction of diphenylacetylene was sluggish (entries 9 and 10). The phenylzincation of phenylacetylene having a methoxy group at the ortho position exhibited perfect regioselectivity to yield phenylation product **3l** (entry 11). Unfortunately, 2-methyl-3-decyne (**1f)** failed to react because of its steric hindrance (entry 12). Acetylene having an ester group reacted without any observable side reactions (entry 13). The reaction proceeded efficiently with heteroaryl-substituted alkyne **1h** (entry 14). The reaction of alkynyl phosphonate **1i** gave the corresponding product **3p** regioselectively (entry 15). Bulky triethylsilyl-substituted alkyne was inert under the reaction conditions, and the reaction of diyne **1j** gave **3q** selectively (eq. 1). Attempts to use terminal alkynes resulted in low yields (less than 20%) as well as formation of 1:1 mixtures of regioisomers.

Table 3. Scope of Arylzinc Reagents and Alkynes[a]

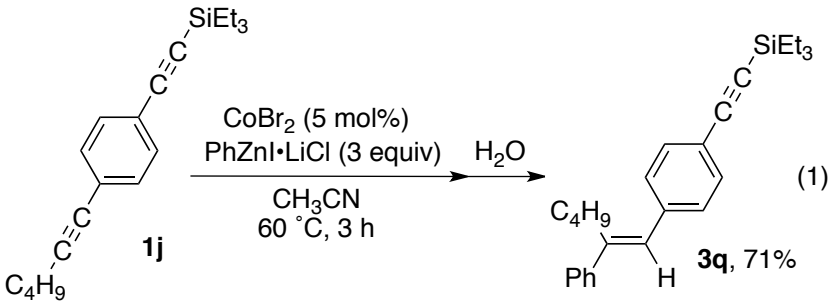


1b : R = CH_3, R' = C_5H_{11}
1c : R = CH_3, R' = Ph
1d : R = Ph, R' = Ph
1e : R = CH_3, R' = 2–$MeOC_6H_4$
1f : R = C_6H_{13}, R ' = ^{i}Pr
1g : R = $EtO_2C(CH_2)_4$, R' = 2-$MeOC_6H_4$
1h : R = C_4H_9, R' = 2-thienyl
1i : R = Ph, R' = $P(O)(OEt)_2$

2b : Ph
2c : 3-MeC_6H_4
2d : 2-MeC_6H_4
2e : 4-BrC_6H_4
2f : 4-$EtO_2CC_6H_4$
2g : 3-$MeOC_6H_4$
2h : 3-$CF_3C_6H_4$

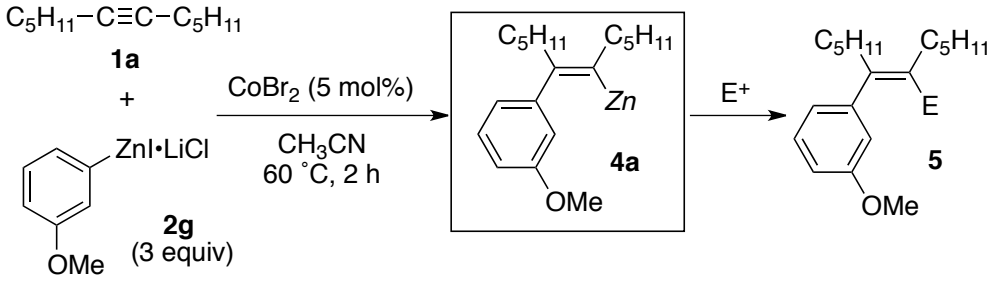
entry	1	2	time (h)	3	yield(%)[b]	3:3'[c]
1[d]	**1a**	**2b**	2 (4)[e]	**3b**	82 (77)[e]	–
2	**1a**	**2c**	3	**3c**	71	–
3	**1a**	**2d**	6	**3d**	trace	–
4	**1a**	**2e**	2	**3e**	64	–
5	**1a**	**2f**	6	**3f**	72	–
6	**1a**	**2g**	3	**3g**	74	–
7	**1a**	**2h**	5	**3h**	53	–
8	**1b**	**2b**	2	**3i**	64	55:45
9	**1c**	**2b**	3	**3j**	89	90:10
10	**1d**	**2b**	8	**3k**	20[f]	–
11[d]	**1e**	**2b**	1.5	**3l**	86	>99:1
12	**1f**	**2b**	1.5	**3m**	trace	–
13[d]	**1g**	**2b**	2	**3n**	86	>99:1
14[d]	**1h**	**2b**	2	**3o**	91	98:2
15[d,g]	**1i**	**2b**	2	**3p**	80	>99:1

[a] Reaction was performed on a 0.3 mmol scale.
[b] Isolated yield.
[c] Ratio of regioisomers was determined by ^{1}H NMR.
[d] P^{t}Bu$_3$ (10 mol%) was added.
[e] Reaction was performed on a 5 mmol scale.
[f] Yields were determined by ^{1}H NMR.
[g] Reaction was performed at room temperature.



With the reliable arylzincation reaction in hand, the author investigated the utility of the intermediary alkenylzinc compounds. Intermediate **4a** reacted with various electrophiles, such as deuterium oxide, iodine, and allyl bromide, to give the corresponding tetrasubstituted alkenes stereoselectively. As for trapping **4a** with allyl bromide, the addition of a catalytic amount of CuCN•2LiCl improved the yield of the corresponding product **5c**. Alkenylzinc intermediate **4a** participated in Negishi coupling reactions.[12] The reactions with iodobenzene and 4-iodobenzonitrile afforded the corresponding diarylethene derivatives **5d** and **5e** stereoselectively.

Scheme 1. Reactions of Alkenylzinc Intermediate **4a** with Various Electrophiles

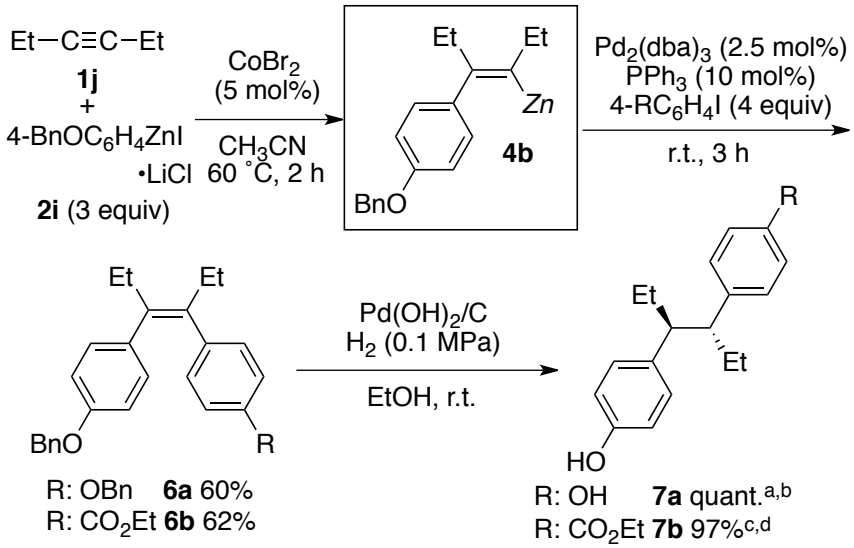


D_2O	: **5a** 77% (*E*/*Z* > 99/1) 92%D
I_2	: **5b** 60% (*E*/*Z* < 1/99)
CH_2=$CHCH_2Br$	: **5c** 65%[a] (*E*/*Z* < 1/99)
PhI	: **5d** 68%[b] (*E*/*Z* < 1/99)
4-IC_6H_4CN	: **5e** 53%[b] (*E*/*Z* < 1/99)

[a] 20 mol% of CuCN•2LiCl was added.
[b] 2.5 mol% of $Pd_2(dba)_3$ and 10 mol% of P(*o*-Tol)$_3$ were added.

Finally, the author attempted to synthesize a synthetic estrogen, *meso*-hexestrol, and its derivative.[13] Treatment of 3-hexyne (**1j**) with 4-benzyloxyphenylzinc reagent **2i** yielded alkenylzinc intermediate **4b**. Negishi coupling reactions of **4b** proceeded smoothly to yield *cis*-stilbestrol derivatives **6a** and **6b**. Reduction of **6a** and **6b** under hydrogen in the presence of $Pd(OH)_2/C$ afforded *meso*-hexestrol (**7a**) and its derivative **7b**, respectively.

Scheme 2. Diastereoselective Synthesis of *meso*-Hexestrol and Its Derivative



R: OBn **6a** 60%
R: CO_2Et **6b** 62%

R: OH **7a** quant.[a,b]
R: CO_2Et **7b** 97%[c,d]

[a] Reaction was performed in the presence of 10 mol% of $Pd(OH)_2/C$ for 4 h.
[b] Contained 4% of diastereomer.
[c] Reaction was performed in the presence of 100 mol% of $Pd(OH)_2/C$ for 0.5 h.
[d] Contained 5% of diastereomer.

Conclusion

The protocol described here provides a mild and efficient method for the preparation of multisubstituted alkenes. The application to the synthesis of *meso*-hexestrol and its derivative highlights the synthetic potential of this reaction.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (300 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to $SiMe_4$ at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. $CoBr_2$ was purchased from Sigma-Aldrich Co. THF was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. Acetonitrile was purchased from Wako Pure Chemical Industries, Ltd., and used after distillation from CaH_2. P^tBu_3 was obtained from Wako Pure Chemical Industries, Ltd., and diluted to prepare a 1.0 M hexane solution. $Pd(OH)_2/C$ was purchased from Sigma-Aldrich Co. All reactions were carried out under argon atmosphere.

Preparation of acetonitrile solutions of arylzinc reagents: An arylzinc reagent in THF were prepared from zinc powder (Wako Pure Chemical Industries, Ltd.,) and the corresponding aryl iodides in THF. An arylzinc iodide • LiCl complex in THF (1.0 M, 0.9 mmol, 0.9 mL) was placed in a 50-mL round-bottomed flask under argon. The THF solvent was evaporated in vacuo. Then, CH_3CN (0.5 mL) was added to the flask to afford an acetonitrile solution of an arylzinc reagent. The solutions were prepared prior to use.

Typical procedure for cobalt-catalyzed reactions: The reaction of 6-dodecyne with

4-methylphenylzinc iodide • LiCl complex is representative. $CoBr_2$ (3.3 mg, 0.015 mmol) was placed in a 20-mL reaction flask under argon. 6-Dodecyne (50 mg, 0.30 mmol) and P^tBu_3 (1.0 M hexane solution, 0.030 mL, 0.030 mmol) were added. Then, 4-methylphenylzinc iodide • LiCl complex in CH_3CN (0.90 mmol) was added. The mixture was stirred at 60 ˚C for 4 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded (*E*)-6-(4-methylphenyl)-6-dodecene (47 mg, 0.19 mmol) in 64% yield.

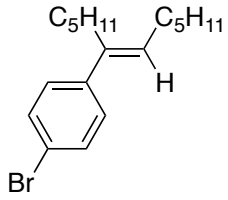
Synthesis of *meso*-hexestrol: $CoBr_2$ (3.3 mg, 0.015 mmol) was placed in a 20-mL reaction flask under argon. 3-Hexyne (25 mg, 0.30 mmol) was added. Then, 4-benzyloxyphenylzinc iodide • LiCl complex in CH_3CN (0.90 mmol) was added. The mixture was stirred at 60 ˚C for 2 h. The mixture was cooled to 0 ˚C. A THF solution of 1-benzyloxy-4-iodobenzene (372 mg, 1.2 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), and PPh_3 (7.9 mg, 0.030 mmol) was added to the solution. The mixture was warmed to 25 ˚C and stirred for 3 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane / ethyl acetate (20/1) as an eluent afforded (*Z*)-3,4-bis(4-benzyloxyphenyl)-3-hexene contaminated with 4,4'-dibenzyloxybiphenyl. Further purification by GPC afforded pure (*Z*)-3,4-bis(4-benzyloxyphenyl)-3-hexene (81 mg, 0.18 mmol) in 60% yield.

(*Z*)-3,4-Bis(4-benzyloxyphenyl)-3-hexene (111 mg, 0.25 mmol) was reduced under hydrogen (0.1 MPa) in the presence of $Pd(OH)_2/C$ (20 wt% of Pd, 13 mg, 0.025 mmol) in ethanol (10 mL). The mixture was filtrated through a pad of Celite, and the filtrate was concentrated in vacuo. Chromatographic purification on silica gel by using hexane/ethyl acetate (5/1) as an eluent afforded *meso*-hexestrol (68 mg, 0.25 mmol) in quantitative yield (including 4% of diastereomer).

Characterization Data

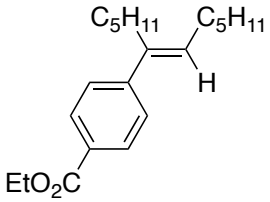
Compounds **7a** is commercially available. Compounds **3a**[6b], **3b**[6b], **3c**[6b], **3g**[6b], **3k**[14], **3j**[6b], **3o**[4a], and **3p**[15] are known compounds and showed the identical spectra according to the literature.

(*E*)-6-(4-Bromophenyl)-6-dodecene (3e)



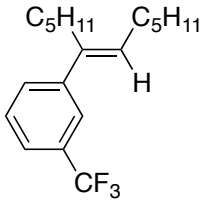
oil. IR (neat) 2927, 2857, 1890, 1587, 1487, 1378, 1073, 1009 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–0.92 (m, 6H), 1.26–1.45 (m, 12H), 2.16 (q, *J* = 7.2 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 5.62 (t, *J* = 7.2 Hz, 1H), 7.18–7.21 (m, 2H), 7.38–7.41 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 14.24, 14.27, 22.69, 22.80, 28.48, 28.74, 29.68 (Two signals merge.), 31.83, 31.92, 120.29, 128.17, 130.00, 131.33, 139.24, 142.57; Found: C, 66.60; H, 8.25%. Calcd for $C_{18}H_{27}Br$: C, 66.87; H, 8.42%.

(*E*)-6-(4-Ethoxycarbonylphenyl)-6-dodecene (3f)



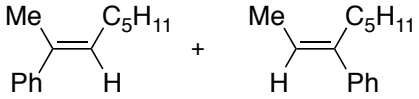
oil. IR (neat) 2928, 2858, 1717, 1607, 1466, 1273, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82–0.93 (m, 6H), 1.23–1.48 (m, 15H), 2.20 (q, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.74 (t, *J* = 7.2 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 2H) ; ^{13}C NMR ($CDCl_3$) δ 14.22, 14.27, 14.56, 22.67, 22.79, 28.52, 28.83, 29.60, 29.64, 31.84, 31.92, 60.96, 126.31, 128.52, 129.68, 131.32, 139.65, 148.24, 166.85; Found: C, 79.71; H, 9.92%. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19%.

(*E*)-6-(3-Trifluoromethylphenyl)-6-dodecene (3h)



oil. IR (neat) 2929, 2360, 1334, 1166, 1128, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.93 (m, 6H), 1.26–1.50 (m, 12H), 2.19 (q, *J* = 7.2 Hz, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 5.68 (t, *J* = 7.2 Hz, 1H), 7.37–7.56 (m, 4H) ; ^{13}C NMR ($CDCl_3$) δ 14.19, 14.26, 22.64, 22.80, 28.44, 28.79, 29.65, 29.72, 31.84, 31.89, 123.21 (q, *J* = 2.0 Hz), 124.52 (q, *J* = 271 Hz), 128.71, 129.76, 130.64 (q, *J* = 32 Hz), 131.01, 139.23, 144.45 (Two sp^2 signals merge.); Found: C, 72.79; H, 8.57%. Calcd for $C_{19}H_{27}F_3$: C, 73.05; H, 8.71%.

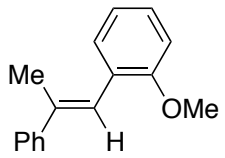
(*E*)-2-Phenyl-2-octene and (*E*)-3-Phenyl-2-octene (3i, 55:45 mixture of regioisomers)



(55/45)

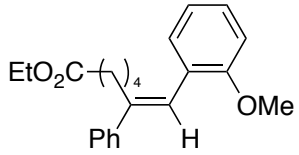
oil. IR (neat) 2926, 1598, 1494, 1378, 1028, 830, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.93 (m, 3H), 1.25–1.48 (m, 6H), 1.79 (d, *J* = 6.9 Hz, 3H × 0.45), 2.03 (s, 3H × 0.55), 2.19 (q, *J* = 7.2 Hz, 2H × 0.55), 2.49 (t, *J* = 7.5 Hz, 2H × 0.45), 5.70–5.81 (m, 1H), 7.18–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.27, 14.29, 14.34, 15.93, 22.72, 22.82, 28.34, 28.95, 29.50, 29.56, 31.82, 31.99, 122.84, 125.77, 126.39, 126.51, 126.58, 128.30, 129.04, 134.62, 141.29, 143.67, 144.25 (Two signals merge.); Found: C, 88.89; H, 10.90%. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71%.

(*E*)-1-(2-Methoxyphenyl)-2-phenyl-1-propene (3l)



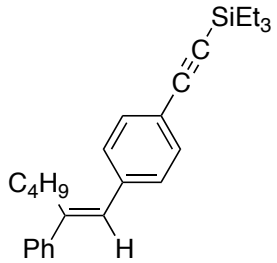
oil. IR (neat) 3017, 2935, 1597, 1486, 1244, 1029, 752, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.84 (s, 3H), 6.89–7.00 (m, 3H), 7.23–7.39 (m, 5H), 7.55–7.58 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 17.55, 55.60, 110.55, 120.21, 123.45, 126.22, 127.23, 127.39, 128.22, 128.40, 130.50, 137.11, 143.89, 157.62; Found: C, 85.79; H, 7.31%. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19%.

Ethyl (*E*)-7-(2-methoxyphenyl)-6-phenyl-6-heptenoate (3n)



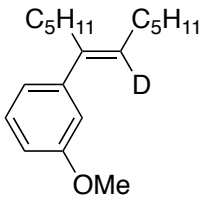
oil. IR (neat) 2936, 1733, 1463, 1245, 1030, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3H), 1.40–1.48 (m, 2H), 1.57–1.64 (m, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 2.68 (t, *J* = 8.1 Hz, 2H), 3.81 (s, 3H), 4.07 (q, *J* = 7.5 Hz, 2H), 6.76 (s, 1H), 6.88–7.00 (m, 2H), 7.25–7.37 (m, 5H), 7.46–7.49 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 14.39, 25.13, 28.38, 29.99, 34.27, 55.56, 60.34, 110.60, 120.31, 124.36, 126.86, 127.23, 127.31, 128.36, 128.46, 129.77, 142.30, 142.82, 157.63, 173.82; Found: C, 77.97; H, 7.96%. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74%.

(*E*)-1-(4-Triethylsilylethynylphenyl)-2-phenyl-1-hexene (3q)



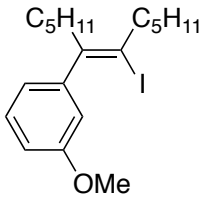
oil. IR (neat) 2956, 2154, 1497, 1226, 1018, 833, 727, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (q, *J* = 7.8 Hz, 6H), 0.84 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.8 Hz, 9H), 1.27–1.43 (m, 4H), 2.68 (t, *J* = 8.4 Hz, 2H), 6.64 (s, 1H), 7.24–7.48 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 4.64, 7.72, 14.05, 22.96, 30.22, 31.04, 92.07, 106.67, 121.42, 126.76, 127.47, 127.67, 128.55, 128.77, 132.12, 138.70, 143.12, 144.41; Found: C, 83.28; H, 9.28%. Calcd for $C_{26}H_{34}Si$: C, 83.36; H, 9.15%.

(*E*)-6-Deuterio-7-(3-methoxyphenyl)-6-dodecene (5a)



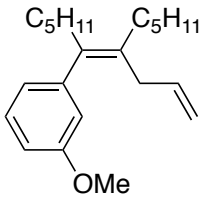
oil. ^{1}H NMR ($CDCl_3$) δ 0.83–0.82 (m, 6H), 1.23–1.43 (m, 12H), 2.17 (t, *J* = 7.2 Hz, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 3.18 (s, 3H), 6.75–6.78 (m, 1H), 6.88–6.95 (m, 2H), 7.18–7.24 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.26, 14.27, 22.70, 22.81, 28.59, 28.63, 29.74, 29.90, 31.84, 32.04, 55.35, 111.60, 112.53, 119.10, 129.18, 129.30 (t, *J* = 22 Hz), 140.02, 145.30, 159.64.

(*Z*)-6-Iodo-7-(3-methoxyphenyl)-6-dodecene (5b)



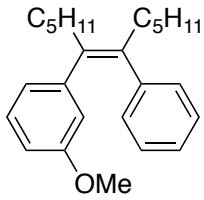
oil. IR (neat) 2927, 2857, 1597, 1579, 1466, 1287, 1050, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (t, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 6.9 Hz, 3H), 1.25–1.38 (m, 10H), 1.54–1.62 (m, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 6.60–6.66 (m, 2H), 6.80–6.83 (m, 1H), 7.22–7.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.20, 14.26, 22.62, 22.79, 28.08, 29.62, 31.00, 31.68, 34.78, 41.32, 55.40, 106.29, 112.29, 114.28, 120.88, 129.23, 147.16, 149.07, 159.35; HRMS Found: 400.1260 (Δ = 0.9 ppm), Calcd for $C_{19}H_{29}IO$: 400.1263.

(*Z*)-4-Pentyl-5-(3-methoxyphenyl)-1,4-decadiene (5c)



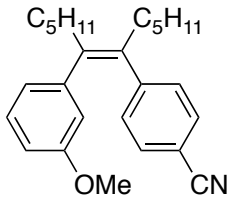
oil. IR (neat) 2957, 1577, 1466, 1285, 1052 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81–0.94 (m, 6H), 1.23–1.46 (m, 12H), 2.13 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.58 (d, *J* = 6.3 Hz, 2H), 3.79 (s, 3H), 4.89–4.95 (m, 2H), 5.63–5.76 (m, 1H), 6.63 (m, 2H), 7.16–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.28, 14.30, 22.76, 22.83, 28.31, 28.73, 30.90, 32.04, 32.33, 34.23, 37.78, 55.30, 111.40, 114.59, 115.13, 121.44, 128.91, 133.48, 137.67, 138.00, 145.45, 159.30; Found: C, 83.83; H, 11.18%. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90%.

(*Z*)-6-(3-Methoxyphenyl)-7-phenyl-6-dodecene (5d)



oil. IR (neat) 2956, 2858, 1597, 1466, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84–0.88 (m, 6H), 1.29–1.40 (m, 12H), 2.49–2.54 (m, 4H), 3.57 (s, 3H), 6.44–6.45 (m, 1H), 6.55–6.56 (m, 2H), 6.92–7.06 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 14.28 (Two signals merge.), 22.76 (Two signals merge.), 28.32, 28.42, 32.03, 32.06, 34.36, 34.52, 55.18, 111.42, 115.65, 122.46, 125.60, 127.55, 128.36, 129.81, 138.29, 138.52, 143.77, 145.08, 158.83; Found: C, 85.53; H, 9.74%. Calcd for $C_{25}H_{34}O$: C, 85.66; H, 9.78%.

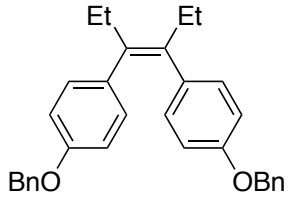
(*Z*)-6-(4-Cyanophenyl)-7-(3-methoxyphenyl)-6-dodecene (5e)



oil. IR (neat) 2929, 2227, 1603, 1466, 1285, 841 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.87 (m, 6H), 1.27–1.28 (m, 12H), 2.49–2.54 (m, 4H), 3.63 (s, 3H), 6.41–6.49 (m, 2H), 6.57–6.60 (m, 1H), 6.96–7.05 (3H), 7.33–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.19, 14.24, 22.66, 22.70, 28.17, 28.26,

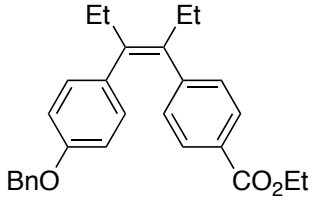
31.84, 31.96, 33.96, 34.50, 55.21, 109.21, 111.50, 115.69, 119.39, 122.37, 128.79, 130.51, 131.49, 136.98, 140.62, 144.09, 149.09, 159.07; HRMS Found: 375.2559 (Δ = –0.8 ppm), Calcd for $C_{26}H_{33}NO$: 375.2562.

(*Z*)-3,4-Bis(4-benzyloxyphenyl)-3-hexene (6a)



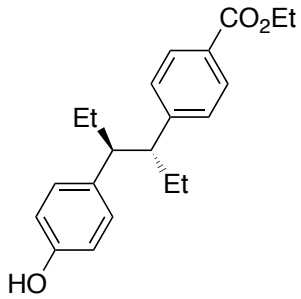
oil. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, *J* = 7.2 Hz, 6H), 2.52 (q, *J* = 7.2 Hz, 4H), 4.95 (s, 4H), 6.68–6.72 (m, 8H), 6.85–6.68 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 13.54, 27.53, 70.00, 113.96, 127.75, 128.03, 128.67, 130.99, 136.16, 137.35, 138.36, 156.68.

(*Z*)-3-(4-Benzyloxyphenyl)-4-(4-ethoxycarbonylphenyl)-3-hexene (6b)



oil. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 6H), 1.35 (t, *J* = 7.2 Hz, 3H), 2.50–2.57 (m, 4H), 4.31 (q, *J* = 7.2 Hz, 2H), 4.94 (s, 2H), 6.66–6.69 (m, 2H), 6.82–6.85 (m, 2H), 7.00–7.03 (m, 2H), 7.29–7.37 (m, 5H), 7.75–7.77 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.45, 13.43, 14.51, 27.25, 27.58, 60.88, 70.00, 114.08, 127.54, 127.77, 128.05, 128.67, 128.99, 129.99, 130.91, 135.36, 137.20, 138.25, 140.08, 147.84, 157.02, 166.92.

3-(4-Ethoxycarbonylphenyl)-4-(4-hydroxyphenyl)hexane (7b)



solid. m.p. = 138–139 ˚C. IR (nujol) 3330, 3184, 1685, 1594, 1461, 1170, 853, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.48–0.54 (m, 6H), 1.25–1.46 (m, 7H), 2.50–2.60 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 6.79–6.83 (m, 2H), 6.97–7.01 (m, 2H), 7.21–7.24 (m, 2H), 7.97–8.00 (m, 2H) (The OH signal was not detected.); ^{13}C NMR ($CDCl_3$) δ 12.30, 12.33, 14.55, 27.30, 27.51, 57.33, 54.73, 60.96, 115.38, 128.46, 128.57, 129.40, 129.68, 150.71, 167.00 (Two signals merge.); HRMS Found: 326.1879 (Δ = –0.8 ppm), Calcd for $C_{21}H_{26}O_3$: 326.1882.

References and Notes

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Chapter 3

Cobalt-Catalyzed Benzylzincation of Alkynes

Cobalt salts catalyze benzylzincation of alkynes to afford benzylated multisubstituted alkenes with high regio and stereoselectivity. The scope of the reaction is wide enough to apply unfunctionalized alkynes as well as arylacetylenes. The reaction offers a new route to the regio- and stereoselective synthesis of an estrogen receptor antagonist.

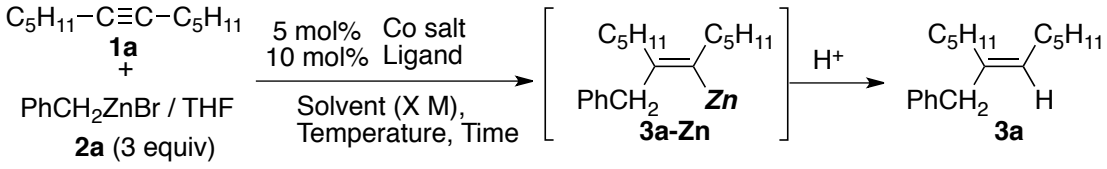
Introduction

Multisubstituted alkenes are among the most important structures in organic chemistry. In particular, multisubstituted alkenes bearing a benzyl group are essential fragments present in the key precursors of lignans[1] and in pharmacologically important molecules.[2] Although there are numerous methods for the preparation of alkenes, the regio- and stereoselective synthesis of benzylated multisubstituted alkenes is still challenging. Thus, development of general and efficient routes to benzylated alkenes is in high demand. In Chapter 3, the author wishes to report cobalt-catalyzed[3] benzylzincation[4–7] of alkynes to afford benzylated multisubstituted alkenes. The reaction is applicable to the regio- and stereoselective synthesis of an estrogen receptor antagonist.

Results and Discussion

Treatment of 6-dodecyne (**1a**) with benzylzinc bromide (**2a**) in the presence of cobalt(II) bromide and triphenylphosphine in propionitrile at 60 ˚C for 20 min followed by hydrolysis gave the corresponding benzylated product **3a** in 74% yield with 89/11 ratios on the *E*/*Z* selectivity (Table 1, entry 1).[8,9] Other cobalt salts also provided **3a** in moderate yields with good *E* selectivity except cobalt fluoride(II), which completely suppressed the reaction (Table 1, entry 2 vs entries 3 and 4). The study on the effect for phosphorous ligands revealed that employing electron-rich tri(4-methoxyphenyl)phosphine afforded **3a** in a better yield (Table 1, entry 10). Further investigation showed the reaction proceeded at room temperature when the reaction was performed in a higher concentration (Table 1, entry 11). The use of propionitrile as the solvent was crucial and the use of acetonitrile retarded the reaction (Table 1, entry 11 vs. entry 12). When the reaction was carried out in THF, no benzylated product was obtained (Table 1, entry 13).

Table 1. Optimization of the Benzylzincation of 6-Dodecyne[a]



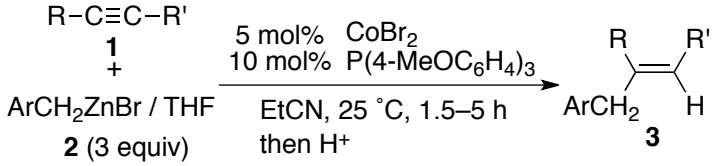
Entry	Co Salt/Ligand	Solvent (X M)	Temperature/Time	Yield (*E*/*Z*)[b]
1	$CoBr_2/PPh_3$	EtCN (0.1)	60 ˚C/20 min	74% (89/11)
2	CoF_2/PPh_3	EtCN (0.1)	60 ˚C/20 min	0
3	$CoCl_2/PPh_3$	EtCN (0.1)	60 ˚C/20 min	57% (93/7)
4	$Co(OAc)_2/PPh_3$	EtCN (0.1)	60 ˚C/20 min	62% (92/8)
5	$CoBr_2/PMe_3$	EtCN (0.1)	60 ˚C/20 min	71% (89/19)
6	$CoBr_2/P(OEt)_3$	EtCN (0.1)	60 ˚C/20 min	40% (92/8)
7	$CoBr_2/P(2\text{-furyl})_3$[c]	EtCN (0.1)	60 ˚C/20 min	0
8	$CoBr_2/P^tBu_3$	EtCN (0.1)	60 ˚C/20 min	0
9	$CoBr_2$/dppm	EtCN (0.1)	60 ˚C/20 min	0
10	$CoBr_2/P(4\text{-}MeOC_6H_4)_3$	EtCN (0.1)	60 ˚C/20 min	82% (87/12)
11	$CoBr_2/P(4\text{-}MeOC_6H_4)_3$	EtCN (0.3)	25 ˚C/1.5 h	90%[c] (96/4)
12	$CoBr_2/P(4\text{-}MeOC_6H_4)_3$	MeCN (0.3)	25 ˚C/1.5 h	40% (>99/1)
13	$CoBr_2/P(4\text{-}MeOC_6H_4)_3$	THF (0.3)	25 ˚C/1.5 h	0

[a] Reaction was performed on a 0.3 mmol scale.
[b] Yields and *E*/*Z* ratios were determined by ^1H NMR spectroscopy.
[c] Isolated yield.

The scope of benzylzinc reagents and alkynes was studied, and the results are summarized in Table 1. Symmetrical alkynes, such as 4-octyne (**1b**) and 1,4-dibenzyloxy-2-butyne (**1c**), participated in the reaction in high yield and with high stereoselectivity (Table 2, entries 1–3). The reaction of terminal alkynes (**1d–1f**) proceeded regioselectively to yield *gem*-disubstituted alkenes (Table 2, entries 4–6). However, the reaction of 2-octyne (**1g**) provided a 48:52 mixture of regioisomers (Table 2, entry 7). Unfortunately, sterically hindered 2-methyl-3-decyne (**1h**) failed to react (Table 2, entry 8). The reactions with 4-methylbenzyl- and 3-methylbenzylzinc bromide afforded **3i** and **3j** in 93 and 94% yields, respectively (Table 2, entries 9 and 10). A bulky 2-methylbenzylzinc reagent also participated in the reaction (Table 2, entry 11). The benzylzincation with 2-thienylmethylzinc bromide (**2e**) and 3-methoxybenzylzinc bromide (**2f**)

occurred with perfect stereoselectivity (Table 2, entries 12 and 13). The benzylzinc reagent bearing a chloro or bromo group was also applicable to provide the corresponding product without any observable side reactions (Table 2, entries 14 and 15). Attempts on benzylzincation with electron-deficient 4-$CF_3C_6H_4CH_2ZnBr$ (**2i**) failed and **1b** was recovered. (Table 2, entry 16). It is worth noting that no cyclotrimerization of the alkyne was occurred owing to the mild reaction conditions.[10]

Table 2. Scope of Benzylzinc Reagents and Aliphatic Alkynes[a]



1b : R = C_3H_7, R' = C_3H_7
1c : R = $BnOCH_2$, R' = CH_2OBn
1d : R = ^{t}Bu, R' = H
1e : R = $HO(CH_2)_2$, R' = H
1f : R = $C_5H_{11}CH(OBn)$, R' = H
1g : R = CH_3, R' = C_5H_{11}
1h : R = ^{i}Pr, R' = C_6H_{13}

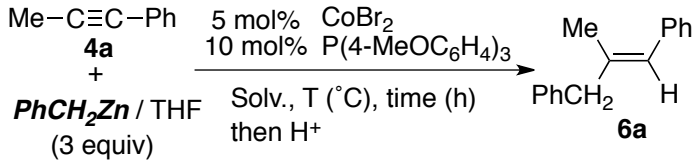
2b : Ar = 4-MeC_6H_4
2c : Ar = 3-MeC_6H_4
2d : Ar = 2-MeC_6H_4
2e : Ar = 2-thienyl
2f : Ar = 3-$MeOC_6H_4$
2g : Ar = 4-ClC_6H_4
2h : Ar = 4-BrC_6H_4
2i : Ar = 4-$CF_3C_6H_4$

entry	1	2	3	Yield(%)[b]	*E*/*Z*[c]	r.r.[d]
1	**1b**	**2a**	**3b**	86	96:4	–
2[e]	**1b**	**2a**	**3b**	94	95:5	–
3	**1c**	**2a**	**3c**	88	<1:99	–
4	**1d**	**2b**	**3d**	94	–	>99:1
5	**1e**	**2a**	**3e**	60	–	93:7
6	**1f**	**2a**	**3f**	89	–	91:9
7	**1g**	**2a**	**3g**	83	nd[f]	48:52
8[g]	**1h**	**2a**	**3h**	trace	–	–
9	**1b**	**2b**	**3i**	93	97:3	–
10	**1b**	**2c**	**3j**	94	96:4	–
11	**1b**	**2d**	**3k**	85	97:3	–
12	**1b**	**2e**	**3l**	79	>99:1	–
13	**1b**	**2f**	**3m**	69	>99:1	–
14[h]	**1b**	**2g**	**3n**	94	97:3	–
15[i]	**1b**	**2h**	**3o**	75	96:4	–
16	**1b**	**2i**	**3p**	trace	–	–

[a] Reaction was performed on a 0.3 mmol scale.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy.
[d] Regioisomeric ratio determined by ^{1}H NMR spectroscopy.
[e] Performed on a 5 mmol scale.
[f] Not determined.
[g] Performed at 60 ˚C.
[h] $CoBr_2$ (10 mol%) and P(3,5-Me_2-4-$MeOC_6H_2)_3$ (20 mol%) were used.
[i] $CoBr_2$ (10 mol%) and P(4-$MeOC_6H_4)_3$ (20 mol%) were used.

The author next examined the reaction of the more reactive aryl-substituted alkyne **4a** with benzylzinc bromide (**2a**). Although the reaction completed smoothly, the benzylated product was a 41:59 mixture of regioisomers (Table 3, entry 1). Interestingly, complexation of the zinc reagent with lithium halide resulted in perfect regioselectivitiy, albeit the yields of **6a** were low (Table 3, entries 2–3).[11,12] The reaction with $PhCH_2ZnBr$•MgClBr (**2ac**), which was prepared from $PhCH_2MgCl$ and $ZnBr_2$ also afforded **6a** with perfect regioselectivity. Further investigation revealed that the use of dibenzylzinc reagent **5a** was effective and that the reaction proceeded at 25 ˚C to give **6a** in 54% yield. Finally, the author found that the addition of propionitrile was not crucial for the reaction of aryl-substituted alkynes. Hence, the reaction was carried out without propionitrile to give **6a** in 82% yield (Table 3, entry 6). It is worth noting that benzylmetalation did not proceed when benzylmagnesium reagent was employed (Table 3, entry 7).

Table 3. Optimization of Benzylzincation of 1-Phenyl-1-propyne

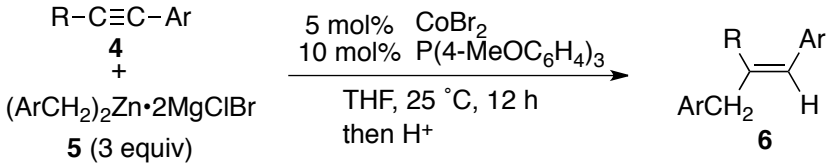


entry	zinc reagent	solvent	temp (˚C)	time (h)	yield (%)[a]	r.r.[b]
1	$PhCH_2ZnBr$ (**2a**)	EtCN	25	1.5	78[c]	41:59
2	$PhCH_2ZnBr$•LiCl (**2aa**)	EtCN	60	12	33	>99:1
3	$PhCH_2ZnBr$•LiBr (**2ab**)	EtCN	60	12	40	>99:1
4	$PhCH_2ZnBr$•MgClBr (**2ac**)	EtCN	60	12	27	>99:1
5	$(PhCH_2)_2Zn$•2MgClBr (**5a**)	EtCN	25	12	54	>99:1
6	$(PhCH_2)_2Zn$•2MgClBr (**5a**)	none	25	12	82	>99:1
7	$PhCH_2MgCl$	none	25	12	13[d]	>99:1

[a] ^1H NMR yield. *E/Z* ratios of **6a** was over 99:1 unless otherwise noted.
[b] Regioisomeric ratio determined by ^1H NMR spectroscopy.
[c] *E/Z* ratio of **6a** was 93:7.
[d] *E/Z* ratio of **6a** was 62:38.

The scope of dibenzylzinc reagents and aryl-substituted alkynes is summarized in Table 4. The reaction of aryl-substituted alkynes bearing an electron-withdrawing group and an electron-donating group reacted smoothly (Table 4, entries 1 and 2). The reaction of sterically hindered 1-(2-methylphenyl)-1-octyne (**4d**) provided the benzylated product **6d** in high yield. The ester group of **4e** survived and **6e** was obtained in 61% yield (Table 4, entry 4). The reaction with 4-methyl-, 4-fluoro-, and 4-methoxybenzylzinc reagents proceeded smoothly to give the corresponding benzylated products (Table 4, entries 5–7). The sterically hindered 2-methylbenzylzinc reagents reacted in moderate yield (Table 4, entry 8).

Table 4. Scope of Dibenzylzinc Reagents and Aryl-Substituted Alkynes[a]



4b : R = C_6H_{13}, Ar = 4-$CF_3C_6H_4$
4c : R = C_6H_{13}, Ar = 4-$MeOC_6H_4$
4d : R = C_6H_{13}, Ar = 2-MeC_6H_4
4e : R = $EtO_2C(CH_2)_4$, Ar = Ph
4f : R = C_6H_{13}, Ar = Ph

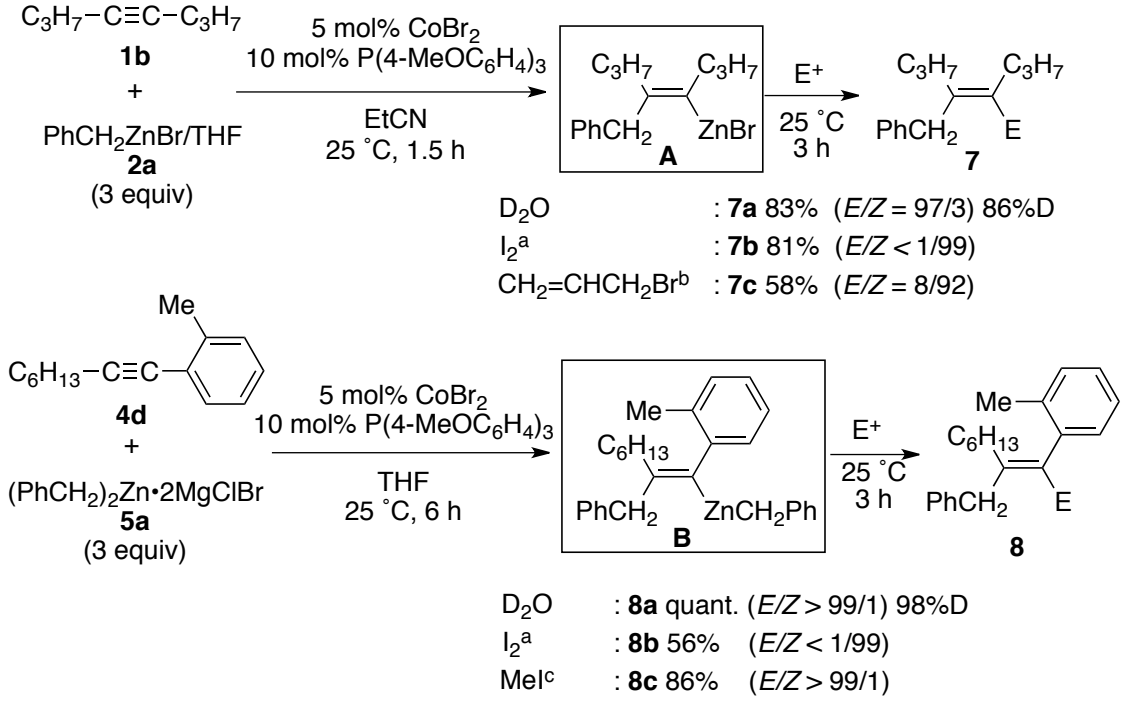
5a : Ar = Ph
5b : Ar = 4-MeC_6H_4
5c : Ar = 4-FC_6H_4
5d : Ar = 4-$MeOC_6H_4$
5e : Ar = 2-MeC_6H_4

entry	4	5	6	yield(%)[b]	*E/Z*[c]	r.r.[d]
1	**4b**	**5a**	**6b**	71	>99:1	>99:1
2	**4c**	**5a**	**6c**	50	>99:1	90:10
3	**4d**	**5a**	**6d**	96	>99:1	>99:1
4	**4e**	**5a**	**6e**	61	97:3	94:6
5	**4f**	**5b**	**6f**	66	97:3	95:5
6	**4f**	**5c**	**6g**	62	97:3	95:5
7	**4f**	**5d**	**6h**	63	97:3	95:5
8	**4f**	**5e**	**6i**	40	92:8	89:11

[a] Reaction was performed on a 0.3 mmol scale.
[b] Isolated yield.
[c] *E/Z* ratio of the major regioisomer **6** was determined by ^{1}H NMR spectroscopy.
[d] Regioisomeric ratio was determined by ^{1}H NMR spectroscopy.

Having the efficient protocols for the benzylzincation reaction in hand, the author examined the reaction of alkenylzinc intermediates with various electrophiles. The alkenylzinc intermediate **A**, which was prepared by the reaction of **1b** with **2a**, reacted with D_2O and I_2 to afford **7a** and **7b**, respectively (Scheme 1, top). As for the reaction of allyl bromide, the addition of ^{i}PrMgCl•LiCl[11a] to the alkenylzinc intermediate **A** was necessary due to the low reactivity of **A**. The alkenylzinc intermediate **B** also reacted smoothly to afford tetrasubstituted alkenes **8a**–**8c** regio- and stereoselectively in good yields (Scheme 1, bottom).

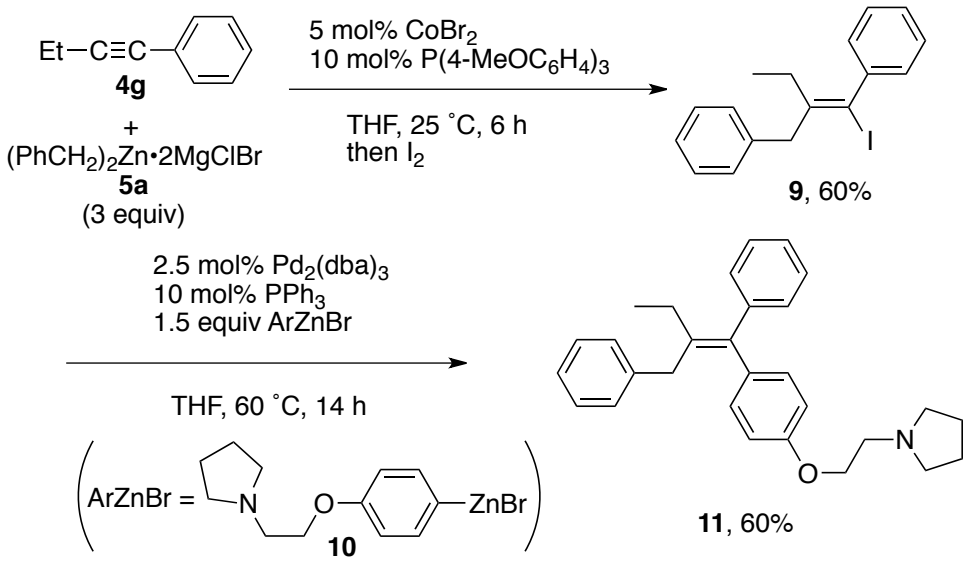
Scheme 1. Reactions of Alkenylzinc Intermediates with Electrophiles



Reagents and Conditions
[a] 0 °C, 5 h.
[b] (i) ^{i}PrMgCl•LiCl/THF (3 equiv.), 0 °C 0.5 h; (ii) CuCN•2LiCl (20 mol%), allyl bromide.
[c] CuCN•2LiCl (20 mol%), MeI.

Finally, the author attempted to synthesize estrogen receptor antagonist **11** (Scheme 2). Benzylzincation of **4g** followed by an addition of iodine gave the corresponding vinyl iodide **9** in 60% yield. Then, Negishi coupling of **9** with arylzinc reagent **10** afforded **11** in 60% yield. The efficient two-step synthesis highlights the synthetic advantage of the benzylzincation.

Scheme 2. Regio- and Diastereoselective Synthesis of Estrogen Receptor Antagonist



Conclusion

The author has developed cobalt-catalyzed benzylzincation reaction of alkynes. The reaction proceeded smoothly at ambient temperature to afford tri- and tetrasubstituted benzylated alkenes regio- and stereoselectively.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (300 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to $SiMe_4$ at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. $CoBr_2$ was purchased from Sigma-Aldrich Co. $P(4\text{-}MeOC_6H_4)_3$ was obtained from Tokyo Chemical Industries, Ltd. THF was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. Propionitrile was purchased from Tokyo Chemical Industries, Ltd., and used after distillation from CaH_2 and stored under argon. Benzylzinc reagents were prepared from the corresponding benzyl bromides and zinc powder. Dibenzylzinc reagents were prepared from the corresponding benzylmagnesium reagents and $ZnBr_2$. All reactions were carried out under argon atmosphere.

Typical procedure for the preparation of benzylzinc reagents: Zn powder (13 mmol) was placed in a 50-mL reaction flask. THF (10 mL) wad added. TMSCl (0.01 mmol) and 1,2-dibromoethane (0.05 mmol) were added subsequently. The mixture was stirred for 10 min at room temperature. Then, the corresponding benzyl bromide (10 mmol) was added slowly to keep the solvent gently refluxed. After addition, the mixture was stirred for 3 h at room temperature.

Typical procedure for cobalt-catalyzed benzylzincation of dialkylacetylenes and terminal acetylenes: The reaction of 6-dodecyne with benzylzinc bromide is representative (eq. 1). $CoBr_2$ (3.3 mg, 0.015 mmol) and $P(4\text{-}MeOC_6H_4)_3$ (10.7 mg, 0.03 mmol) were placed in a 20-mL reaction flask under argon. Propionitrile (1 mL) and benzylzinc bromide (0.90 mmol, 0.90 mL, 1 M solution of THF) were added. Then, 6-dodecyne (**1a**, 50 mg, 0.30 mmol) was added. The mixture was stirred at 25 ˚C for 1.5 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded (*E*)-6-phenylmethyl-6-dodecene (**3a**, 70 mg, 0.27 mmol) in 90% yield.

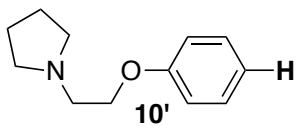
Typical procedure for the preparation of dibenzylzinc reagents: Anhydrous $ZnBr_2$ (10 mmol) was placed in a 50-mL reaction flask and dried for 20 min at 150–170 ˚C under high vacuum. The flask was refilled with argon and cooled to 0 ˚C. The corresponding benzylmagnesium chloride (20 mmol, 20 mL, 1 M in THF) was slowly added to the flask and the mixture was stirred for 10 min. Then, the mixture was warmed to room temperature.

Typical procedure for cobalt-catalyzed benzylzincation of arylacetylenes: The reaction of 1-(2-methylphenyl)-1-octyne with dibenzylzinc reagent is representative (Table 3, entry 3). $CoBr_2$ (3.3 mg, 0.015 mmol) and $P(4\text{-}MeOC_6H_4)_3$ (10.7 mg, 0.03 mmol) were placed in a 20-mL reaction flask under argon. 1-(2-Methylphenyl)-1-octyne (**4d**, 60 mg, 0.30 mmol) was added. Then, the dibenzylzinc reagent (**5a**, 0.90 mmol, 1.8 mL, 0.5 M in THF) was added. The mixture was stirred at 25 ˚C for 12 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded (*E*)-1-(2-methylphenyl)-2-phenylmethyl-1-octene (**6d**, 84 mg, 0.29 mmol) in 96% yield.

Synthesis of Estrogen Receptor Antagonist 11:

Synthesis of **9**: $CoBr_2$ (3.3 mg, 0.015 mmol) and $P(4\text{-}MeOC_6H_4)_3$ (10.7 mg, 0.03 mmol) were placed in a 20-mL reaction flask under argon. 1-Phenyl-1-butyne (39 mg, 0.30 mmol) was added. Then, the dibenzylzinc reagent (**5a**, 0.90 mmol, 1.8 mL, 0.5 M in THF) was added. The mixture was stirred at 25 ˚C for 6 h. The mixture was cooled to 0 ˚C. I_2 (2.0 mmol, 1 mL, 2 M in THF) was slowly added at 0 ˚C. Then, the mixture was warmed to 25 ˚C and stirred for 3 h. A saturated aqueous solution of $Na_2S_2O_3$ (5 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded (*Z*)-1-iodo-1-phenyl-2-phenylmethyl-1-butene (**9**) contaminated with 1,2-diphenylethane. Further purification by GPC afforded pure 1-iodo-1-phenyl-2-phenylmethyl-1-butene (**9**, 62 mg, 0.18mmol, *E*/*Z* = 2/98) in 60% yield.

Synthesis of **11**: $Pd_2(dba)_3$ (3.4 mg, 0.00375 mmol) and PPh_3 (3.9 mg, 0.015 mmol) were placed in a 20-mL reaction flask under argon. THF (2 mL) and (*Z*)-1-iodo-1-phenyl-2-phenylmethyl-1-butene (105 mg, 0.30 mmol) were subsequently added. Then, arylzinc reagent **10**, prepared from the corresponding arylmagnesium reagent and $ZnBr_2$, was added and the mixture was stirred at 60 ˚C for 14 h. The mixture was diluted by ethyl acetate (50 mL). The organic layer was washed with an aqueous solution of HCl (1 M, 5 mL) three times (**11•HCl** remained in the organic layer and only **10'•HCl** was partitioned in the aqueous layer). The organic part was washed by an aqueous solution of NaOH (1 M) and dried over Na_2SO_4 and concentrated in vacuo (**11•HCl** was naturalized to **11**). Chromatographic purification on silica gel by using $CHCl_3$ / MeOH / Et_3N = 30 : 1 : 0.1 as an eluent afforded **11** (74 mg, 0.18 mmol) in 60% yield.

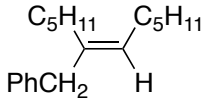


10'

Characterization Data

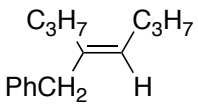
Compounds **6a**[13] and **11**[2] are known compounds and showed the identical spectra that are shown in the literature.

(*E*)-6-phenylmethyl-6-dodecene (3a)



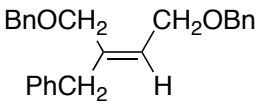
oil. IR (neat) 2927, 1718, 1493, 1378, 1074, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84–0.91 (m, 6H), 1.07–1.35 (m, 12H), 1.92 (t, *J* = 8.1 Hz, 2H), 2.01 (q, *J* = 7.5 Hz, 2H), 3.29 (s, 2H), 5.20 (t, *J* = 7.5 Hz, 1H), 7.15–7.19 (m, 2H), 7.26–7.29 (m, 3H) ; ^{13}C NMR ($CDCl_3$) δ 14.24, 14.29, 22.75, 22.79, 27.99, 28.15, 29.67, 29.92, 31.83, 32.05, 43.81, 125.97, 127.65, 128.30, 129.12, 138.82, 140.99; Found: C, 88.42; H, 11.51%. Calcd for $C_{19}H_{30}$: C, 88.30; H, 11.70%.

(*E*)-4-phenylmethyl-4-octene (3b)



oil. IR (neat) 3027, 2959, 1493, 732, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81–0.95 (m, 6H), 1.30–1.46 (m, 4H), 1.92 (t, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 7.5 Hz, 2H), 3.29 (s, 2H), 5.74 (t, *J* = 7.2 Hz, 1H), 7.16–7.19 (m, 2H), 7.26–7.29 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 14.10, 14.30, 21.62, 23.37, 30.12, 31.79, 43.78, 125.97, 127.68, 128.31, 129.12, 138.74, 140.97; Found: C, 89.09; H, 11.06%. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96%.

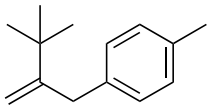
(*Z*)-1,4-dibenzyloxy-2-phenylmethyl-2-butene (3c)



oil. IR (neat) 3031, 2854, 1604, 1365, 1072, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (s, 2H), 3.92 (s, 2H), 4.06 (d, *J* = 6.6 Hz, 2H), 4.40 (s, 2H), 4.47 (s, 2H), 5.65 (t, *J* = 6.6 Hz, 1H), 7.17–7.36 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 41.73, 66.17, 66.79, 72.24, 72.45, 126.36, 127.34, 127.79, 127.83,

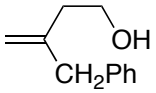
127.94, 128.02, 128.52, 128.55, 128.58, 129.39, 138.42, 139.38, 139.97 (Two signals merge.); Found: C, 83.75; H, 7.30%. Calcd for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31%.

3,3-dimethyl-2-(4-methylphenyl)methyl-1-butene (3d)



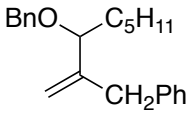
oil. IR (neat) 2965, 2870, 1633, 1515, 1361, 1147 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 9H), 2.32 (s, 3H), 3.34 (s, 2H), 4.40 (s, 1H), 4.95 (s, 1H), 7.04–7.11 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.21, 29.68, 36.40, 38.21, 109.58, 129.05, 129.49, 135.33, 138.08, 158.07; Found: C, 89.15; H, 10.85%. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71%.

3-phenylmethyl-3-buten-1-ol (3e)



oil. IR (neat) 3340, 2908, 1643, 1041, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.26 (t, J = 6.3 Hz, 2H), 3.38 (s, 2H), 3.67–3.70 (m, 2H), 4.91 (s, 1H), 4.94 (s, 1H), 7.18–7.38 (m, 5H) (The signal of O<u>H</u> was not observed); ^{13}C NMR ($CDCl_3$) δ 38.71, 43.04, 60.55, 114.01, 126.48, 128.60, 129.14, 139.38, 145.52; Found: C, 81.38; H, 8.70%. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.69%.

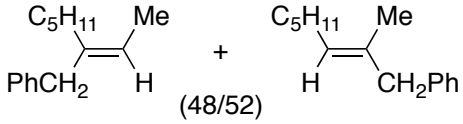
3-benzyloxy-2-phenylmethyl-1-octene (3f)



oil. IR (neat) 3028, 2930, 1602, 1496, 1070, 907, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J = 7.2 Hz, 3H), 1.11–1.72 (m, 8H), 3.27 (d, J = 15.9 Hz, 1H), 3.41 (d, J = 15.9 Hz, 1H), 3.75 (t, J = 6.0 Hz, 1H), 4.20 (d, J = 11.7 Hz, 1H), 4.49 (d, J = 11.7 Hz, 1H), 4.76 (s, 1H), 5.08 (s, 1H), 7.07–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.25, 22.78, 25.71, 31.86, 34.41, 37.50, 70.21, 82.76, 114.39, 126.23, 127.58, 128.05, 128.46, 128.48, 129.71, 138.94, 139.68, 148.92; Found: C,

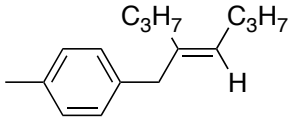
85.70; H, 9.37%. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15%.

(*E*)-3-phenylmethyl-2-octene + (*E*)-2-methyl-1-phenyl-2-octene (48:52 mixture of regioisomers) (3g)



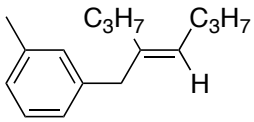
oil. IR (neat) 3083, 2927, 1603, 1453, 1075, 735, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.94 (m, 3H), 1.17–1.41 (m, 6H), 1.52 (s, 3H × 0.52), 1.60 (d, *J* = 6.9 Hz, 3H × 0.48), 1.92–2.05 (m, 2H), 3.28 (m, 2H), 5.21–5.29 (m, 1H), 7.15–7.20 (m, 3H), 7.25–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.51, 14.24, 14.29, 15.94, 22.77, 22.78, 27.85, 28.18, 29.47, 29.68, 31.77, 32.00, 43.78, 46.49, 120.92, 125.99, 126.03, 127.20, 128.32, 128.35, 129.00, 129.20, 134.28, 140.01, 140.78, 140.90; Found: C, 89.01; H, 10.94%. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96%.

(*E*)-4-(4-methylphenyl)methyl-4-octene (3i)



oil. IR (neat) 2959, 2871, 1513, 1457, 803 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84–0.94 (m, 6H), 1.34–1.45 (m, 4H), 1.92 (t, *J* = 7.2 Hz, 2H), 2.06 (q, *J* = 7.5 Hz, 2H), 2.33 (s, 3H), 3.26 (s, 2H), 5.22 (t, *J* = 7.5 Hz, 1H), 7.05–7.11 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.10, 14.30, 21.22, 21.62, 23.38, 30.12, 31.75, 43.32, 127.42, 128.98, 129.02, 135.39, 137.86, 138.94; Found: C, 88.64; H, 11.21%. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18%.

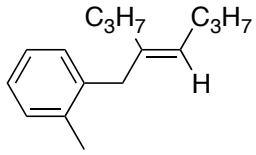
(*E*)-4-(3-methylphenyl)methyl-4-octene (3j)



oil. IR (neat) 2959, 2870, 1607, 1457, 780, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 1.31–1.44 (m, 4H), 1.92 (t, *J* = 7.5 Hz, 2H), 2.01 (q, *J* = 7.5 Hz,

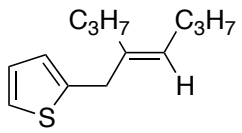
2H), 2.32 (s, 3H), 3.25 (s, 2H), 5.21 (t, J = 7.5 Hz, 1H), 6.95–7.00 (m, 3H), 7.13–7.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.09, 14.29, 21.60, 21.63, 23.38, 30.13, 31.79, 43.68, 126.14, 126.72, 127.57, 128.18, 129.91, 137.82, 138.80, 140.89; Found: C, 88.71; H, 10.97%. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18%.

(*E*)-4-(2-methylphenyl)methyl-4-octene (3k)



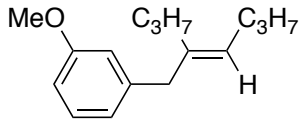
oil. IR (neat) 2958, 2870, 1492, 1378, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H), 1.26–1.48 (m, 4H), 1.95–2.06 (m, 4H), 2.25 (s, 3H), 3.28 (s, 2H), 4.94 (t, J = 7.2 Hz, 1H), 7.09–7.13 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.08, 14.37, 19.60, 21.86, 23.31, 30.10, 32.74, 40.92, 125.86, 126.17, 126.91, 130.07, 130.19, 137.11, 137.62, 138.75; Found: C, 89.04; H, 11.17%. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18%.

(*E*)-4-(2-thienyl)methyl-4-octene (3l)



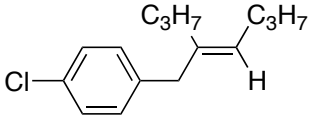
oil. IR (neat) 2958, 2870, 1464, 1078, 772, 638 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H), 1.31–1.41 (m, 4H), 1.93–2.04 (m, 4H), 3.30 (s, 2H), 5.22 (t, J = 7.5 Hz, 1H), 6.89–6.92 (m, 2H), 7.21–7.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.09, 14.31, 21.66, 23.33, 30.10, 31.96, 38.24, 121.05, 125.14, 127.26, 128.89, 138.35, 141.59; Found: C, 75.17; H, 9.76%. Calcd for $C_{13}H_{20}S$: C, 74.94; H, 9.67%.

(*E*)-4-(3-methoxyphenyl)methyl-4-octene (3m)



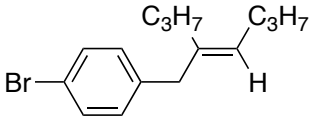
oil. IR (neat) 2958, 2870, 1600, 1454, 1258, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 1.33–1.42 (m, 4H), 1.92 (t, *J* = 7.5 Hz, 2H), 2.01 (q, *J* = 7.5 Hz, 2H), 3.27 (s, 2H), 3.79 (s, 3H), 5.23 (t, *J* = 7.5 Hz, 1H), 6.72–6.78 (m, 3H), 7.16–7.21 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.08, 14.29, 21.64, 23.35, 30.12, 31.80, 43.81, 55.29, 111.31, 114.78, 121.63, 127.84, 129.22, 138.56, 142.69, 159.72 ; Found: C, 82.51; H, 10.43%. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41%.

(*E*)-4-(4-chlorophenyl)methyl-4-octene (3n)



oil. IR (neat) 2958, 2870, 1490, 1092, 1016, 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.93 (m, 6H), 1.28–1.43 (m, 4H), 1.90 (t, *J* = 7.2 Hz, 2H), 2.01 (q, *J* = 7.5 Hz, 2H), 3.25 (s, 2H), 5.19 (t, *J* = 7.5 Hz, 1 H), 7.08–7.11 (m, 2H), 7.21–7.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.08, 14.27, 21.58, 23.32, 30.10, 31.79, 43.09, 128.09, 128.42, 130.44, 131.70, 138.35, 139.43; Found: C, 76.14; H, 8.87%. Calcd for $C_{15}H_{21}Cl$: C, 76.09; H, 8.94%.

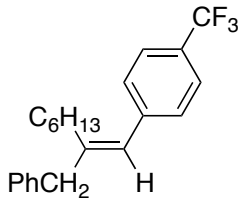
(*E*)-4-(4-bromophenyl)methyl-4-octene (3o)



oil. IR (neat) 2957, 2870, 1730, 1487, 1071, 802 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 1.28–1.43 (m, 4H), 1.89 (t, *J* = 7.5 Hz, 2H), 2.00 (q, *J* = 7.5 Hz, 2 H), 3.23 (s, 2H), 5.19 (t, *J* = 7.5 Hz, 1H), 7.02–7.05 (m, 2H), 7.36–7.39 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.08, 14.27, 21.58, 23.31, 30.10, 31.80, 43.15, 119.75, 128.15, 130.88, 131.38,

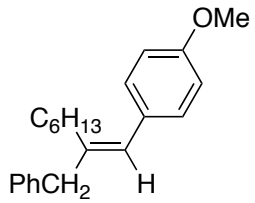
138.27, 139.97; Found: C, 64.23; H, 7.46%. Calcd for $C_{15}H_{21}Br$: C, 64.06; H, 7.53%.

(*E*)-1-(4-trifluoromethylphenyl)-2-phenylmethyl-1-octene (6b)



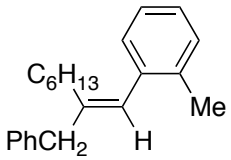
oil. IR (neat) 2931, 2862, 1612, 1326, 1126 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 6.0 Hz, 3H), 1.22–1.27 (m, 6H), 1.45–1.50 (m, 2H), 2.14 (t, J = 7.5 Hz, 2H), 3.50 (s, 2H), 6.29 (s, 1H), 7.23–7.35 (m, 7H), 7.54–7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.22, 22.75, 28.29, 29.45, 30.62, 31.74, 44.00, 124.53 (q, J = 272 Hz), 125.87 (q, J = 4.0 Hz), 126.01, 126.48, 128.25 (q, J = 32.6 Hz), 128.60, 129.03, 129.31, 139.68, 142.18, 145.41; HRMS Found: 346.1910 (Δ = 0.6 ppm), Calcd for $C_{22}H_{25}F_3$: 346.1908.

(*E*)-1-(4-methoxyphenyl)-2-phenylmethyl-1-octene (6c)



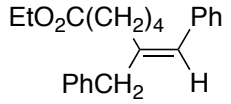
oil. IR (neat) 2923, 1512, 1249, 1033, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.90 (m, 3H), 1.23–1.53 (m, 8H), 2.14 (t, J = 8.1 Hz, 2H), 3.46 (s, 2H), 3.80 (s, 3H), 6.24 (s, 1H), 6.83–6.86 (m, 2H), 7.14–7.32 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.26, 22.79, 28.32, 29.56, 30.48, 31.81, 44.14, 55.41, 113.67, 126.23, 126.69, 128.46, 129.25, 129.92, 131.09, 140.36, 141.65, 158.05; Found: C, 85.55; H, 9.11%. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15%.

(*E*)-1-(2-methylphenyl)-2-phenylmethyl-1-octene (6d)



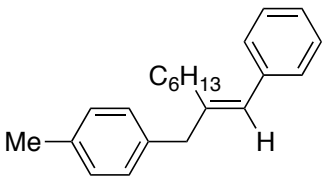
oil. IR (neat) 3024, 2924, 1650, 740, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.19–1.45 (m, 8H), 2.01 (t, *J* = 6.9 Hz, 2H), 2.25 (s, 3H), 3.53 (s, 2H), 6.28 (s, 1H), 7.14–7.37 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.23, 20.22, 22.75, 28.13, 29.27, 30.13, 31.74, 43.29, 125.45, 126.24, 126.62, 128.49, 129.22, 129.29, 129.77, 136.54, 137.90, 140.36, 142.44 (Two signals merge.); Found: C, 90.39; H, 9.69%. Calcd for $C_{22}H_{28}$: C, 90.35; H, 9.65%.

Ethyl (*E*)-7-phenyl-6-phenylmethyl-6-heptenoate (6e)



oil. IR (neat) 3024, 2939, 1736, 1450, 1180, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.44–1.63 (m, 4H), 2.15–2.25 (m, 4H), 3.48 (s, 2H), 4.10 (q, *J* = 6.6 Hz, 2H), 6.33 (s, 1H), 7.16–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.43, 25.05, 27.74, 30.02, 34.23, 43.93, 60.37, 126.35 (Two signals merge.), 127.75, 128.30, 128.52, 128.79, 129.22, 138.33, 139.97, 142.17, 173.96; Found: C, 81.77; H, 8.12%. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13%.

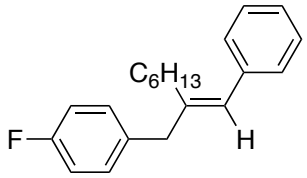
(*E*)-2-(4-methylphenyl)methyl-1-phenyl-1-octene (6f)



oil. IR (neat) 2924, 1512, 1026, 802, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, *J* = 6.9 Hz, 3H), 1.20–1.51 (m, 8H), 2.15 (t, *J* = 7.8 Hz, 2H), 2.33 (s, 3H), 3.44 (s, 2H), 6.30 (s, 1H), 7.12–7.33 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.24, 21.23, 22.78, 28.33, 29.52, 30.45, 31.79, 43.63, 126.18, 127.06, 128.23, 128.84, 129.15, 129.19, 135.74, 137.08, 138.61, 143.25; Found: C, 90.45; H, 9.69%.

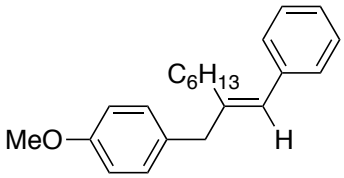
Calcd for $C_{22}H_{28}$: C, 90.35; H, 9.65%.

(*E*)-2-(4-fluorophenyl)methyl-1-phenyl-1-octene (6g)



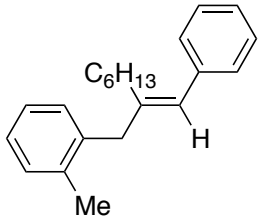
oil. IR (neat) 3024, 2924, 1604, 1505, 1226, 825, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t *J* = 6.9 Hz, 3H), 1.22–1.29 (m, 6H), 1.41–1.48 (m, 2H), 2.14 (t, *J* = 7.8 Hz, 2H), 3.45 (s, 2H), 6.28 (s, 1H), 6.79–7.02 (m, 2H), 7.18–7.34 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.23, 22.76, 28.31, 29.50, 30.47, 31.77, 43.24, 115.26 (d, *J* = 21 Hz), 126.34, 127.42, 128.29, 128.81, 130.59 (d, *J* = 8.2 Hz), 135.77 (d, *J* = 2.8 Hz), 138.38, 142.87, 161.70 (d, *J* = 244 Hz); Found: C, 85.37; H, 8.63%. Calcd for $C_{21}H_{25}F$: C, 85.09; H, 8.50%.

(*E*)-2-(4-methoxyphenyl)methyl-1-phenyl-1-octene (6h)



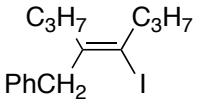
oil. IR (neat) 2854, 1512, 1250, 1081, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83–0.90 (m, 3H), 1.19–1.53 (m, 8H), 2.12–2.17 (m, 2H), 3.42 (s, 2H), 3.79 (s, 3H), 6.28 (s, 1H), 6.81–6.91 (m, 2H), 7.14–7.33 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.26, 22.78, 28.32, 29.53, 30.43, 31.79, 43.19, 55.43, 113.89, 126.19, 126.92, 128.24, 128.82, 130.17, 132.19, 138.58, 143.41, 158.19; Found: C, 85.81; H, 9.25%. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15%.

(*E*)-2-(2-methylphenyl)methyl-1-phenyl-1-octene (6i)



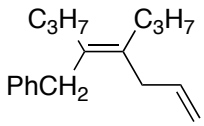
oil. IR (neat) 3055, 2924, 1659, 1458, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–0.89 (m, 3H), 1.16–1.55 (m, 8H), 2.19–2.25 (m, 2H), 2.32 (s, 3H), 3.47 (s, 2H), 6.02 (s, 1H), 7.09–7.31 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.26, 19.71, 22.80, 28.62, 29.60, 31.51, 31.81, 41.33, 126.05, 126.14, 126.53, 128.14, 128.20, 128.73, 130.31, 130.39, 137.20, 138.10, 138.66, 142.15; HRMS Found: 292.2187 (Δ = –1.3 ppm), Calcd for $C_{22}H_{28}$: 292.2191.

(*Z*)-4-iodo-5-phenylmethyl-4-octene (7b)



oil. IR (neat) 3024, 2962, 1605, 1095, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.5 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 1.32–1.44 (m, 2H), 1.57–1.67 (m, 2H), 2.06–2.11 (m, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 3.69 (s, 2H), 7.18–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.21, 14.21, 22.15, 23.35, 33.39, 43.42, 48.49, 107.52, 126.41, 128.55, 128.61, 139.23, 143.31; HRMS Found: 328.0685 (Δ = –0.9 ppm), Calcd for $C_{15}H_{21}I$: 328.0688.

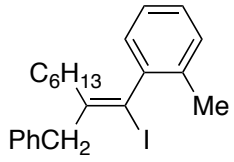
(*Z*)-5-phenylmethyl-4-propyl-1,4-octadiene (7c)



oil. IR (neat) 3078, 2962, 1821, 1458, 995 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, *J* = 6.9 Hz, 3H), 0.94 (t, *J* = 6.9 Hz, 3H), 1.33–1.50 (m, 4H), 1.92–1.97 (m, 2H), 2.05–2.10 (m, 2H), 2.84 (d, *J* = 6.0 Hz, 2H), 3.40 (s, 2H), 4.95–5.05 (m, 2H), 5.71–5.82 (m, 1H), 7.13–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.50, 14.58, 22.30, 22.32, 33.91, 34.15, 36.68, 37.14, 114.83, 125.82, 128.39, 128.60, 133.13,

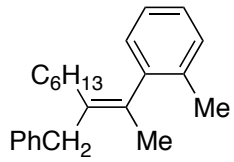
133.35, 137.15, 141.10; HRMS Found: 242.2037 (Δ = 1.1 ppm), Calcd for $C_{18}H_{26}$: 242.2035.

(*Z*)-1-iodo-1-(2-methylphenyl)-2-phenylmethyl-1-octene (8b)



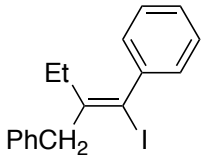
oil. IR (neat) 3062, 2924, 1604, 1458, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (t, *J* = 7.5 Hz, 3H), 1.01–1.28 (m, 8H), 1.80 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 3.75 (d, *J* = 14.7 Hz, 1H), 3.96 (d, *J* = 14.7 Hz, 1H), 7.14–7.35 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.15, 19.74, 22.56, 27.98, 29.05, 31.45, 31.48, 46.35, 97.84, 126.06, 126.60, 128.07, 128.70, 128.72, 128.82, 130.49, 135.21, 139.10, 143.76, 146.61; HRMS Found: 418.1164 (Δ = 1.5 ppm), Calcd for $C_{22}H_{27}I$: 418.1157.

(*E*)-2-(2-methylphenyl)-3-phenylmethyl-2-nonene (8c)



oil. IR (neat) 3024, 2924, 1604, 1458, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (t, *J* = 7.2 Hz, 3H), 0.98–1.26 (m, 8H), 1.63–1.70 (m, 2H), 1.97 (s, 3H), 2.22 (s, 3H), 3.49 (d, *J* = 15.0 Hz, 1H), 3.67 (d, *J* = 15.0 Hz, 1H), 7.00–7.33 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.20, 19.59, 20.80, 22.65, 28.09, 29.39, 31.68, 32.64, 36.53, 125.79, 125.94, 126.39, 128.51, 128.67, 128.73, 130.02, 132.36, 134.58, 135.07, 141.02, 144.55; Found: C, 89.94; H, 10.02%. Calcd for $C_{23}H_{30}$: C, 90.13; H, 9.87%.

(*Z*)-1-iodo-1-phenyl-2-phenylmethyl-1-butene (9)



oil. IR (neat) 3024, 2970, 1597, 1072, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3H), 1.98 (q, J = 7.2 Hz, 2H), 3.87 (s, 2H), 7.22–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 13.50, 25.06, 46.42, 126.60, 127.70, 128.44, 128.54, 128.67, 128.70, 138.85, 145.02, 148.07 (Two signals merge); HRMS Found: 348.0375 (Δ = 2.6 ppm), Calcd for $C_{17}H_{17}I$: 348.0384.

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Chapter 4

Nickel-Catalyzed Carbometalation Reactions of [2-(1-Propynyl)phenyl]methanol with 1-Alkenylmagnesium Reagents

Treatment of [2-(1-propynyl)phenyl]methanol with 1-alkenyl Grignard reagents under nickel catalysis results in carbomagnesiation across the alkynyl part. The 1-alkenylation reaction proceeds in a syn fashion to yield the corresponding 1,3-butadienyl-substituted benzyl alcohol.

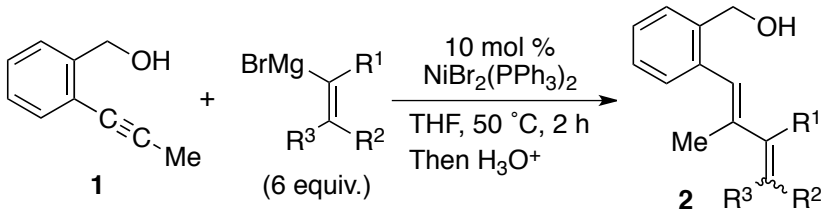
Introduction

Transition metal-catalyzed carbometalation of alkynes is a powerful tool for the synthesis of multisubstituted alkenes.[1] However, 1-alkenylation reaction of alkyne with 1-alkenylmetal reagents is difficult to achieve, while there are many examples of addition reactions of aryl-,[2] allyl-,[3] alkynyl-,[4] and alkylmetal[5] reagents to alkynes. Here, the author reports an example of 1-alkenylation reaction of an alkyne, [2-(1-propynyl)phenyl]methanol (**1**), with 1-alkenylmagnesium bromide.

Results and Discussion

Treatment of **1** with an excess of vinylmagnesium bromide in the presence of $NiBr_2(PPh_3)_2$ in THF at 20 ˚C for 5 h provided the vinylated product **2a** in good yield (Table 1, entry 1). The vinylation reaction proceeded to completion within 1 h at 50 ˚C (entry 2). The alkenylation reactions with Grignard reagents bearing a substituent R^1, R^2, or R^3 did not proceed at 20 ˚C. The reaction of **1** with isopropenylmagnesium bromide provided the adduct **2b** in good yield (entry 3). However, a trimethylsilyl or a phenyl group as R^1 considerably retarded the reaction (entries 4 and 5). The reaction is sensitive to the steric factor at the 1 positions of the 1-alkenyl Grignard reagents. The reaction with 1-propenylmagnesium bromide (*E*/*Z* = 2:8)[6] afforded the product **2e** in good yield in a 1*E*, 3*E*/1*E*, 3*Z* ratio of 25:75 (entry 6). The stereochemistry of the product reflects that of the Grignard reagent. Interestingly, the reaction with 2-trimethylsilylethenylmagnesium bromide yielded the 1*E*, 3*E* isomer exclusively (entry 7). The exclusive formation indicates that (*E*)-2-trimethylsilylethenylmagnesium bromide would be more reactive than its *Z* form because of the steric hindrance. The use of a 1:1 mixture of (*E*)- and (*Z*)-styrylmagnesium reagent provided the *E* adduct predominantly (entry 8). A 1-alkenyl Grignard reagent, 2-methyl-1-propenylmagnesium bromide, reacted smoothly with **1** under the nickel catalysis (entry 9).

Table 1. 1-Alkenylation of [2-(1-Propynyl)phenyl]methanol (**1**) with 1-Alkenylmagnesium Reagents under Nickel Catalysis



Entry	R^1	R^2	R^3	**2**	Yield
1[a]	H	H	H	**2a**	72%
2[b]	H	H	H	**2a**	70%
3	Me	H	H	**2b**	63%
4	Me_3Si	H	H	**2c**	<20%
5	Ph	H	H	**2d**	<5%
6	H	Me (H) (2:8)[c]	H (Me)	**2e**	75% (25:75)[d]
7	H	Me_3Si (H) (8:2)[c]	H (Me_3Si)	**2f**	74% (>99:1)[d]
8	H	Ph (H) (5:5)[c]	H (Ph)	**2g**	74% (83:17)[d]
9	H	Me	Me	**2h**	74%

[a]Performed at 20 ˚C for 5 h.
[b]Performed for 1 h.
[c]*E*/*Z* ratio of the Grignard reagent.
[d]1*E*, 3*E*/1*E*, 3*Z* ratio of **2**.

The reactions of other alkynes were unsatisfactory. The methyl ether **3** was much less reactive (eq. 1). Replacement of the methyl group of **1** with a butyl group resulted in significant decrease in reaction efficiency (eq. 2). The reaction of 1-phenylpropyne (**7**) having no heteroatom for 12 h provided 1,3-diene **8** in a similar yield (eq. 3). A diphenylacetylene derivative **9** underwent the vinylation slowly, providing a mixture of regioisomers **10** and **11** (eq. 4). The reactions of other alkynes shown in Figure 1 resulted in failure.

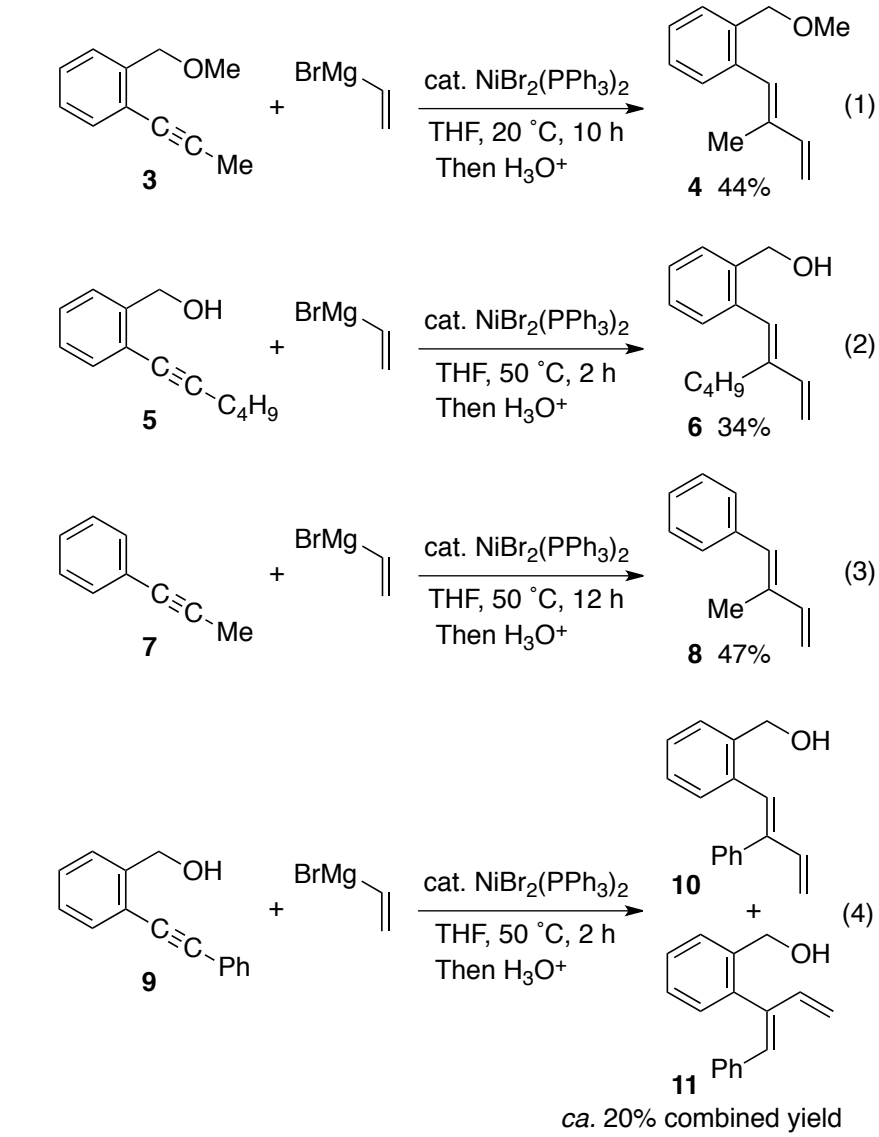
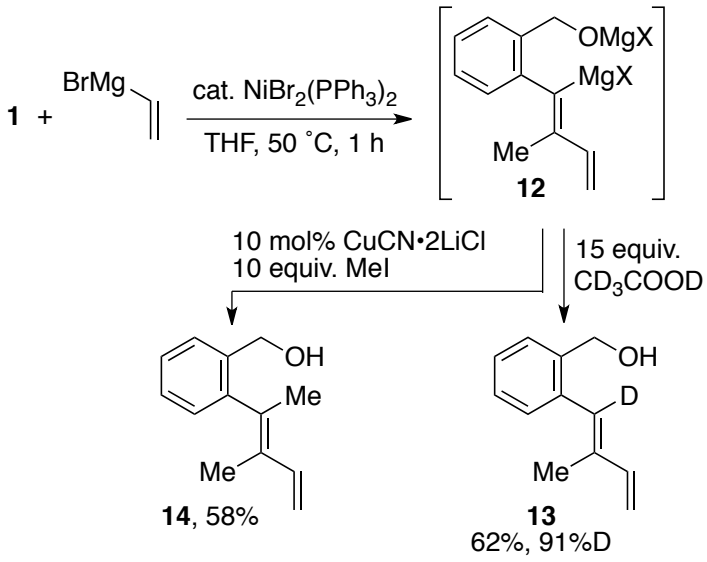

OMe
BrMg
cat. NiBr2(PPh3)2
THF, 20 ˚C, 10 h
Then H3O+
Me
3
4 44%
(1)
OH
C4H9
5
6 34%
(2)
7
8 47%
(3)
Ph
9
10
+
11
(4)
ca. 20% combined yield
little conversion
NH2
complex mixture
O

Figure 1.

The *syn* mode of the carbometalation was confirmed by NOE analysis of **2b**. Irradiation of the methyl group at the 3 position enhanced the signal of the proton at the 1 position, geminal to the aromatic ring. The author also performed spectroscopic comparison of **8** with an authentic sample prepared by the Wittig methylenation reaction of (*E*)-*a*-methylcinnamaldehyde.

The vinylmagnesiated adduct **12** was trapped with CD_3COOD or iodomethane in the presence of CuCN•2LiCl (Scheme 1). Unfortunately, many attempts to trap the intermediate **12** with I_2, allyl bromide, benzoyl chloride, benzaldehyde, and iodobenzene resulted in failure. The intermediate is not reactive probably because of the proximal alkoxide moiety and steric hindrance.

Scheme 1. Trapping with Electrophiles



Conclusion

The author has found examples of carbometalation with 1-alkenylmetal reagents. The reaction proceeds in a *syn* fashion, yielding 1,3-butadiene skeleton.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (300 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to $CHCl_3$ at 7.26 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

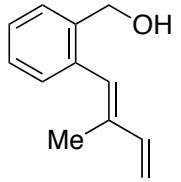
Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Anhydrous $NiBr_2(PPh_3)_2$ was prepared according to the literature.[7] 1-Alkenylmagnesium bromide was prepared from magnesium metal and the corresponding 1-alkenyl bromide in THF. THF was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. All reactions were carried out under argon atmosphere.

Typical procedure for nickel-catalyzed 1-alkenylmagnesiation of alkynes: The reaction of [2-(1-propynyl)phenyl]methanol (**1**) with vinylmagnesium bromide (Table 1, entry 2) is representative. Bis(triphenylphosphine) Nickel(II) bromide (19 mg, 0.025 mmol) was placed in a 20-mL reaction flask. THF (1 mL), [2-(1-propynyl)phenyl]methanol (**1**, 37 mg, 0.25 mmol), vinylmagnesium bromide (1.0 M THF solution, 1.5 mL, 1.5 mmol) were sequentially added at 25 ˚C. The resulting mixture was heated at 50 ˚C for 1 h. After the mixture was cooled to room temperature, the reaction was quenched with water. The products were extracted with ethyl acetate three times. The combined organic layer was dried over Na_2SO_4 and concentrated. Silica gel column purification (hexane/ethyl acetate = 5/1) of the crude product provided (*E*)-[2-(2-methyl-1,3-dutadienyl)phenyl]methanol (**2a**, 30 mg, 0.18 mmol) in 70% isolated yield.

General procedure for the vinylmagnesiation and the subsequent reaction with methyl iodide (Scheme 1): Bis(triphenylphosphine) Nickel(II) bromide (19 mg, 0.025 mmol) was placed in a 20-mL reaction flask. THF (1 mL), [2-(1-propynyl)phenyl]methanol (**1**, 37 mg, 0.25 mmol), vinylmagnesium bromide (1.0 M THF solution, 1.5 mL, 1.5 mmol) were sequentially added at 25 ˚C. The resulting mixture was heated at 50 ˚C for 1 h. After the mixture was cooled to 0 ˚C, methyl iodide (0.16 mL, 2.5 mmol) and CuCN·2LiCl (1.0 M in THF, 0.025 mL, 0.025 mmol) were added. The mixture was warmed to 25 ˚C and stirred for 4 h. The reaction mixture was poured into saturated ammonium chloride solution. The products were extracted with ethyl acetate three times. The combined organic layer was dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) of the crude product provided the corresponding product **14** (27 mg, 0.15 mmol) in 58% isolated yield.

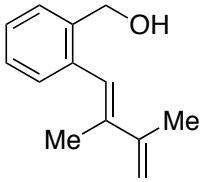
Characterization Data

(*E*)-[2-(2-Methyl-1,3-butadienyl)phenyl]methanol (2a)



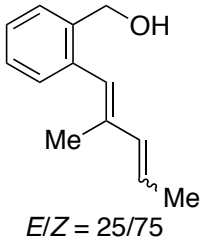
IR(neat): 3319, 2918, 1604, 1448, 1015, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.61 (t, *J* = 6.0 Hz, 1H), 1.85 (d, *J* = 1.2 Hz, 3H), 4.66 (d, *J* = 6.0 Hz, 2H), 5.16 (d, *J* = 10.8 Hz, 1H), 5.31 (d, *J* = 17.4 Hz, 1H), 6.59 (dd, *J* = 10.8, 17.4 Hz, 1H), 6.63 (s, 1H), 7.19–7.30 (m, 3H), 7.42–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.45, 63.66, 113.67, 127.47, 127.51, 127.76, 129.06, 129.98, 136.24, 137.61, 139.09, 141.35; Found: C, 82.59: H, 8.12%. Calcd for $C_{12}H_{14}O$: C, 82.72: H, 8.10%.

(1*E*)-[2-(2,3-Dimethyl -1,3-butadienyl)phenyl]methanol (2b)



IR(neat): 3245, 2922, 1473, 1041, 888, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.64 (t, *J* = 6.0 Hz, 1H), 1.86 (d, *J* = 0.9 Hz, 3H), 2.06 (s, 3H), 4.65 (d, *J* = 6.0 Hz, 2H), 5.08 (s, 1H), 5.20 (d, *J* = 0.9 Hz, 1H), 6.72 (s, 1H), 7.16–7.19 (m, 1H), 7.26–7.30 (m, 2H), 7.42–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.69, 21.38, 63.95, 113.99, 125.12, 127.54, 127.75, 127.85, 130.27, 137.42, 138.91, 139.33, 144.70; Found: C, 82.73: H, 8.65%. Calcd for $C_{13}H_{16}O$: C, 82.94: H, 8.57%.

(1*E*,3*E*)- and (1*E*,3*Z*)-[2-(2-Methyl-1,3-pentadienyl)phenyl]methanol (*E*/*Z* = 25/75) (2e)

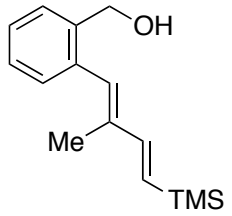


E/*Z* = 25/75

IR(neat): 3567, 2918, 1733, 1457, 1017, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.63 (t, *J* = 6.0 Hz, 1H),

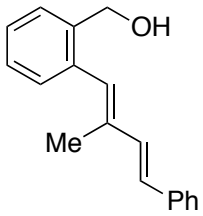
1.82–1.92 (m, 6H), 4.64–4.68 (m, 2H), 5.59 (dq, *J* = 7.2, 11.7 Hz, 0.75 x 1H), 5.81 (dq, *J* = 6.6, 15.3 Hz, 0.25 x 1H), 6.01 (d, *J* = 11.7 Hz, 0.75 x 1H), 6.29 (d, *J* = 15.3 Hz, 1H), 6.49 (s, 1H), 7.17–7.31 (m, 3H), 7.40–7.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.19, 15.12, 18.54, 18.78, 63.73, 125.57, 125.78, 126.24, 127.17, 127.21, 127.47, 127.67, 127.70, 129.96, 130.09, 133.65, 135.91, 136.56, 136.89, 139.08; Found: C, 82.95: H, 8.57%. Calcd for $C_{13}H_{16}O$: C, 82.94: H, 8.40%.

(1*E*,3*E*)-[2-(2-Methyl-4-trimethylsilyl-1,3-butadienyl)phenyl]methanol (2f)



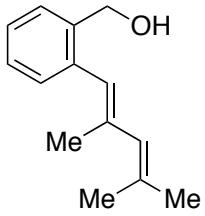
IR(neat): 3245, 2955, 1570, 1248, 871, 796 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.12 (s, 9H), 1.81 (t, *J* = 1.2 Hz, 3H), 4.64 (s, 2H), 5.95 (d, *J* = 18.6 Hz, 1H), 6.65 (s, 1H), 6.73 (d, *J* = 18.6 Hz, 1H), 7.17–7.28 (m, 3H), 7.39–7.42 (m, 1H) (O<u>H</u> proton was not observed.); ^{13}C NMR ($CDCl_3$) δ –0.97, 13.68, 63.69, 127.44, 127.52, 127.80, 129.33, 129.63, 129.93, 136.43, 138.74, 139.08, 148.22; Found: C, 73.40: H, 9.14%. Calcd for $C_{15}H_{22}OSi$: C, 73.11: H, 9.00%.

(1*E*,3*E*)-[2-(2-Methyl-4-phenyl-1,3-butadienyl)phenyl]methanol (2g)



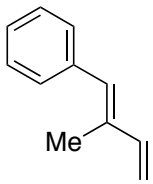
IR(neat): 3319, 2920, 1719, 1420, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.62 (t, *J* = 6.3 Hz, 1H), 1.99 (d, *J* = 1.5 Hz, 3H), 4.70 (d, *J* = 6.0 Hz, 2H), 6.67 (d, *J* = 16.0 Hz, 1H), 6.78 (s, 1H), 7.03 (d, *J* = 16.0 Hz, 1H), 7.16–7.49 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 14.23, 63.77, 126.64, 127.48, 127.56, 127.64, 127.86, 128.62, 128.86, 129.60, 130.06, 133.61, 136.39, 137.41, 137.63, 139.13; Found: C, 86.24: H, 7.20%. Calcd for $C_{18}H_{18}O$: C, 86.36: H, 7.25%.

(*E*)-[2-(2-Methyl-1,3-butadienyl)phenyl]methanol (2h)



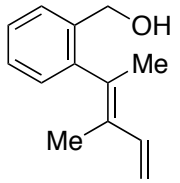
IR(neat): 3292, 2911, 1652, 1448, 1040, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.61 (m, 1H), 1.81 (d, *J* = 1.5 Hz, 3H), 1.84 (d, *J* = 1.2 Hz, 1H), 1.89 (d, *J* = 1.2 Hz, 3H), 4.67 (s, 2H), 5.80 (d, *J* = 1.2 Hz, 1H), 6.38 (s, 1H), 7.20–7.29 (m, 3H), 7.41–7.44 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.94, 19.90, 27.17, 63.79, 125.87, 127.02, 127.46, 127.64, 128.97, 130.03, 134.42, 136.90, 137.48, 139.05; Found: C, 83.07: H, 9.01%. Calcd for $C_{14}H_{18}O$: C, 83.12: H, 8.97%.

(*E*)- 2-Methyl-1-phenyl-1,3-butadiene (8)



IR(neat): 2918, 1260, 803, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.00 (d, *J* = 1.2 Hz, 1H), 5.13 (dd, *J* = 0.6, 10.7 Hz, 1H), 5.30 (dd, *J* = 0.6, 15.8 Hz, 1H), 6.55 (ddd, *J* = 0.6, 10.7, 15.8 Hz, 1H), 6.53 (s, 1H), 7.20–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.35, 113.15, 126.79, 128.31, 129.39, 131.83, 136.16, 137.92, 142.07; Found: C, 91.72: H, 8.53%. Calcd for $C_{11}H_{12}$: C, 91.61: H, 8.39%.

(*E*)-[2-(1,2-Dimethyl-1,3-butadienyl)phenyl]methanol (14)



IR(neat): 3609, 2922, 1457, 1023, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.53 (d, *J* = 1.2 Hz, 3H), 1.57 (d, *J* = 6.0 Hz, 3H), 2.07 (d, *J* = 1.2 Hz, 1H), 4.55 (d, *J* = 5.7 Hz, 2H), 5.17 (dd, *J* = 1.2, 10.8 Hz), 5.27 (dd, *J* = 17.4 Hz, 1H), 6.95 (d, *J* = 10.8 Hz, 1H), 6.99–7.03 (m, 1H), 7.27–7.30 (m, 2H),

7.47–7.50 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.50, 20.63, 63.31, 113.89, 127.15, 127.76, 127.94, 128.18, 130.00, 134.81, 135.05, 137.57, 143.69.

References and Notes

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3. (a) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076. (b) Nishikawa, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2795. (c) Yasui, H.; Nishikawa, T.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1271.
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5. (a) Nishimae, S.; Inoue, R.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **1998**, 785. (b) Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 621. (c) Zhang, D.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 15050.
6. The *E*/*Z* ratios of the Grignard reagents were determined as follows: The reaction of benzaldehyde with an equimolar amount of alkenylmagnesium bromide afforded the corresponding allyl alcohol in excellent yield. The *E*/*Z* ratio of the allyl alcohol would be roughly equal to the *E*/*Z* ratio of the Grignard reagent used.
7. Zhang, J.; Ke, Z.; Bao, F.; Long, J.; Gao, H.; Zhu, F.; Wu, Q. *J. Mol. Catal. A: Chem.* **2006**,

249, 31.

Chapter 5

Silver-Catalyzed Transmetalation between Chlorosilanes and Aryl and Alkenyl Grignard Reagents for Synthesis of Tetraorganosilanes

Substitution reactions of chlorosilanes with aryl Grignard reagents take place under silver catalysis to afford tetraorganosilanes. The transformation is regarded as silver-catalyzed transmetalation between chlorosilanes and Grignard reagents. The reaction would be promoted by diarylargentate reagents generated in situ.

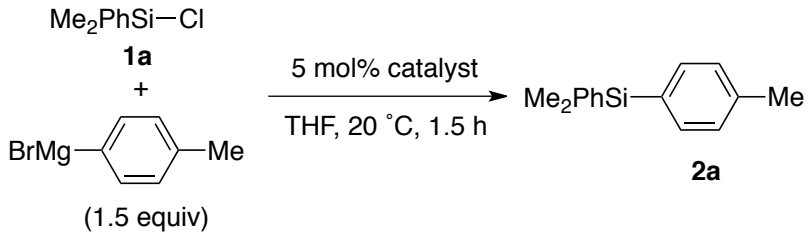
Introduction

The nucleophilic substitution reaction of chlorosilanes with organometallic reagents is a fundamental method for forming carbon–silicon bonds.[1] The reactions of chlorotriorganosilanes with organolithium reagents generally proceed smoothly at low temperatures (–78 ˚C). On the other hand, reactions with the less reactive, yet readily available, organomagnesium reagents often require prolonged reaction times and high temperatures (solvent bp), and result in moderate yields of tetraorganosilanes.[2] In Chapter 5, the author reports that silver salts can catalyze the reactions of chlorotriorganosilanes with organomagnesium reagents to yield a variety of tetraorganosilanes efficiently; this reveals a new aspect of silver catalysis.[3–5]

Results and Discussion

Treatment of chlorodimethylphenylsilane (**1a**) with 4-methylphenylmagnesium bromide in the presence of a catalytic amount of silver nitrate in THF at 20 ˚C for 1.5 h provided the corresponding tetraorganosilane **2a** in 93% yield (Table 1, entry 2).[6] The transformation is regarded as silver-catalyzed transmetalation between chlorosilane and the Grignard reagent. Notably, **2a** was obtained in only 13% yield in the absence of silver nitrate (Table 1, entry 1). Other silver salts, such as silver halides, acetate, and triflate, accelerated the carbon–silicon bond formation (Table 1, entries 3–7). Other group 11 metal halides, such as copper(I) bromide and gold(I) chloride, also promoted the reaction with only slightly lower efficiency (Table 1, entries 8 and 9). Nickel and palladium salts failed to catalyze the reaction (Table 1, entries 10 and 11).

Table 1. Metal-Catalyzed Reaction of Chlorodimethylphenylsilane with 4-Methylphenylmagnesium Bromide[a]

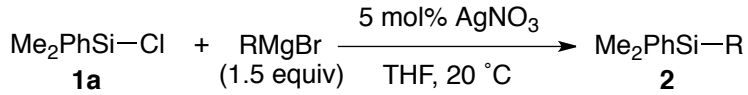


entry	catalyst	yield(%)[b]	entry	catalyst	yield(%)[b]
1	none	13	7	AgOTf	83
2	$AgNO_3$	93(92)[c]	8	CuBr	75
3	AgCl	86	9	AuCl	78
4	AgBr	91	10	$NiCl_2$	24
5	AgI	86	11	$Pd(OAc)_2$	9
6	AgOAc	91			

[a] Performed on a 0.5 mmol scale.
[b] Yield was determined by ^1H NMR spectroscopy.
[c] Isolated yield.

The Grignard reagents scope was studied and the results are summarized in Table 2.[7] The reactions with 2-naphthyl, 4-fluorophenyl, 4-methoxyphenyl, and 4-(triisopropylsiloxy)phenyl Grignard reagents (Table 2, entries 1–4) proceeded as smoothly as those described in Table 1. Sterically hindered 2-methylphenylmagnesium bromide was less reactive, and a prolonged reaction time was essential for the reaction to proceed to completion (Table 2, entry 5). An aryl Grignard reagent having an electron-withdrawing trifluoromethyl group reacted with chlorosilane **1a** slowly in the presence of silver nitrate (Table 2, entry 6). A bulky alkenylmagnesium reagent also participated in the reaction (Table 2, entry 7).[8] Unfortunately, attempts to introduce an alkyl group failed because of the instability of the alkylsilver species (Table 2, entry 8).

Table 2. Silver-Catalyzed Reaction of **1a** with Various Grignard Reagents[a]

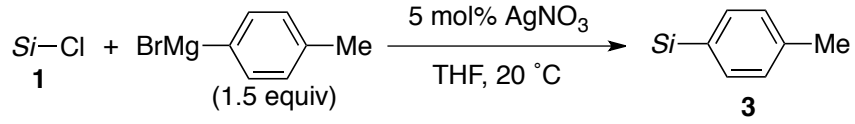


entry	R	time (h)	**2**	yield(%)[b]
1	2-naphthyl	1.5	**2b**	71
2	4-FC_6H_4	1.5	**2c**	92
3	4-$MeOC_6H_4$	1.5	**2d**	97
4	4-(^{i}Pr$_3$SiO)C_6H_4	1.5	**2e**	96
5	2-MeC_6H_4	24	**2f**	88
6	3-$CF_3C_6H_4$	20	**2g**	80
7	CH_2=C($SiMe_3$)	4.5	**2h**	78
8	^{i}Pr	1.5	**2i**	0

[a] Performed on a 0.5 mmol scale.
[b] Isolated yield.

The reactions of bulkier chloromethyldiphenylsilane and chlorotriethylsilane with 4-methylphenylmagnesium bromide under silver catalysis proceeded to completion after extended reaction times (Table 3, entries 1 and 2). Chlorosilanes having an olefinic moiety (Table 3, entries 3 and 4) or a chloromethyl moiety (Table 3, entry 5) reacted without any observable side reactions. Notably, the reaction could be performed on a scale as large as 50 mmol (with respect to **1f**). Sterically congested chlorotriisopropylsilane failed to react (Table 3, entry 6).

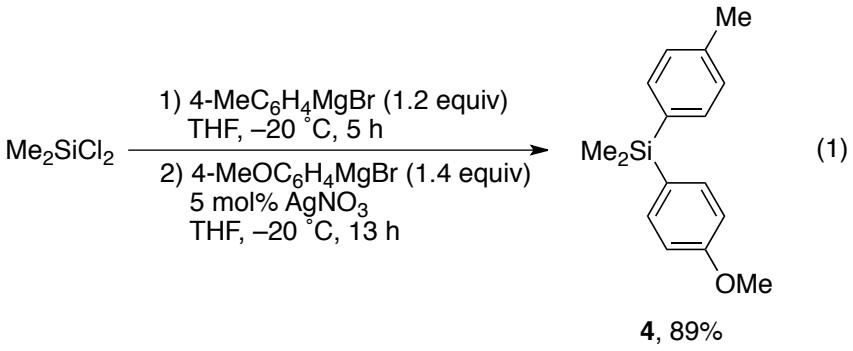
Table 3. Scope of Chlorosilanes[a]



entry	**1**, *Si*	time (h)	**3**	yield(%)[b]
1	**1b**, $MePh_2Si$	10	**3a**	87
2	**1c**, Et_3Si	9.5	**3b**	73
3	**1d**, $(CH_2{=}CHCH_2)Me_2Si$	11	**3c**	80
4	**1e**, $(CH_2{=}CH)Ph_2Si$	18	**3d**	74
5	**1f**, $(ClCH_2)Me_2Si$	3	**3e**[c]	74(79)[d]
6	**1g**, $^iPr_3Si$	10	**3f**	trace

[a] Performed on a 0.5 mmol scale.
[b] Isolated yield.
[c] PhMgBr was used instead of 4-MeC_6H_4MgBr.
[d] Performed on a 50 mmol scale.

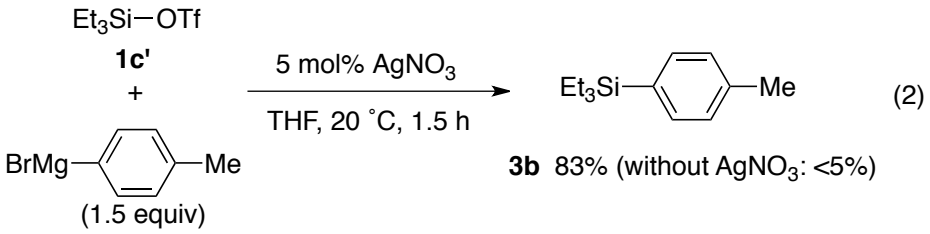
The author was also able to introduce two different aryl groups onto dichlorodimethylsilane in one-pot process (eq. 1). The first arylation proceeded in the absence of the silver catalyst; silver nitrate was then added along with the second Grignard reagent to yield **4** in excellent yield.



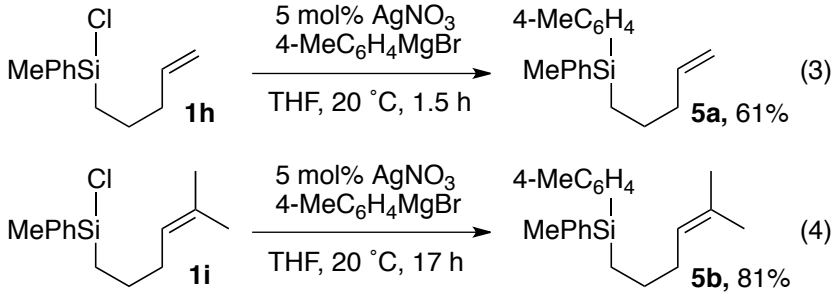
(1)

The silver-catalyzed reaction was highly effective, not only for chlorosilanes but also for

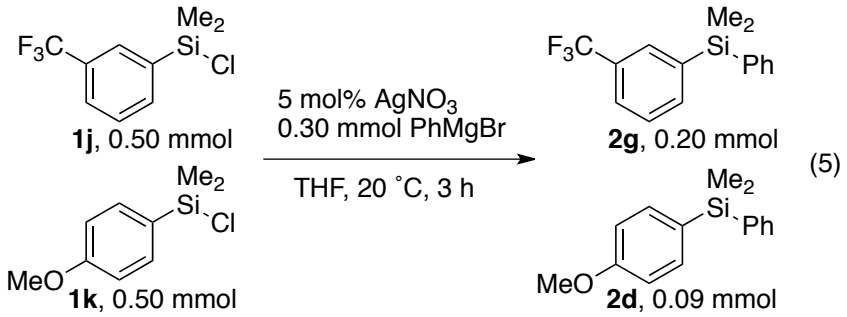
the reaction of silyl triflate **1c'** (eq. 2). This result suggests that silver nitrate does not serve to capture the chloride ion of **1** by precipitating of silver chloride.



Given that the reaction mechanism would involve a silicon-centered radical intermediate or a silyl cation species, 5-*exo* or 6-*endo* cyclization might occur in the silver-catalyzed reactions of **1h** and **1i** (eqs. 3 and 4). However, the reactions resulted in simple arylation, and no cyclized products were observed.

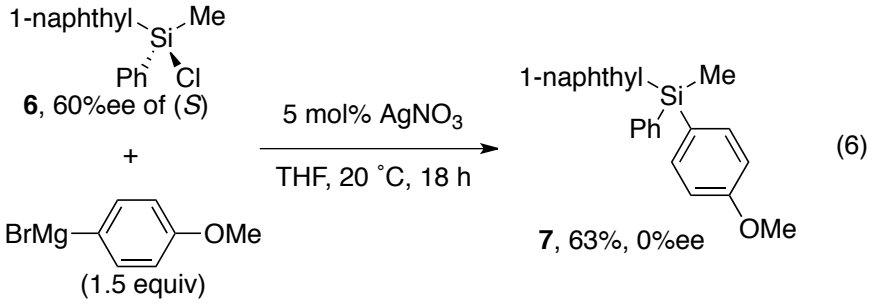


Treatment of a mixture of **1j** and **1k** with an aryl Grignard reagent under silver catalysis resulted in the predominant formation of **2g**, which is derived from **1j** (eq. 5). The electron density of the silicon atom of **1j** is likely to be lower than that of **1k**. The resulting substituent effect for the aryl groups of **1j** and **1k** can thus eliminate the possibility of the formation of a silyl cation or cationlike intermediate.



(5)

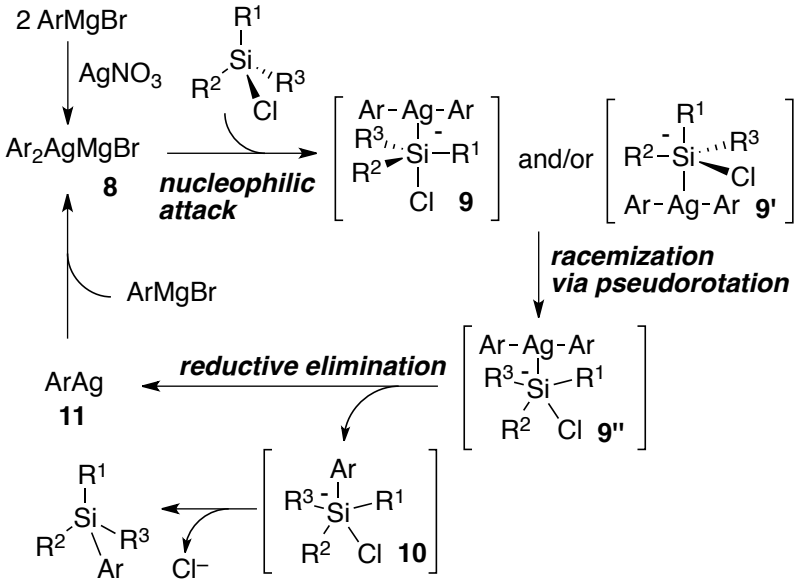
Generally, uncatalyzed nucleophilic substitution reactions of chlorosilanes proceed with either retention or inversion of configuration.[9] However, the silver-catalyzed reaction of chiral **6**[10] (60% ee, *S* configuration) provided the corresponding product **7** in racemic form (eq. 6). Such racemization upon nucleophilic substitution of chlorosilanes is rarely reported.



(6)

Based on our results (eqs. 2–6), the author proposes the reaction mechanism depicted in Scheme 1. Initially, diarylargentate species **8** would be generated in situ,[11] followed by nucleophilic attack of the argentate complex upon the chlorosilane to afford silicate **9** or **9'** bearing a Si–Ag(III) bond.[12] Reductive elimination from **9** or **9'** would be slow[12] and **9** or **9'** could undergo pseudorotation,[9] resulting in the loss of the initial stereochemistry. After the scrambling, reductive elimination from **9''** would occur to afford silicate **10** with concomitant formation of arylsilver **11**. Silicate **10** would liberate a chloride ion to afford the product. By the action of the aryl Grignard reagent, **11** would be converted into the initial argentate **8**.

Scheme 1. Proposed Mechanism[a]



[a] Intermediates **9"** and **10** should have trigonal-bipyramidal structures, although the position of each substituent is not clear.

Conclusion

The protocol described here provides a mild and efficient method for the preparation of tetraorganosilanes, and will be applicable to the synthesis of organosilicon reagents and organosilicon-based advanced materials. There are many effective reactions that employ combinations of organomagnesium reagents and copper catalysts. On the other hand, little is known about the useful reactivity of organomagnesium reagents using silver catalysis.[4a, 5] The present reaction will open up new possibilities for silver-catalyzed reactions with organometallic reagents.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (300 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to $SiMe_4$ at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. $AgNO_3$ was purchased from Wako Pure Chemical Industries, Ltd. Arylmagnesium bromide was prepared from magnesium turnings (Nacalai Tesque, Inc.) and the corresponding bromoarene in THF. THF was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. Chlorosilanes were purchased from Shin-Etsu Chemical Co., Ltd. and Tokyo Chemical Industry Co., Ltd. The starting material **6**[10] was prepared according to the literature.

Typical procedure for silver-catalyzed reactions: The reaction of **1a** with 4-methylphenylmagnesium bromide (Table 1, entry 2) is representative. $AgNO_3$ (4.2 mg, 0.025 mmol) was placed in a 20-mL reaction flask under argon. Chlorodimethylphenylsilane (85 mg, 0.50 mmol) in THF (5 mL) was added to the flask. Then, 4-methylphenylmagnesium bromide (1.0 M THF solution, 0.75 mL, 0.75 mmol) was added. The mixture was stirred at 20 ˚C for 1.5 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent

afforded dimethyl(4-methylphenyl)phenylsilane (**2a**, 104 mg, 0.46 mmol) in 92% yield.

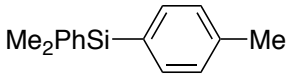
Typical procedure for large scale reaction (Table 3, entry 5): $AgNO_3$ (425 mg, 2.5 mmol) was placed in a 300-mL reaction flask under argon, and THF (50 mL) was then added. Chloro(chloromethyl)dimethylsilane (7.15 g, 50 mmol) in THF (50 mL) was added to the flask. The flask was cooled to 0 ˚C. Phenylmagnesium bromide (1.0 M THF solution, 75 mL, 75 mmol) was subsequently added over 0.5 h. After the completion of the addition, the mixture was warmed to 20 ˚C and stirred at the same temperature for 3 h. The reaction mixture was quenched with a ice-cold saturated aqueous solution of NH_4Cl (50 mL). The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. After evaporation, the residue was distilled to give (chloromethyl)dimethylphenylsilane (**3e**, 7.3 g, 40 mmol, bp 90 ˚C at 9 mmHg) in 79% yield.

Typical procedure for synthesis of diaryldimethylsilanes: Dichlorodimethylsilane (65 mg, 0.5 mmol) was placed in a 20-mL reaction flask under argon in THF (5 mL). The flask was cooled to –20 ˚C. 4-Methylphenylmagnesium bromide (1.0 M THF solution, 0.6 mL, 0.6 mmol) was slowly introduced to the flask. The reaction mixture was stirred for 5 h at –20 ˚C. After being stirred, 4-methoxyphenylmagnesium bromide (1.0 M THF solution, 0.7 mmol, 0.7 mL) and $AgNO_3$ (4.2 mg, 0.025 mmol) were sequentially added at the same temperature. The mixture was stirred for 13 h at –20 ˚C. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane / ethyl acetate = 20 : 1 as an eluent afforded (4-methoxyphenyl)dimethyl(4-methylphenyl)silane (**4**, 114 mg, 0.45 mmol) in 89% yield.

Characterization Data

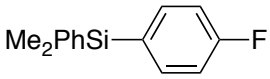
Products **2b**[13]**, 2d**[14]**,** and **3e**[15] are known compounds and showed the identical spectra according to the literature.

Dimethyl(4-methylphenyl)phenylsilane (2a):



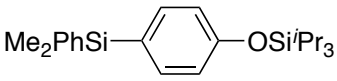
oil. IR (neat) 3041, 2959, 1605, 1427, 1106, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.57 (s, 6H), 2.38 (s, 3H), 7.20–7.57 (m, 9H) ; ^{13}C NMR ($CDCl_3$) δ –2.13, 21.66, 127.96, 128.84, 129.20, 134.34, 134.42, 134.72, 138.68, 139.17; Found: C, 79.61; H, 8.09%. Calcd for $C_{15}H_{18}Si$: C, 79.58; H, 8.01%.

(4-Fluorophenyl)dimethylphenylsilane (2c):



oil. IR (neat) 2958, 1895, 1588, 1499, 1104 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (s, 6H), 7.05–7.11 (m, 2H), 7.38–7.56 (m, 7H) ; ^{13}C NMR ($CDCl_3$) δ –2.11, 115.15 (d, J = 19.6 Hz) , 128.06, 129.41, 133.89 (d, J = 3.4 Hz), 134.29, 136.28 (d, J = 7.1 Hz), 138.14, 163.94 (d, J = 247 Hz); Found: C, 72.96; H, 6.83%. Calcd for $C_{14}H_{15}FSi$: C, 73.00; H, 6.56%.

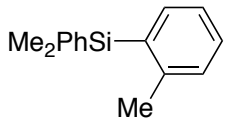
Dimethylphenyl(4-triisopropylsiloxy)silane (2e):



oil. IR (neat) 2946, 1591, 1501, 1273, 1112, 814 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.51 (s, 6H), 1.10 (d, J = 6.9 Hz, 18H), 1.09–1.31 (m, 3H), 6.85–6.87 (m, 2H), 7.31–7.37 (m, 5H), 7.48–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$) δ –1.98, 12.88, 18.12, 119.66, 127.90, 129.11, 129.37, 134.34, 135.75, 139.07,

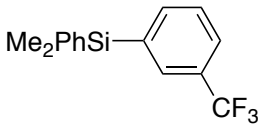
157.25; HRMS Found: 384.2307 (Δ = 0.5 ppm), Calcd for $C_{23}H_{36}OSi_2$: 384.2305.

Dimethyl(2-methylphenyl)phenylsilane (2f):



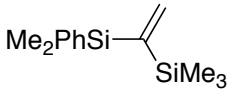
oil. IR (neat) 2959, 2230, 1599, 1385, 1109, 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (s, 6H), 2.26 (s, 3H), 7.12–7.50 (m, 9H); ^{13}C NMR ($CDCl_3$) δ –1.21, 23.34, 125.10, 128.00, 129.10, 129.77, 130.04, 134.16, 135.54, 136.32, 139.13, 144.28; Found: C, 79.80; H, 8.29%. Calcd for $C_{15}H_{18}Si$: C, 79.58; H, 8.01%.

(3-Trifluoromethylphenyl)dimethylphenylsilane (2g):



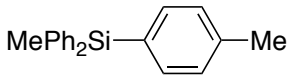
oil. IR (neat) 1600, 1429, 1327, 1119, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.61 (s, 6H), 7.36–7.86 (m, 9H); ^{13}C NMR ($CDCl_3$) δ –2.38, 124.57 (q, J = 271 Hz), 126.03 (q, J = 3.8 Hz), 128.19, 128.25, 129.65, 130.19 (q, J = 32 Hz), 130.58 (q, J = 3.8 Hz), 131.68 (q, J = 32 Hz), 134.30, 137.74, 139.99; Found: C, 64.27; H, 5.12%. Calcd for $C_{15}H_{15}F_3Si$: C, 64.26; H, 5.39%.

1-Trimethylsilyl-1-dimethylphenylsilylethene (2h):



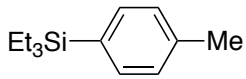
oil. IR (neat) 2956, 1428, 1249, 1111, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 9H), 0.40 (s, 6H), 6.33 (d, J = 4.8 Hz, 1H), 6.42 (d, J = 4.8 Hz, 1H), 7.34–7.37 (m, 3H), 7.48–7.51(m, 2H); ^{13}C NMR ($CDCl_3$) δ –1.56, –0.14, 127.79, 128.97, 134.24, 139.26, 142.07, 152.91; Found: C, 66.30; H, 9.24%. Calcd for $C_{13}H_{22}Si_2$: C, 66.59; H, 9.46%.

Methyl(4-methylphenyl)diphenylsilane (3a):



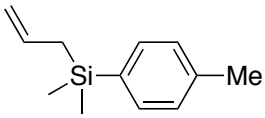
oil. IR (neat) 3068, 1600, 1428, 1110, 788 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (s, 3H), 2.35 (s, 3H), 7.16–7.52 (m, 14H); ^{13}C NMR ($CDCl_3$) δ –2.13, 21.71, 128.00, 128.90, 129.49, 132.58, 135.44, 135.52, 136.55, 139.51; Found: C, 83.15; H, 7.01%. Calcd for $C_{20}H_{20}Si$: C, 83.28; H, 6.99%.

Triethyl(4-methylphenyl)silane (3b):



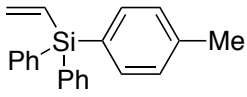
oil. IR (neat) 2954, 1605, 1459, 1105, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73–0.81 (m, 6H), 0.92–0.98 (m, 9H), 2.34 (s, 3H), 7.15–7.18 (m, 2H), 7.37–7.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 3.57, 7.61, 21.65, 128.71, 133.86, 134.42, 138.66; Found: C, 75.38; H, 10.94%. Calcd for $C_{13}H_{22}Si$: C, 75.65; H, 10.74%.

Allyldimethyl(4-methylphenyl)silane (3c):



oil. IR (neat) 2957, 1634, 1248, 1107, 838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.26 (s, 6H), 1.74 (d, J = 8.1 Hz, 2H), 2.35 (s, 3H), 4.81–4.89 (m, 2H), 5.70–5.85 (m, 1H), 7.16–7.19 (m, 2H), 7.40–7.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ –3.23, 21.64, 23.96, 113.44, 128.77, 133.85, 134.95, 135.16, 139.04; Found: C, 75.48; H, 9.71%. Calcd for $C_{12}H_{18}Si$: C, 75.71; H, 9.53%.

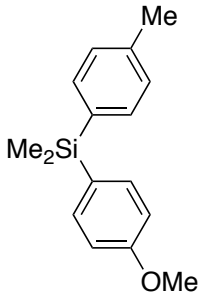
(4-Methylphenyl)diphenylvinylsilane (3d):



oil. IR (neat) 3064, 1599, 1428, 1110, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 5.79 (dd, J =

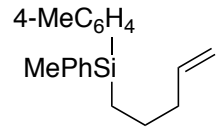
3.6 Hz, 20.1 Hz, 1H), 6.30 (dd, *J* = 3.6 Hz, 14.4 Hz, 1H), 6.68 (dd, *J* = 14.4 Hz, 20.1 Hz, 1H), 7.17–7.54 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 21.74, 128.01, 128.93, 129.67, 130.60, 134.22, 134.60, 136.11, 136.18, 136.82, 139.71; Found: C, 84.01; H, 6.68%. Calcd for $C_{21}H_{20}Si$: C, 83.94; H, 6.71%.

(4-Methoxyphenyl)dimethyl(4-methylphenyl)silane (4):



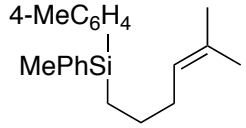
oil. IR (neat) 2956, 1595, 1502, 1278, 1113, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.50 (s, 6H), 2.34 (s, 3H), 3.80 (s, 3H), 6.88–6.91 (m, 2H), 7.15–7.18 (m, 2H), 7.39–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$) δ –1.92, 21.65, 55.20, 113.74, 128.81 129.45, 134.38, 135.16, 135.81, 139.07, 160.62; HRMS Found: 256.1286 (Δ = 1.0 ppm), Calcd for $C_{16}H_{20}OSi$: 256.1283.

5-[Methyl(4-methylphenyl)phenylsilyl]-1-pentene (5a):



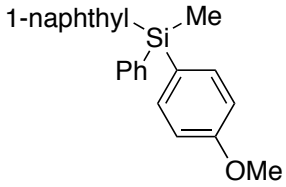
oil. IR (neat) 2923, 1639, 1428, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.52 (s, 3H), 1.03–1.08 (m, 2H), 1.42–1.52 (m, 2H), 2.08 (q, *J* = 6.6 Hz, 2H), 2.34 (s, 3H), 4.91–5.00 (m, 2H), 5.70–5.83 (m, 1H), 7.39–7.74 (m, 9H); ^{13}C NMR ($CDCl_3$) δ –4.19, 14.01, 21.67, 23.51, 37.78, 114.87, 127.94, 128.84, 129.20, 133.76, 134.63, 134.70, 137.77, 138.90, 139.16.

2-Methyl-6-methyl(4-methylphenyl)phenylsilyl-2-hexene (5b):



oil. IR (neat) 2923, 1603, 1427, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.51 (s, 3H), 1.02–1.08 (m, 2H), 1.35–1.49 (m, 2H), 1.56 (s, 3H), 1.67 (s, 3H), 2.00 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 5.08 (t, *J* = 7.2 Hz, 1H), 7.15–7.17 (m, 2H), 7.31–7.51 (m, 7H); ^{13}C NMR ($CDCl_3$) δ –4.16, 14.21, 17.94, 21.67, 24.33, 25.93, 32.09, 124.70, 127.92, 128.82, 129.15, 131.79, 133.90, 134.64, 134.71, 137.91, 139.10; HRMS Found: 308.1958 (Δ = –0.7 ppm), Calcd for $C_{21}H_{28}Si$: 308.1960.

(4-methoxyphenyl)methyl(1-naphthyl)phenylsilane (7):



oil. IR (neat) 2854, 1591, 1458, 1377, 1107, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 3H), 3.80 (s, 3H), 6.89–6.91 (m, 2H), 7.23–7.54 (m, 11H), 7.84–7.92 (m, 3H); ^{13}C NMR ($CDCl_3$) δ –1.65, 55.18, 113.91, 125.29, 125.58, 125.81, 127.40, 128.09, 129.07, 129.27, 129.45, 130.61, 133.62, 134.49, 135.47, 136.68, 137.00, 137.16, 137.34, 160.83; HRMS Found: 354.1437 (Δ = –0.9 ppm), Calcd for $C_{24}H_{22}OSi$: 354.1140.

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5. Silver-catalyzed coupling reaction of alkyl Grignard reagent and alkyl halide where the alkyl groups are the same: (a) Tamura, M.; Kochi, J. K. *Synthesis* **1971**, 303–305; silver-catalyzed oxidative homocoupling reactions of Grignard reagents: (b) Nagano, T.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1152–1153; (c) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1120–1127; silver- catalyzed cross-coupling reactions of allylic Grignard reagents and alkyl

halides: (d) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 969–971.

6. The reaction proceeded with similar efficiency when it was performed in the presence of triphenylphosphane (10 mol%). However, the use of tri-tert-butylphosphane as well as an *N*-heterocyclic carbene ligand (SIMes·HCl; Mes = 2,4,6-trimethyl-phenyl) led to decreased yields of **2a**, 84% and 78%, respectively.
7. For each reaction in Tables 2 and 3, the author confirmed that the process was inefficient in the absence of the silver catalyst.
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15. Commercially available from Shin-Etsu Chemical Co., Ltd.

Chapter 6

Zinc-Catalyzed Nucleophilic Substitution Reaction of Chlorosilanes with Organomagnesium Reagents

Zinc-catalyzed nucleophilic substitution reactions of chlorosilanes with organomagnesium reagents afford various tetraorganosilanes under mild reaction conditions. The reactions can be performed on large scale and allow efficient preparation of functionalized tetraorganosilanes.

Chapter 6

Introduction

The nucleophilic substitution reaction of chlorosilanes with organometallic reagents is a fundamental method to synthesize various tetraorganosilanes. The reactions of chlorosilanes with organolithium reagents generally proceed smoothly at very low temperature.[1] However, the reactions with the less reactive organomagnesium reagents often require prolonged reaction times and high temperature to complete the reaction. Addition of a catalytic amount of cyanide or thiocyanate is known to facilitate the transmetalation reaction of chlorosilanes with organomagnesium reagents.[2] However, the use of the toxic anions should be avoided.

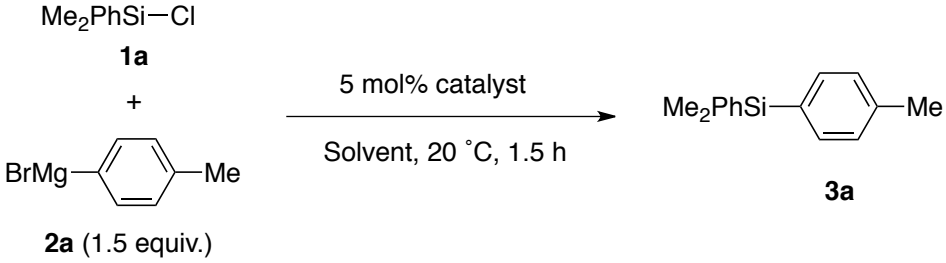
Results and Discussion

During the course of the author's study on metal-catalyzed transmetalation of chlorosilanes,[3] the author found zinc salts are efficient catalysts for transmetalation reactions between chlorosilanes and organomagnesium reagents. Zinc has many practical advantages as a catalyst due to its low cost, environmental friendliness, and low toxicity.[2] In addition, the present zinc-catalyzed reactions have proved to be more versatile than the previous silver-catalyzed ones.[3,4]

Treatment of chlorodimethylphenylsilane (**1a**) with 4-methylphenylmagnesium bromide (**2a**) in the presence of a catalytic amount of zinc chloride in THF at 20 ˚C for 1.5 h provided the corresponding tetraorganosilane **3a** in 67% yield (Table 1, entry 2). In the absence of zinc chloride, **3a** was obtained in only 13% yield (Table 1, entry 1). Other zinc salts, such as zinc halides, acetate, and zinc chloride • *N*,*N*,*N*',*N*'-tetramethylethylenediamine complex ($ZnCl_2$•TMEDA), accelerated the reaction (Table 1, entries 3–7). The author chose $ZnCl_2$•TMEDA as the best catalyst because $ZnCl_2$•TMEDA is stable and easy to handle under air as well as being sufficiently active. Finally, the use of 1,4-dioxane improved the catalytic activity, and the reaction completed within 1 h with the aid of only 1 mol % of the catalyst to

furnish **3a** in 84% yield (Table 1, entry 8). Zinc fluoride, which showed a competing catalytic activity in THF, was not effective in 1,4-dioxane (entry 5 vs. entry 9).[5]

Table 1. Zinc-Catalyzed Reaction of Chlorodimethylphenylsilane with 4-Methylphenylmagnesium Bromide



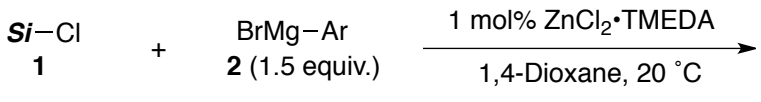
entry	catalyst	solvent	yield(%)[a]
1	none	THF	13
2	$ZnCl_2$	THF	67
3	$ZnBr_2$	THF	75
4	ZnI_2	THF	69
5	ZnF_2	THF	80
6	$Zn(OAc)_2$	THF	62
7	$ZnCl_2$•TMEDA	THF	77
8	$ZnCl_2$•TMEDA[b]	1,4-Dioxane	84[c]
9	ZnF_2	1,4-Dioxane	18

[a] The yields were determined by ^1H NMR spectroscopy.
[b] The reaction was performed with 1 mol% of $ZnCl_2$•TMEDA for 1 h.
[c] Isolated yield.

The scope of arylmagnesium reagents and chlorosilanes was studied, and the results are summarized in Table 2. The reactions with sterically hindered, electron-rich, and electron-deficient arylmagnesium reagents (Table 2, entries 1–3) proceeded as smoothly as that described in entry 8 in Table 1. A chlorosilane **1b** having a chloromethyl moiety (Table 2, entry 4) reacted without any observable side reactions. The reaction of bulkier chloromethyldiphenylsilane (**1c**) with 4-methylphenylmagnesium bromide under zinc catalysis proceeded to completion after extended reaction time (Table 2, entry 5). However, the reaction of

chlorotriethylsilane (**1d**) was slow and did not complete even at 40 ˚C for 12 h (Table 2, entry 6).[6] The reaction of more reactive triethylsilyl triflate (**1d'**) proceeded smoothly at 20 ˚C in 7 h and the yield was improved to 73% (Table 2, entry 7). Sterically congested *t*-butylchlorodimethylsilane failed to react with arylmagnesium reagents (Table 2, entry 8).

Table 2. Scope of Chlorosilanes and Arylmagnesium Reagents[a]



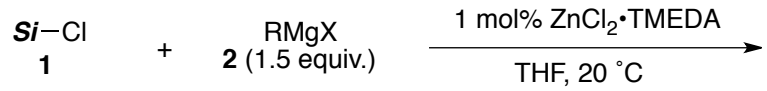
entry	**1**, ***Si***	**2**, Ar	time (h)	**3**	yield(%)[b]
1	**1a**, $PhMe_2Si$	**2b**, 2-MeC_6H_4	5	**3b**	92
2	**1a**, $PhMe_2Si$	**2c**, 4-$MeOC_6H_4$	1	**3c**	87
3	**1a**, $PhMe_2Si$	**2d**, 3-$CF_3C_6H_4$	3	**3d**	99
4	**1b**, $(ClCH_2)Me_2Si$	**2e**, Ph	15	**3e**	74
5	**1c**, Ph_2MeSi	**2a**, 4-MeC_6H_4	3	**3f**	89
6	**1d**, Et_3Si	**2a**, 4-MeC_6H_4	2	**3g**	30[c]
7	**1d'**[d], Et_3Si	**2a**, 4-MeC_6H_4	12	**3h**	73
8	**1e**, $^tBuMe_2Si$	**2a**, 4-MeC_6H_4	7	**3i**	trace[e]

[a] Performed on a 0.5 mmol scale.
[b] Isolated yield.
[c] The reaction was performed at 40 ˚C.
[d] Et_3SiOTf (**1d'**) was used instead of Et_3SiCl (**1d**).
[e] The reaction was performed at 100 ˚C.

Generally, the thermal stability of organosilver reagents was poor.[7] Therefore, only aryl- and bulky 1-alkenylmagnesium reagents were applicable to the arylation and alkenylation of chlorosilanes under the silver catalysis.[3] On the other hand, zinc catalysis broadened the scope of the organomagnesium reagents. Treatment of chlorodimethylphenylsilane (**1a**) with isopropenylmagnesium bromide (**2f**) in the presence of a catalytic amount of $ZnCl_2$•TMEDA in THF[8] provided the corresponding tetraorganosilane **4a** in 84% yield (Table 3, entry 1). Silane **4a** was obtained in 46% yield in the presence of silver nitrate[3] instead of $ZnCl_2$•TMEDA. The reaction with vinylmagnesium bromide also proceeded smoothly (Table 3, entry 2). Not only

vinylmagnesium reagents but also benzylmagnesium reagent was applicable (Table 3, entry 3). Sterically congested chlorotriisopropylsilane (**1f**) was treated with allylmagnesium chloride. The corresponding allylsilane **4d** was obtained in 91% yield (Table 3, entry 4). Under the silver catalysis **1f** was too congested to react. Treatment of chlorotriisopropylsilane with butylmagnesium bromide in the presence of zinc salts did not provide the corresponding butylsilane **4e** (Table 3, entry 5).[9]

Table 3. Scope of Organomagnesium Reagents[a]

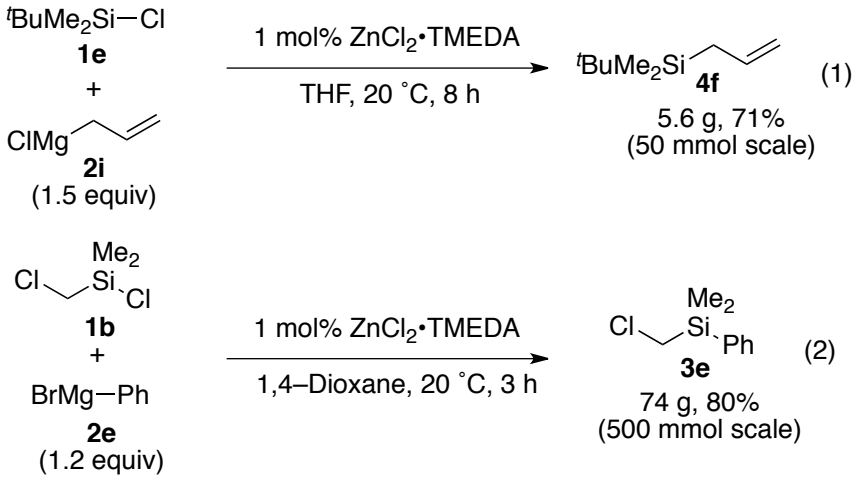


entry	**1**, ***Si***	**2**, RMgX	time (h)	**4**	yield(%)[b]
1	**1a**, $PhMe_2Si$	**2f**, CH_2=CMeMgBr	3	**4a**	84 (46)[c]
2	**1c**, Ph_2MeSi	**2g**, CH_2=CHMgBr	2	**4b**	71
3	**1e**, $^tBuMe_2Si$	**2h**, $PhCH_2MgCl$	7	**4c**	70
4	**1f**, $^iPr_3Si$	**2i**, CH_2=$CHCH_2MgCl$	12	**4d**	91 (trace)[c]
5	**1f**, $^iPr_3Si$	**2j**, BuMgBr	1	**4e**	trace

[a] Performed on a 0.5 mmol scale.
[b] Isolated yield.
[c] $AgNO_3$ was used instead of $ZnCl_2$•TMEDA.

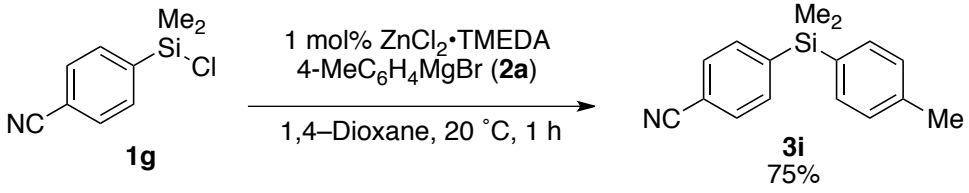
The reaction can be performed on a large scale. *tert*-Butylchlorodimethylsilane (**1e**, 50 mmol) was treated with allylmagnesium chloride (**2i**) in the presence of 1 mol % of $ZnCl_2$•TMEDA for 8 h. After distillation, allyl(*tert*-butyl)dimethylsilane (**4f**) was obtained in 71% yield (Scheme 1, eq. 1). Treatment of 500 mmol of chloro(chloromethyl)dimethylsilane (**1b**) with 1.2 equiv of phenylmagnesium bromide for 3 h provided 74 g (80%) of (chloromethyl)dimethylphenylsilane (**3e**) (Scheme 1, eq. 2).

Scheme 1. Large-Scale Reactions



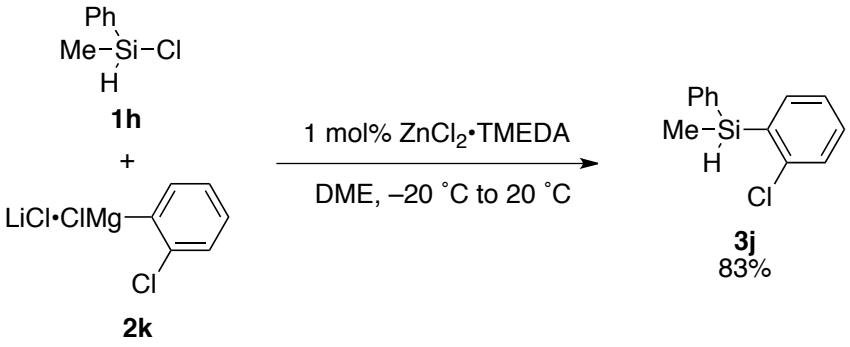
Because this reaction can proceed under mild reaction conditions, functionalized chlorosilanes such as chloro(4-cyanophenyl)dimethylsilane (**1g**) were also available for this method (Scheme 2).

Scheme 2. Reaction of Functionalized Chlorosilane



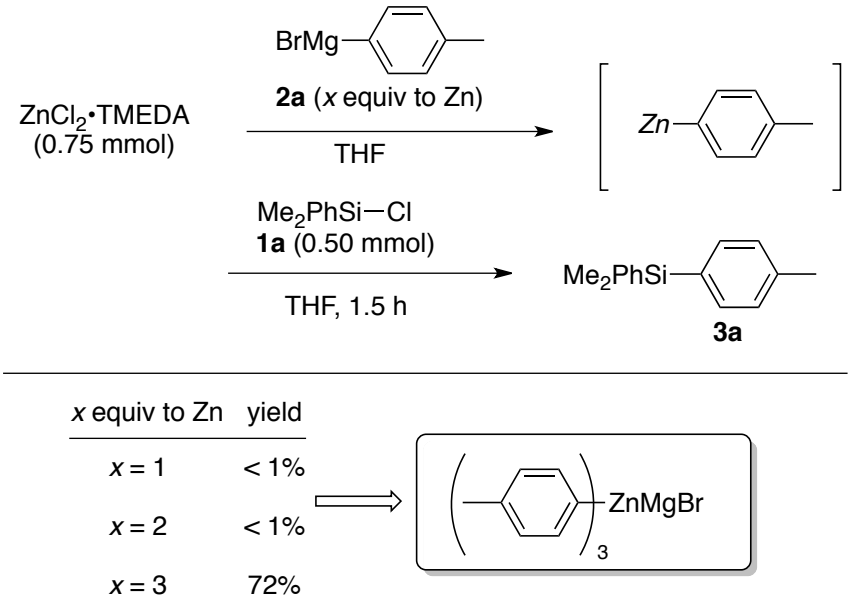
Treatment of chloromethylphenylsilane (**1h**) with 2-chlorophenylmagnesium chloride • LiCl complex, which was prepared by halogen-magnesium exchange,[11] provided the corresponding organosilane **3j** in 83% yield (Scheme 3). The reaction was clean, and only a trace amount of disiloxane $(PhMeHSi)_2O$ was detected.

Scheme 3. Reaction with 2-Chlorophenylmagnesium Chloride • LiCl complex



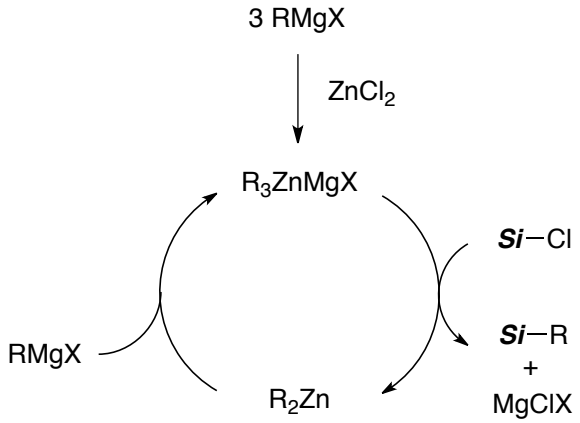
To gain information about the active species of this reaction, the reaction of **1a** with stoichiometric zinc reagents was examined with varying amounts of 4-MeC_6H_4MgBr. Treatment of **1a** (0.5 mmol) with a zinc complex, prepared from $ZnCl_2$•TMEDA (0.75 mmol) and 4-MeC_6H_4MgBr (0.75 mmol), did not provide **3a** at all. A diarylzinc reagent, generated from $ZnCl_2$•TMEDA (0.75 mmol) and 4-MeC_6H_4MgBr (1.5 mmol), also failed to react with **1a**. A reagent prepared from $ZnCl_2$•TMEDA (0.75 mmol) and 4-MeC_6H_4MgBr (2.25 mmol) dramatically changed the outcome. The desired arylsilane **3a** was obtained in 72% yield (Scheme 4). Hence, the active species of this reaction would be a zincate, $(4\text{-}MeC_6H_4)_3ZnMgX$ (X = Cl or Br).[12]

Scheme 4. Reactions of **1a** with Arylzinc Reagents



Scheme 5 illustrates a plausible reaction mechanism. Triorganozincate is initially generated from zinc chloride and 3 equiv of a Grignard reagent. The zincate effects smooth organic group transfer to afford the corresponding silane with concomitant formation of diorganozinc. The initial triorganozincate is regenerated by the reaction of diorganozinc with the remaining Grignard reagent. The exact role of TMEDA is not clear at this stage.

Scheme 5. Plausible Mechanism



Conclusion

The author reports the zinc-catalyzed nucleophilic substitution reaction of chlorosilanes with organomagnesium reagents. The reaction described here provides a mild and efficient method for the preparation of tetraorganosilanes.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (300 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on Varian Mercury 300 and UNITY INOVA 500 spectrometers and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to $SiMe_4$ at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. $ZnCl_2$•TMEDA was purchased from Aldrich Chemical Co., Inc. and used as it is. Arylmagnesium bromide was prepared from magnesium turnings (Nacalai Tesque, Inc.) and the corresponding bromoarene in THF. THF was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. 1,4-Dioxane was purchased from Wako Pure Chemical Industries Ltd. And used as it is. Chlorosilanes were purchased from Aldrich Chemical Co., Inc., Shin-Etsu Chemical Co., Ltd., and Tokyo Chemical Industry Co., Ltd.

Typical Procedure for Zinc-Catalyzed Reactions: The reaction of **1a** with 4-methylphenylmagnesium bromide (Table 1, entry 8) is representative. $ZnCl_2$•TMEDA (1.3 mg, 0.005 mmol) was placed in a 20-mL reaction flask under argon. Chlorodimethylphenylsilane (85 mg, 0.50 mmol) in 1,4-dioxane (1 mL) was added to the flask. Then, 4-methylphenylmagnesium bromide (1.0 M THF solution, 0.75 mL, 0.75 mmol) was added. The mixture was stirred at 20 ˚C for 1 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined

organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded dimethyl(4-methylphenyl)phenylsilane (**3a**, 95.2 mg, 0.42 mmol) in 84% yield.

Procedure for Large-Scale Reaction (Scheme 1, eq. 2): $ZnCl_2$•TMEDA (1.26 g, 5 mmol) was placed in a 2-L reaction flask under argon. Chloro(chloromethyl)dimethylsilane (71.5 g, 500 mmol) in 1,4-dioxane (500 mL) was added to the flask. The flask was cooled to 0 ˚C. Phenylmagnesium bromide (1.2 M THF solution, 500 mL, 600 mmol) was subsequently added over 20 min. After the completion of the addition, the mixture was warmed to 20 ˚C and stirred at the same temperature for 3 h. The reaction mixture was quenched with an ice-cold saturated aqueous solution of NH_4Cl (300 mL). The organic compounds were extracted with ethyl acetate three times (3 × 100 mL). The combined organic part was washed with brine (100 mL). Then, the organic part was dried over Na_2SO_4 and concentrated in vacuo. After evaporation, the residue was distilled to give (chloromethyl)dimethylphenylsilane (**3e**, 74.0 g, 400 mmol, bp 105 ˚C at 19 mmHg) in 80% yield.

The (chloromethyl)dimethylphenylsilane synthesis reaction was checked by Jane Panteleev and Mark Lautens in the *Organic Synthesis*. The procedures performed by checker were shown below.

(Chloromethyl)dimethylphenylsilane synthesis. A flame-dried 1-L, three-necked, round-bottomed flask is equipped with a 500-mL pressure equalizing dropping funnel fitted with a septum, a two-way stopcock with an argon inlet, an internal temperature probe, and a 5-cm egg-shaped stirring bar. Dichloro(*N,N,N',N'*-tetramethylethylenediamine)zinc (0.64 g, 2.5 mmol, 1 mol%)[13] is placed in the flask, and the apparatus is purged with argon. 1,4-Dioxane (240 mL)[14] is added to the flask at 23 °C. Chloro(chloromethyl)dimethylsilane (33.8 mL, 250 mmol)[1] is added to the flask through the dropping funnel at 23 °C. The dropping funnel is rinsed

with 1,4-dioxane (10 mL). The mixture is cooled in an ice/water bath over 10 min. Phenylmagnesium bromide[15] (1.0 M in THF, 300 mL, 300 mmol, 1.2 equiv) is then transferred to the dropping funnel using a 14 guage metal cannula and is added dropwise to the mixture over 30 min with cooling in an ice/water bath. The addition immediately leads to the formation of white salts. A gentle exothermic reaction takes place. After the completion of the addition, the resulting mixture is allowed to warm to ambient temperature (23 °C) and stirred for an additional 2 h. The reaction mixture is poured over 5 min into a rapidly stirred ice-cold saturated aqueous ammonium chloride solution (150 mL)[14] in a 1-L Erlenmeyer flask equipped with a 5-cm octagonal magnetic stirring bar. The mixture is transferred to a 1-L separatory funnel, and the Erlenmeyer and round-bottomed flasks are rinsed with ethyl acetate (25 mL each)[14]. The organic phase is separated, and the aqueous layer is extracted with ethyl acetate (50 mL × 3). The combined organic layers are washed with brine (50 mL), dried once over anhydrous Na_2SO_4 (25 g)[14], filtered through filter paper, and concentrated with a rotary evaporator (35 °C, 34–38 mmHg). Evaporation is stopped at the time when the volume of the mixture is reduced to approximately 75 mL[16]. The mixture is transferred to a 100-mL round-bottomed flask equipped with a magnetic stirring bar. The flask is then equipped with a Vigreux column (20 cm) topped with a distillation head and receiver. Vacuum (23 mmHg) is applied, and remaining 1,4-dioxane is removed until bubbling ceases. The flask is gradually heated in an oil bath to a bath temperature of 155 °C. After the temperature of the fraction reaches 115 °C, a forerun (ca. 1 mL) is collected and discarded. The desired product is then obtained, distilling at 115 °C (23 mmHg). The product weighs 37–38 g (200–203 mmol, 80–81%) and is obtained as a stable, clear, colorless liquid[17,18].

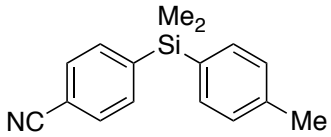
Procedure for the Synthesis of 2-Chlorophenylphenylmethylsilane. 2-Chloroiodobenzene (179 mg, 0.75 mmol) was placed in a 20-mL reaction flask under argon and dissolved in DME (1 mL). The flask was cooled to –20 °C. ^{i}PrMgCl·LiCl (1.0 M THF solution, 0.80 mL, 0.80 mmol) was introduced dropwise to the flask. The reaction mixture was stirred for 1 h at –20 °C.

$ZnCl_2$•TMEDA (1.3 mg, 0.005 mmol) and chloromethylphenylsilane (**1h**, 78.3 mg, 0.50 mmol) were sequentially added at the same temperature. The mixture was stirred for 8 h at –20 °C. The mixture was allowed to warm slowly to 20 °C and stirred for 12 h at the same temperature. A saturated aqueous solution of NH_4Cl (2 mL) was then added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography with hexane as an eluent afforded 2-chlorophenylmethylphenylsilane (**3j**, 97.4 mg, 0.42 mmol) in 83% yield.

Characterization Data

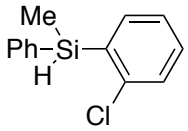
Products **3a**–**g**,[3] **4a**,[19] **4c**,[20] and **4d**[21] are known compounds and showed the identical spectra according to the literature.

(4-Cyanophenyl)dimethyl(4-methylphenyl)silane (3i):



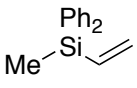
oil; IR (neat) 2959, 2230, 1599, 1385, 1109, 818 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.56 (s, 6H), 2.36 (s, 3H), 7.18–7.21 (m, 2H), 7.37–7.40 (m, 2H), 7.59 (s, 4H); ^{13}C NMR ($CDCl_3$) δ –2.52, 21.66, 112.73, 119.18, 129.07, 131.15, 132.91, 134.30, 134.74, 139.81, 145.85; HRMS found 251.1127 (Δ = –1.4 ppm), calcd for $C_{16}H_{17}NSi$ 251.1130.

2-Chlorophenylmethylphenylsilane (3j):



oil; IR (neat) 3052, 2139, 1581, 1428, 1252 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (d, *J* = 3.9 Hz, 3H), 5.05 (q, *J* = 3.9 Hz, 1H), 7.19-7.42 (m, 7H), 7.57-7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ –4.95, 126.30, 128.15, 129.26, 129.81, 131.49, 134.54, 135.14, 135.27, 137.41, 141.48. Anal. Calcd for $C_{13}H_{13}ClSi$: C, 67.08; H, 5.63. Found: C, 67.09; H, 5.77.

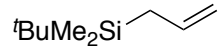
Methyldiphenylvinylsilane (4b):



oil; IR (neat) 3069, 1593, 1428, 1251, 1113 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63 (s, 3H), 5.78 (dd, *J* =

3.9, 20.1 Hz, 1H), 6.19 (dd, *J* = 3.9, 14.4 Hz, 1H), 6.47 (dd, *J* = 14.4, 20.1 Hz, 1H), 7.36-7.37 (m, 6H), 7.50-7.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ –3.96, 128.02, 129.49, 135.01, 135.11, 135.99, 136.41. Anal. Calcd for $C_{15}H_{16}Si$: C, 80.30; H, 7.19. Found: C, 80.54; H, 7.20.

Allyl(*tert*-butyl)dimethylsilane (4f):



oil; IR (neat) 2929, 1632, 1472, 1252, 893 cm^{-1}; ^{1}H NMR ($CDCl_3$) –0.05 (s, 6H), 0.89 (s, 9H), 1.53 (d, *J* = 8.1 Hz, 2H), 4.79–4.88 (m, 2H), 5.73-5.87 (m, 1H); ^{13}C NMR ($CDCl_3$) –6.44, 16.95, 20.85, 26.74, 112.85, 135.90. Anal. Calcd for $C_9H_{20}Si$: C, 69.14; H, 12.89. Found: C, 69.05; H, 13.06.

References and Notes

1. (a) *Science of Synthesis (Houben-Weyl)*; Fleming, I., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2002; Vol. 4, Chapter. 4.4. (b) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; Wiley: New York, 2000, Chapter 5. (c) Birkofer, L.; Stuhl, O. *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1989; Chapter 10.
2. Lennon, P. J.; Mack, D. P.; Thompson, Q. E. *Organometallics* **1989**, *8*, 1121–1122.
3. Murakami, K.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 5833–5835.
4. Historically, alkylations of halosilane were demonstrated for the first time by using diorganozinc reagents under harsh reaction conditions: (a) Friedel, C.; Crafts, J. M. *Ann.* **1863**, *127*, 28–29. (b) Friedel, C.; Crafts, J. M. *Ann.* **1865**, *136*, 203–204.
5. Treatment of **1a** with zinc fluoride in THF provided Me_2PhSiF, which is more reactive toward the nucleophilic substitution with **2a**. Thus, the mechanism of activating chlorosilane **1a** may be different from that of other zinc salts.
6. The reaction of chlorotriethylsilane proceeded smoothly in the presence of a catalytic amount of silver nitrate, see ref 3.
7. Schmidbaur, H.; Bayler, A. *The chemistry of organic derivatives of gold and silver*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1999; Chapter 7.
8. THF was the best solvent in the reactions with vinyl-, benzyl-, and allylmagnesium reagents. 1,4-Dioxane retarded the reactions.
9. Treatment of chloromethyldiphenylsilane with 4-pentenylmagnesium bromide for 3 h provided the desired product in 32% yield in the absence of any zinc salts. However, no acceleration of the reaction was observed even when zinc salts were added.
10. Ultrasound irradiation was required for the synthesis of allylsilane **4f**, see: Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954–4961.

11. Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336.

12. For recent examples of zincate chemistry see: (a) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998–9999. (b) Studte, C.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 5451–5455. (c) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, K. *Angew. Chem., Int. Ed.* **2007**, *47*, 3802–3824. (d) Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2004**, *126*, 11146–11147. (e) Uchiyama, M.; Nakamura, S.; Ohwada, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 10897–10903. (f) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934–4946. (g) Uchiyama, M.; Furumoto, S.; Saito, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 11425–11433.

13. Dichloro(*N,N,N',N'*-tetramethylethylenediamine)zinc (98%) and chloro(chloromethyl)dimethylsilane (98%) were purchased from Aldrich Chemical Co., Inc. and used as is.

14. 1,4-Dioxane (99%, anhydrous, water <50 ppm), ammonium chloride (99.5%), ethyl acetate (99%), and anhydrous sodium sulfate (99%) were obtained from Wako Pure Chemical Industries Ltd. and were used as received by the submitters. 1,4-Dioxane (99.8%, anhydrous, <0.003% water) and ethyl acetate (>99.5%) were purchased from Aldrich Chemical Co., Inc. and used as received by the checkers. Ammonium chloride (99.5%) and anhydrous sodium sulfate (99%) were purchased from ACP Chemicals Inc., and used as they were by the checkers.

15. Phenylmagnesium bromide solution (1.0 M in tetrahydrofuran) was purchased from Aldrich Chemical Co., Inc, and was used as received by the checkers. The submitters synthesized phenylmagnesium bromide (1.0 M in tetrahydrofuran) from bromobenzene and magnesium turnings.

16. The submitters concentrated the solution using a rotary evaporator (30 °C, 10 mmHg) and noted that the yield of (chloromethyl)dimethylphenylsilane can be decreased when evaporation is performed under lower pressure or for a prolonged time.

17. The product exhibits the following physicochemical properties: IR (film, NaCl) 3070, 2963, 1427, 1250, 1119, 841, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.42 (s, 6 H), 2.96 (s, 2 H), 7.35–7.44 (m, 3 H), 7.52–7.57 (m, 2 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ: –4.5, 30.4, 128.0, 129.7, 133.7, 136.1; MS (EI) *m/z* (relative intensity): 186 (2), 184 (13), 171 (9), 155 (10), 135 (100); HRMS (EI): *m/z* calcd. for $C_9H_{13}ClSi$ 184.0475; found 184.0473.
18. The purity (99%) was determined by GC using a Phenomenex ZB-5 ms column (30 m × 0.25 mm with 0.25 μm film thickness) (oven temperature: 50 °C for 5 min, ramp 50 °C per min to 300 °C; outlet flow: 1 mL/min; carrier gas: helium; retention time: 6.3 min). The submitters report: Anal. calcd. for $C_9H_{13}ClSi$: C, 58.51; H, 7.09; found: C, 58.45; H, 7.03.
19. Fleming, I.; Rowley, M.; Cuadrado, P.; González-Nogal, A. M.; Pulido, F. J. *Tetrahedron* **1989**, *45*, 413–424.
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Appendix

Rhodium-Catalyzed Arylzincation of Terminal Allenes Providing Allylzinc Reagents and Its Application to Versatile Three-component Coupling Reaction

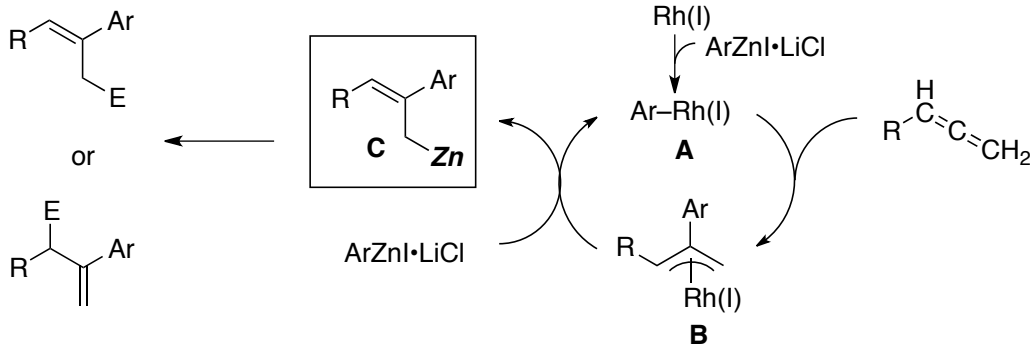
Rhodium-catalyzed regioselective arylzincation of terminal allenes affords synthetically useful functionalized allylzinc reagents. The allylzinc reagents react with a variety of electrophiles such as acetonitrile, offering a more versatile three-component coupling reaction.

Introduction

Multicomponent reactions of allenes have been attracting increasing attention owing to their inherent efficiency.[1] Among them, transition-metal-catalyzed three-component couplings involving allenes, organometallics, and carbonyls provide diversity-oriented synthesis of useful homoallylic alcohols.[2-4] In most cases, the couplings consist of (1) transmetalation from an organometallic reagent to a transition metal, (2) carbometalation of allene, and (3) nucleophilic attack of the resulting allylic transition metal to carbonyl. However, the couplings still remain unsatisfactory despite its importance: the electrophiles are limited to aldehydes and imines because of the low reactivity of the allylic transition metal intermediates.

Herein, the author withes to report rhodium-catalyzed arylzincation[5] of terminal allenes (Scheme 1).[6-9] The reaction represents a rare example of carbometalation of allenes accompanying accumulation of allylic metals in a reaction flask. The key is smooth transmetalation between allylrhodium **B** and arylzinc species. The resulting allylzinc reagents **C** are reactive enough to allylate a wider variety of electrophiles, realizing a more versatile three-component coupling reaction.

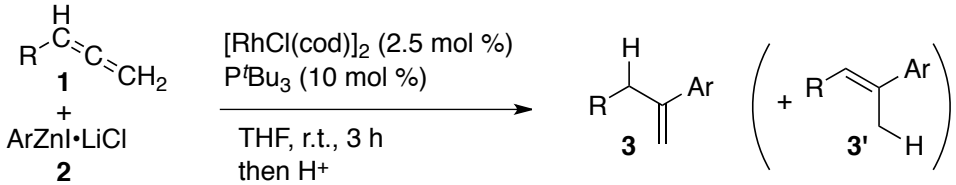
Scheme 1. Proposed Mechanism for Arylzincation of Allenes



Results and Discussion

Treatment of 1,2-tridecadiene (**1a**) with a phenylzinc iodide • LiCl complex in THF[10] in the presence of $[RhCl(cod)]_2$ and P^tBu_3 at room temperature for 3 h gave the corresponding arylated product **3a** in high yields (Table 1, entries 1 and 2). The reaction with 4-bromophenylzinc reagent **2b** also proceeded smoothly, leaving the bromo group untouched (entry 3). Arylzinc reagents bearing an electron-withdrawing or an electron-donating group were also applicable (entries 4 and 5). However, bulky 2-methylphenylzinc reagents **2e** failed to react (entry 6). Phenylzincation of allene **1b**-**1d** proceeded smoothly without loss of the siloxy, tosylamide, and additional olefinic moieties (entries 7–9). The reaction of 1-phenyl-1,2-propadiene (**1e**) afforded the phenylated product **3i** in 84% yield (entry 10).

Table 1. Scope of Allenes and Arylzinc Reagents[a]



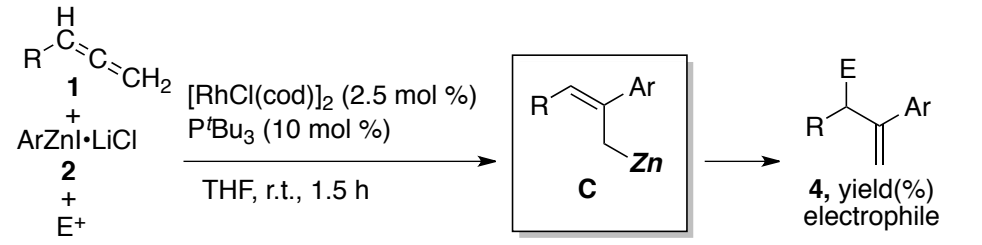
Entry	**1**, R	**2**, Ar	**3**, Yield(%)[b]
1	**1a**, $C_{10}H_{21}$	**2a**, Ph	**3a**, 80
2	**1a**, $C_{10}H_{21}$	**2a**, Ph	**3a**, 84[c]
3	**1a**, $C_{10}H_{21}$	**2b**, 4-BrC_6H_4	**3b**, 77
4	**1a**, $C_{10}H_{21}$	**2c**, 3-$CF_3C_6H_4$	**3c**, 74
5	**1a**, $C_{10}H_{21}$	**2d**, 3-$MeOC_6H_4$	**3d**, 77
6	**1a**, $C_{10}H_{21}$	**2e**, 2-MeC_6H_4	**3e**, Trace
7	**1b**, TBDMSO$(CH_2)_2$	**2a**, Ph	**3f**, 81
8	**1c**, Ts(Bn)N$(CH_2)_9$	**2a**, Ph	**3g**, 78
9	**1d**, CH_2=CH$(CH_2)_8$	**2a**, Ph	**3h**, 67
10[d]	**1e**, Ph	**2a**, Ph	**3i**, 84[e]

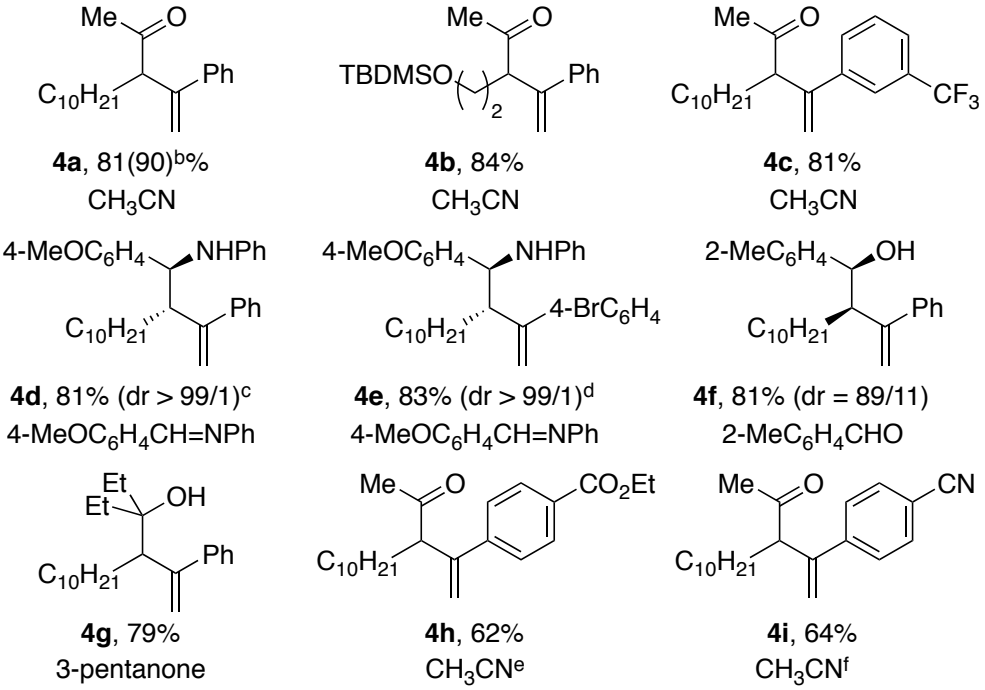
[a]The reaction was performed on a 0.3 mmol scale.
[b]A small amount of product **3'** was also obtained. The ratio of **3**/**3'** was 9/1 unless otherwise noted.
[c]The reaction was performed on a 3 mmol scale.
[d]Performed at 66 ˚C for 1.5 h.
[e]The ratio of **3i**/**3i'** was 97/3.

When acetonitrile was added to the allylzinc reagent **C** (1.7 equiv) derived from **1a** and **2a**, the corresponding ketone **4a** was obtained in 62% yield. Instead, a Barbier-type reaction by mixing **1a**, **2a**, and acetonitrile together under the rhodium catalysis improved the yield of **4a** up to 81% (Table 2). Barbier-type reactions of **C** with imines proceeded diastereoselectively to yield homoallylamines **4d** and **4e**. Aldehyde and ketone also participated in the reaction, and homoallyl alcohols **4f** and **4g** were obtained in good yields. Arylzinc reagents bearing an ester or a nitrile group were also applicable to the reaction without the loss of the functional groups by using excess amounts of acetonitrile.

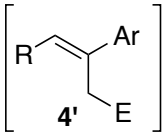
The high yield and isomer ratio of **4f** suggest that the allylzinc **C**, not allylrhodium **B**, is responsible for the allylation reaction. An allylzinc reagent was prepared from 1-chloro-2-phenyl-2-tridecene, zinc powder, and lithium chloride.[11] Treatment of 2-methylbenzaldehyde with the allylzinc reagent afforded **4f** quantitatively in a diastereomeric ratio of 86:14. The ratio is very similar to that in Table 2. In contrast, the reaction with an allylrhodium reagent, derived from the allylzinc reagent and [RhCl(P^tBu_3)], gave a rather complex mixture which includes the major isomer of **4f** exclusively in 42% yield.

Table 2. Reaction of Allylzinc Intermediates with Various Electrophiles[a]



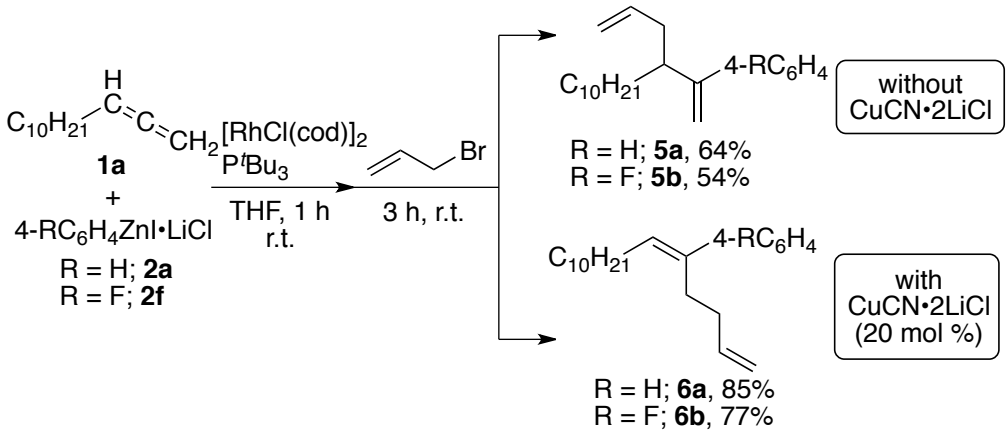


[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), electrophile (0.3 mmol).
[b]The reaction was performed on a 3 mmol scale.
[c]9% of isomer **4d'** was contained.
[d]10% of isomer **4e'** was contained.
[e]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), CH_3CN (0.9 mmol).
[f]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), CH_3CN (1 mL, 18 mmol).



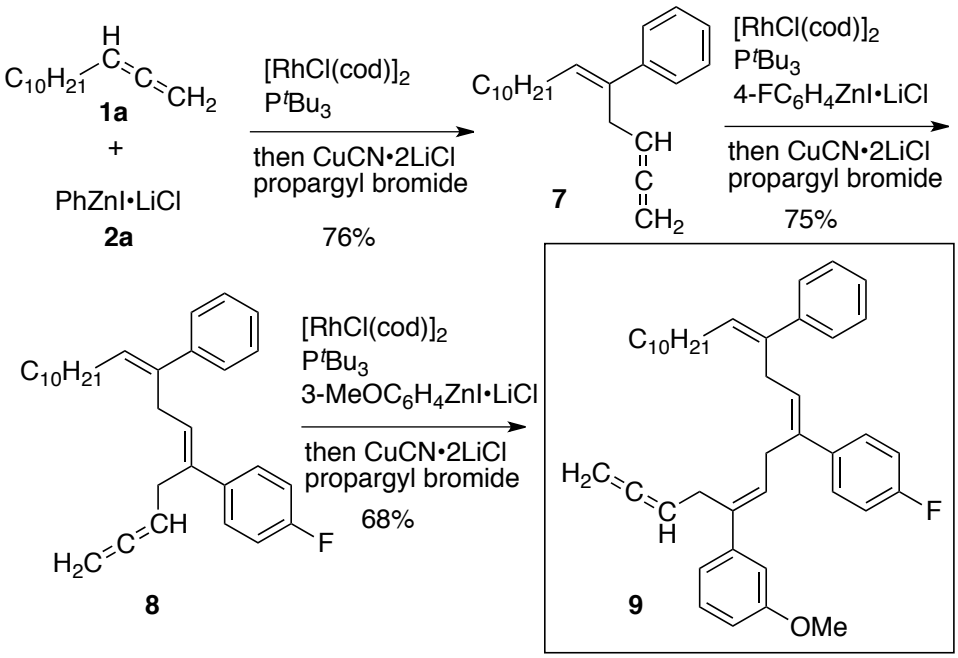
Allylzinc intermediates reacted with not only carbonyl compounds but also allyl bromide (Scheme 2). Treatment of allylzinc intermediates with allyl bromide afforded **5a** and **5b** in good yields. Interestingly, the sense of the regioselectivity was opposite when a copper catalyst was used (**6a** and **6b**).[12]

Scheme 2. Regioselective Reaction with Allyl Bromide Controlled by the Addition of a Catalytic Amount of CuCN•2LiCl



Finally, the author applied the reaction to the synthesis of stereodefined skipped polyene[13] via iterative arylzincation reactions (Scheme 3). Treatment of allene **1a** with phenylzinc reagent **2a** and subsequent reaction with propargyl bromide afforded the corresponding product **7** that has a terminal allene moiety in 76% yield. Iterative arylzincation reactions gave stereodefined (5*E*,8*E*,11*E*)-11-phenyl-8-(4-fluorophenyl)-5-(3-methoxyphenyl)-1,2,5,8,11-docosapenaene (**9**). It is noteworthy that no isomerization of the olefinic moiety of **9** was observed despite the basic reaction conditions.

Scheme 3. Synthesis of Stereodefined Skipped Polyene via Iterative Arylzincation Reaction



Conclusion

The author has found arylzincation of allenes to provide allyliczinc intermediate efficiently. The intermediate smoothly reacted with various electrophiles.

Experimental Section

Instrumentation and Chemicals

^{1}H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on a UNITY INOVA 500 spectrometer and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to $SiMe_4$ at 0.00 ppm for ^{1}H and relative to $CDCl_3$ at 77.2 ppm for ^{13}C unless otherwise noted. IR spectra were determined on a SHIMADZU FTIR-8200PC spectrometer. Mass spectra were determined on a JEOL Mstation 700 spectrometer. TLC analyses were performed on commercial glass plates bearing a 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakogel 200 mesh) was used for column chromatography. Elemental analyses were carried out at the Elemental Analysis Center of Kyoto University.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. $[RhCl(cod)]_2$ and P^tBu_3 were purchased from Wako Pure Chemical Industries, Ltd. THF was purchased from Kanto Chemical Co., stored under nitrogen, and used as it is. Arylzinc reagents were prepared from the corresponding aryl iodide and zinc powder (Wako Pure Chemical Industries, Ltd.) in the presence of LiCl (Wako Pure Chemical Industries, Ltd.)[10]. Allenes were prepared by the reaction reported by Crabbé[14] and Ma[15]. All reactions were carried out under argon atmosphere.

Typical procedure for rhodium-catalyzed reactions: The reaction of 1,2-tridecadiene with phenylzinc iodide • LiCl complex is representative. $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol) and P^tBu_3 (0.03 mL, 0.03 mmol, 1 M in hexane) were placed in a 20-mL reaction flask under argon. Phenylzinc iodide • LiCl complex (0.45 mL, 0.45 mmol, 1 M in THF) was added. Then, 1,2-tridecadiene (54 mg, 0.30 mmol) was added. The mixture was stirred at 25 °C for 3 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent

afforded 2-phenyl-1-tridecene (62 mg, 0.24 mmol) in 80% yield (contaminated with 7% of (*E*)-2-phenyl-2-tridecene).

Procedure for arylzincation of 1-phenyl-1,2-propadiene (1e): $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol) and P^tBu_3 (0.03 mL, 0.03 mmol, 1 M in hexane) were placed in a 20-mL reaction flask under argon. Phenylzinc iodide • LiCl complex (0.45 mL, 0.45 mmol, 1 M in THF) was added. The mixture was warmed to 66 ˚C. Then, 1-phenyl-1,2-propadiene (35 mg, 0.30 mmol) was slowly added over 10 min. The mixture was stirred at 66 ˚C for 1.5 h. After the reaction mixture was cooled to room temperature, an aqueous solution of HCl (1 M, 5 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded 2,3-diphenyl-1-propene (49 mg, 0.25 mmol) in 84% yield (contaminated with 3% of (*E*)-1,2-diphenyl-1-propene).

Typical procedure for rhodium-catalyzed reactions followed by subsequent reaction with electrophiles: The reaction of 1,2-tridecadiene with phenylzinc iodide • LiCl complex followed by subsequent reaction with acetonitrile is representative. $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol) and P^tBu_3 (0.03 mL, 0.03 mmol, 1 M in hexane) were placed in a 20-mL reaction flask under argon. Phenylzinc iodide • LiCl complex (0.50 mL, 0.50 mmol, 1 M in THF) was added. Then, acetonitrile (12 mg, 0.3 mmol) and 1,2-tridecadiene (90 mg, 0.50 mmol) was added. The mixture was stirred at 25 ˚C for 1.5 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane/ethyl acetate (20/1) as an eluent afforded 3-decyl-4-phenyl-4-penten-2-one (**4a**) (72 mg, 0.24 mmol) in 81% yield.

Typical procedure for rhodium-catalyzed reactions followed by subsequent reaction with allyl bromide: The reaction of 1,2-tridecadiene with phenylzinc iodide • LiCl complex followed by subsequent reaction with allyl bromide is representative. $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol) and P^tBu_3 (0.03 mL, 0.03 mmol, 1 M in hexane) were placed in a 20-mL reaction flask under argon. Phenylzinc iodide • LiCl complex (0.50 mL, 0.50 mmol, 1 M in THF) was added. Then, 1,2-tridecadiene (90 mg, 0.50 mmol) was added. The mixture was stirred at 25 ˚C for 1 h. CuCN•2LiCl (0.06 mL, 0.06 mmol. 1 M in THF) and allyl bromide (36 mg, 0.30 mmol) were subsequently added to the solution. The mixture was stirred for 3 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane as an eluent afforded 3-decyl-2-phenyl-1,5-hexadiene (**5a**) (57 mg, 0.19 mmol) in 64% yield.

Synthesis of skipped polyene:

Synthesis of **7**: $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol) and P^tBu_3 (0.03 mL, 0.03 mmol, 1 M in hexane) were placed in a 20-mL reaction flask under argon. Phenylzinc iodide • LiCl complex (0.50 mL, 0.50 mmol, 1 M in THF) was added. Then, 1,2-tridecadiene (90 mg, 0.50 mmol) was added. The mixture was stirred at 25 ˚C for 1 h. CuCN•2LiCl (0.06 mL, 0.06 mmol. 1 M in THF) and propargyl bromide (36 mg, 0.30 mmol) were subsequently added to the solution. The mixture was stirred for 3 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane/ethyl acetate (30/1) as an eluent afforded (*E*)-5-phenyl-1,2,5-hexadecatriene (**7**) (68 mg, 0.23 mmol) in 76% yield.

Synthesis of **8**: $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol) and P^tBu_3 (0.03 mL, 0.03 mmol, 1 M in hexane) were placed in a 20-mL reaction flask under argon. 4-Fluorophenylzinc iodide • LiCl

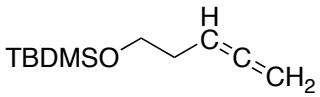
complex (0.60 mL, 0.60 mmol, 1 M in THF) was added. Then, (*E*)-5-phenyl-1,2,5-hexadecatriene (**7**) (178 mg, 0.60 mmol) was added. The mixture was stirred at 25 ˚C for 1 h. CuCN•2LiCl (0.06 mL, 0.06 mmol. 1 M in THF) and propargyl bromide (36 mg, 0.30 mmol) were subsequently added to the solution. The mixture was stirred for 3 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane/ethyl acetate (30/1) as an eluent afforded (5*E*,8*E*)-5-(4-fluorophenyl)-8-phenyl-1,2,5,8-nonadecatetraene (**8**) (99 mg, 0.23 mmol) in 75% yield.

Synthesis of **9**: $[RhCl(cod)]_2$ (3.7 mg, 0.0075 mmol) and P^tBu_3 (0.03 mL, 0.03 mmol, 1 M in hexane) were placed in a 20-mL reaction flask under argon. 3-Methoxyphenylzinc iodide • LiCl complex (0.45 mL, 0.45 mmol, 1 M in THF) was added. Then, (5*E*,8*E*)-5-(4-fluorophenyl)-8-phenyl-1,2,5,8-nonadecatetraene (**8**) (129 mg, 0.30 mmol) was added. The mixture was stirred at 25 ˚C for 1 h. CuCN•2LiCl (0.12 mL, 0.12 mmol. 1 M in THF) and propargyl bromide (71 mg, 0.60 mmol) were subsequently added to the solution. The mixture was stirred for 3 h. A saturated aqueous solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with ethyl acetate three times. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel by using hexane/ethyl acetate (30/1) as an eluent afforded (5*E*,8*E*,11*E*)-8-(4-fluorophenyl)-5-(3-methoxyphenyl)-11-phenyl-1,2,5,8,11-docosapentaene (**9**) (115 mg, 0.20 mmol) in 68% yield.

Characterization Data

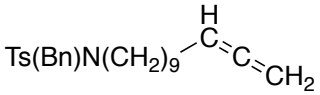
Compounds **1a**[15], **1e**[16], **3i**[17], and **3i'**[5k] are known compounds and showed the identical spectra with those in the literature.

5-(*tert*-butyldimethylsiloxy)-1,2-pentadiene (1b)



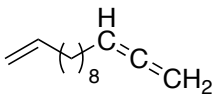
oil. IR (neat) 3735, 2930, 1954, 1717, 1507, 1257, 1102, 837, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 2.20–2.25 (m, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 4.65 (dt, *J* = 7.0 Hz, 3.0 Hz, 2 H), 5.11 (quint., *J* = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ –5.08, 18.52, 26.11, 32.20, 62.98, 74.66, 86.84, 209.25; Found: C, 66.35; H, 11.45%. Calcd for $C_{11}H_{22}OSi$: C, 66.60; H, 11.18%.

***N*-benzyl-*N*-(10,11-dodecadienyl)-*p*-toluenesulfonamide (1c)**



oil. IR (neat) 2924, 2854, 2500, 1952, 1597, 1157, 933, 810, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07–1.40 (m, 14H), 1.95–2.00 (m, 2H), 2.44 (s, 3H), 3.07 (t, *J* = 7.5 Hz, 2H), 4.31 (s, 2H), 4.65 (dt, *J* = 3.5 Hz, 7.0 Hz, 2H), 5.08 (quint., *J* = 7.0 Hz, 1H), 7.25–7.32 (m, 7H), 7.72–7.74 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.69, 26.77, 28.07, 28.44, 29.18, 29.19, 29.27, 29.43, 29.49, 48.26, 52.04, 74.71, 90.26, 127.39, 127.87, 128.47, 128.69, 129.84, 136.83, 137.47, 143.27, 208.70; HRMS Found: 425.2380 (Δ = –2.1 ppm), Calcd for $C_{26}H_{35}O_2NS$: 425.2389.

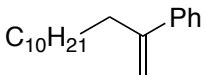
1,2,12-tridecatriene (1d)



oil. IR (neat) 3078, 2924, 2430, 1960, 1643, 995, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29–1.43 (m, 12H), 1.96–2.06 (m, 4H), 4.65 (dt, *J* = 3.5 Hz, 7.0 Hz, 2H), 4.92–5.01 (m, 2H), 5.09 (quint., *J* =

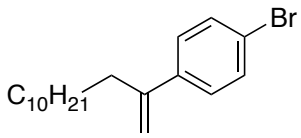
7.0 Hz, 1H), 5.77–5.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.47, 29.13, 29.27, 29.32, 29.33, 29.58, 29.64, 34.01, 74.67, 90.27, 114.29, 139.39, 208.72; Found: C, 87.26; H, 12.20%. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44%.

2-phenyl-1-tridecene (3a)



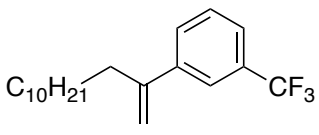
oil. IR (neat) 3065, 2925, 1738, 1628, 1466, 893, 777, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.25–1.31 (m, 16H), 1.42–1.48 (m, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 5.05 (d, *J* = 1.5 Hz, 1H), 5.26 (d, *J* = 1.5 Hz, 1H), 7.20–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.88, 28.47, 29.54 (Two signals merge.), 29.64, 29.80, 29.81, 29.84, 32.11, 35.56, 112.16, 126.31, 127.40, 128.40, 141.71, 149.02; Found: C, 88.04; H, 11.58%. Calcd for $C_{19}H_{30}$: C, 88.30; H, 11.70%.

2-(4-bromophenyl)-1-tridecene (3b)



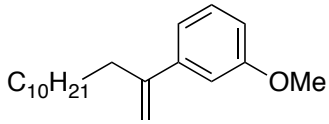
oil. IR (neat) 2924, 2853, 1628, 1075, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.24–1.31 (m, 16H), 1.41 (quint., *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 5.06 (d, *J* = 1.5 Hz, 1H), 5.24 (d, *J* = 1.5 Hz, 1H), 7.23–7.28 (m, 2H), 7.40–7.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.88, 28.35, 29.46, 29.53, 29.61, 29.71, 29.77, 29.82, 32.11, 35.42, 112.80, 121.32, 127.99, 131.49, 140.58, 147.92; Found: C, 67.95; H, 8.82%. Calcd for $C_{19}H_{29}Br$: C, 67.65; H, 8.66%.

2-(3-trifluoromethylphenyl)-1-tridecene (3c)



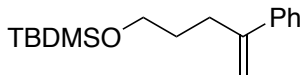
oil. IR (neat) 3085, 2925, 1631, 1468, 1074, 900, 659 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.25–1.31 (m, 16H), 1.44 (quint., *J* = 7.5 Hz, 2H), 2.50 (t, *J* = 7.5 Hz, 2H), 5.14 (d, *J* = 1.0 Hz, 1H), 5.31 (d, *J* = 1.0 Hz, 1H), 7.29–7.64 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.29, 22.90, 28.29, 29.46, 29.56, 29.62, 29.79, 29.84, 29.85, 32.14, 35.38, 113.73, 123.09 (q, *J* = 3.8 Hz), 124.10 (q, *J* = 3.8 Hz), 124.45 (q, *J* =271 Hz), 128.86, 129.58 (d, *J* = 1.4 Hz), 130.87 (q, *J* = 31.5 Hz), 142.57, 147.83; Found: C, 73.75; H, 9.19%. Calcd for $C_{20}H_{29}F_3$: C, 73.59; H, 8.95%.

2-(3-methoxyphenyl)-1-tridecene (3d)



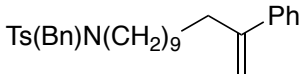
oil. IR (neat) 2924, 2854, 1852, 1049, 895, 787 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.24–1.31 (m, 16H), 1.41–1.47 (m, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 3.82 (s, 3H), 5.04 (d, *J* = 1.5 Hz, 1H), 5.25 (d, *J* = 1.5 Hz, 1H), 6.81 (m, 1H), 6.94 (m, 1H), 7.00 (m, 1H), 7.24 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.31, 22.88, 28.48, 29.55 (Two signals merge.), 29.64, 29.81, 29.82, 29.84, 32.11, 35.63, 55.40, 112.32, 112.36, 112.59, 118.90, 129.33, 143.30, 148.92, 159.69; HRMS Found: 288.2456 (Δ = 1.1 ppm), Calcd for $C_{20}H_{32}O$: 288.2453.

5-(*tert*-butyldimethylsiloxy)-2-phenyl-1-pentene (3f)



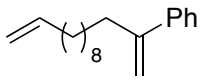
oil. IR (neat) 3905, 2929, 1772, 1447, 1100, 896, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.90 (s, 9H), 1.65–1.70 (m, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 3.63 (t, *J* = 6.5 Hz, 2H), 5.07 (s, 1H), 5.29 (s, 1H), 7.26–7.34 (m, 3H), 7.40–7.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ –5.11, 18.53, 26.16, 31.63, 31.74, 62.75, 112.43, 125.81, 126.31, 127.49, 128.44, 148.38; Found: C, 74.02; H, 10.38%. Calcd for $C_{17}H_{28}OSi$: C, 73.85; H, 10.21%.

_N_-benzyl-_N_-(11-phenyl-11-dodecenyl)-_p_-toluenesulfonamide (3g)



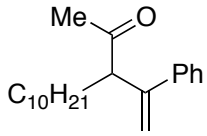
oil. IR (neat) 3032, 2924, 1805, 1597, 1157, 895, 656 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05–1.29 (m, 14H), 1.42 (quint., J = 7.5 Hz, 2H), 2.43 (s, 3H), 2.48 (t, J = 7.5 Hz, 2H), 3.06 (t, J = 7.5 Hz, 2H), 4.31 (s, 2H), 5.04 (d, J = 1.5 Hz, 1H), 5.25 (d, J = 1.5 Hz, 1H), 7.24–7.34 (m, 10H), 7.37–7.41 (m, 2H), 7.71–7.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.69, 26.77, 28.05, 28.43, 29.18, 29.48, 29.52, 29.55, 29.58, 35.54, 48.23, 52.01, 112.19, 126.29, 127.37, 127.41, 127.86, 128.40, 128.45, 128.68, 129.83, 136.81, 137.42, 141.65, 143.27, 148.95; Found: C, 76.05; H, 8.48%. Calcd for $C_{32}H_{41}O_2NS$: C, 76.30; H, 8.20%.

2-phenyl-1,12-tridecadiene (3h)



oil. IR (neat) 3078, 2924, 2854, 1636, 1458, 995, 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29–1.38 (m, 12H), 1.44 (quint., J = 7.5 Hz, 2H), 2.01–2.05 (m, 2H), 2.45 (t, J = 7.5 Hz, 2H), 4.91–5.05 (m, 2H), 5.05 (d, J = 1.5 Hz, 1H), 5.25 (d, J = 1.5 Hz, 1H), 5.77–5.85 (m, 1H), 7.24–7.27 (m, 1H), 7.30–7.34 (m, 2H), 7.39–7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.47, 29.13, 29.32, 29.52, 29.61, 29.65, 29.72, 34.00, 35.57, 112.17, 114.28, 126.31, 127.41, 128.40, 139.45, 141.72, 149.01; Found: C, 89.00; H, 11.14%. Calcd for $C_{19}H_{28}$: C, 88.99; H, 11.01%.

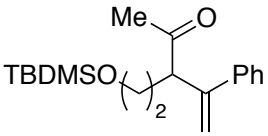
3-decyl-4-phenyl-4-penten-2-one (4a)



oil. IR (neat) 2925, 2853, 1716, 1623, 1173, 905, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.23–1.30 (m, 16H), 1.60 (m, 1H), 1.90 (m, 1H), 2.12 (s, 3H), 3.56 (t, J = 7.0 Hz, 1H),

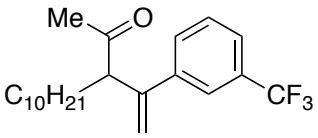
5.17 (s, 1H), 5.47 (s, 1H), 7.28–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.86, 27.91, 28.70, 29.50, 29.62, 29.75, 29.76, 29.80, 30.99, 32.08, 58.94, 115.50, 126.55, 127.99, 128.69, 141.38, 147.10, 208.76; Found: C, 83.79; H, 10.96%. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73%.

3-[2-(*tert*-butyldimethylsiloxy)ethyl]-4-phenyl-4-penten-2-one (4b)



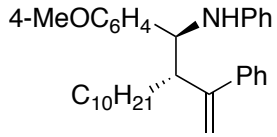
oil. IR (neat) 2955, 2862, 1713, 1620, 1466, 910, 710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (d, J = 3.5 Hz, 6H), 0.89 (s, 9H), 1.79 (m 1H), 2.13 (s, 3H), 2.19 (m, 1H), 3.56–3.63 (m, 2H), 3.90 (t, J = 7.0 Hz, 1H), 5.12 (s, 1H), 5.50 (s, 1H), 7.28–7.36 (m, 3H), 7.44–7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ –5.27, 18.43, 26.09, 29.18, 34.09, 54.46, 60.83, 115.62, 126.54, 128.07, 128.70, 141.23, 146.82, 208.23; Found: C, 71.34; H, 9.57%. Calcd for $C_{19}H_{30}O_2Si$: C, 71.64; H, 9.49%.

3-decyl-4-(3-trifluoromethylphenyl)-4-penten-2-one (4c)



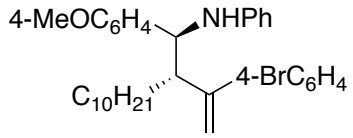
oil. IR (neat) 2927, 2855, 1718, 1453, 1074, 806 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 1.23–1.30 (m, 16H), 1.62 (quint., J = 7.0 Hz, 1H), 1.93 (quint, J = 7.0 Hz, 1H), 2.13 (s, 3H), 3.56 (t, J = 7.0 Hz, 1H), 5.27 (s, 1H), 5.52 (s, 1H), 7.45–7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.28, 22.86, 27.86, 28.70, 29.49, 29.58, 29.73, 29.75, 31.00, 32.08, 58.83, 117.07, 123.40 (q, J = 3.8 Hz), 124.22 (q, J = 271 Hz), 124.72 (q, J = 3.8 Hz), 129.21, 129.83 (d, J = 0.9 Hz), 131.18 (q, J = 32 Hz), 142.20, 145.98, 208.18. (Two signals of sp^3 carbon merge.); Found: C, 71.45; H, 8.66%. Calcd for $C_{22}H_{31}OF_3$: C, 71.71; H, 8.48%.

2-decyl-1-(4-methoxyphenyl)-3,*N*-diphenyl-3-butenamine (4d)[18]



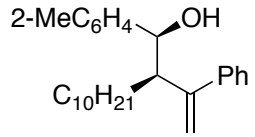
oil. IR (neat) 3410, 3055, 2924, 2854, 1605, 1504, 1034, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.12–1.34 (m, 18H), 2.74 (m, 1H), 3.77 (s, 3H), 4.08 (d, *J* = 8.5 Hz, 1H), 4.39 (broad, 1H), 5.19 (s, 1H) 5.35 (s, 1H), 6.39–6.41 (m, 2H), 6.58 (m, 1H), 6.79–6.83 (m, 2H), 6.97–7.03 (m, 2H), 7.20–7.32 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 14.29, 22.86, 27.56, 29.49, 29.63, 29.72, 29.74, 29.76, 30.68, 32.09, 53.75, 55.38, 61.16, 113.57, 113.86, 116.53, 117.26, 127.45, 127.50, 128.45, 128.76, 129.10, 135.03, 142.47, 147.63, 150.44, 158.75; HRMS Found: 468.3257 (D = –2.0 ppm), Calcd for $C_{33}H_{43}ON$: 468.3345.

3-(4-bromophenyl)-2-decyl-1-(4-methoxyphenyl)-*N*-phenyl-3-butenamine (4e)[18]



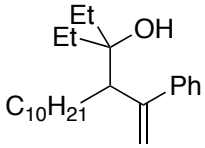
oil. IR (neat) 3410, 2924, 2854, 1605, 1504, 1034, 910, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.11–1.31 (m, 18H), 2.71 (m, 1H), 3.76 (s, 3H), 4.06 (d, *J* = 8.5 Hz, 1H), 5.22 (s, 1H), 5.34 (s, 1H), 6.40–6.42 (m, 2H), 6.60 (m, 1H), 6.76–6.82 (m, 2H), 7.00–7.04 (m, 2H), 7.06–7.12 (m, 2H), 7.15–7.20 (m, 2H), 7.37–7.39 (m, 2H) (N<u>H</u> was not observed.); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.86, 27.59, 29.49, 29.62, 29.67, 29.73, 29.74, 30.61, 32.08, 53.72, 55.40, 60.70, 113.58, 113.89, 117.10, 117.46, 121.53, 128.66, 129.17, 129.18, 131.49, 134.63, 141.19, 147.32, 149.43, 158.80; Found: C, 72.07; H, 7.66%. Calcd for $C_{33}H_{42}ONBr$: C, 72.25; H, 7.72%.

2-decyl-1-(2-methylphenyl)-3-phenyl-3-buten-1-ol (4f)[19]



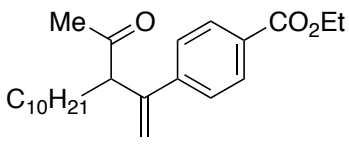
oil. IR (neat) 3441, 2924, 2854, 1628, 1466, 903, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.06–1.30 (m, 16H), 1.69 (q, *J* = 7.0 Hz, 2H), 1.92 (d, *J* = 2.5 Hz, 1H), 2.07 (s, 3H), 2.91 (dt, *J* = 5.0 Hz, 7.0 Hz, 1H), 4.76 (dd, *J* = 2.5 Hz, 5.0 Hz, 1H), 5.20 (s, 1H), 5.36 (s, 1H), 7.03 (m, 1H), 7.07–7.13 (m, 2H), 7.19–7.29 (m, 5H), 7.41 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.31, 19.35, 22.87, 27.40, 27.68, 29.51, 29.69, 29.79, 29.81, 30.08, 32.10, 50.20, 72.00, 114.25, 125.80, 126.84, 126.99, 127.12, 127.49, 128.33, 130.45, 134.55, 140.71, 143.52, 150.69; Found: C, 85.64; H, 10.03%. Calcd for $C_{27}H_{38}O$: C, 85.66; H, 10.12%.

4-decyl-3-ethyl-5-phenyl-5-hexen-3-ol (4g)



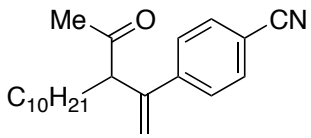
oil. IR (neat) 3487, 2924, 1618, 1464, 1378, 1123, 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (t, *J* = 7.5 Hz, 3H), 0.79 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H), 1.21–1.40 (m, 18H), 1.45–1.55 (m, 2H), 1.60–1.73 (m, 2H), 2.76 (dd, *J* = 3.5 Hz, 12 Hz, 1H), 5.20 (d, *J* = 1.0 Hz, 1H), 5.46 (d, *J* = 1.0 Hz, 1H), 7.25 (m, 1H), 7.30–7.34 (m, 2H), 7.36–7.39 (m, 2H) (O<u>H</u> was not observed.); ^{13}C NMR ($CDCl_3$) δ 7.90, 8.15, 14.30, 22.88, 27.59, 28.38, 29.46, 29.52, 29.78, 29.82, 29.86, 30.00, 30.38, 32.10, 50.04, 76.85, 115.38, 126.66, 127.26, 128.54, 145.84, 150.69; Found: C, 83.37; H, 11.89%. Calcd for $C_{24}H_{40}O$: C, 83.66; H, 11.70%.

3-decyl-4-(4-ethoxycarbonylphenyl)-4-penten-2-one (4h)



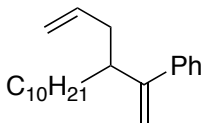
oil. IR (neat) 2924, 2854, 2361, 1720, 1612, 1180, 779 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.23–1.30 (m, 16H), 1.40 (t, *J* = 7.0 Hz, 3H), 1.61 (m, 1H), 1.91 (m, 1H), 2.12 (s, 3H), 3.57 (t, *J* = 7.0 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 5.27 (s, 1H), 5.55 (s, 1H), 7.42–7.45 (m, 2H), 8.00–8.03 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.28, 14.51, 22.85, 27.85, 28.71, 29.48, 29.58, 29.72, 29.75 (Two signals merge.), 30.96, 32.07, 58.77, 61.17, 117.17, 126.53, 129.99, 130.01, 145.73, 146.41, 166.44, 208.31; Found: C, 77.08; H, 9.75%. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74%.

3-decyl-4-(4-cyanophenyl)-4-penten-2-one (4g)



oil. IR (neat) 2924, 2854, 2361, 2230, 1713, 1605, 918 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.23–1.30 (m, 16H), 1.60 (quint., *J* = 7.0 Hz, 1H), 1.92 (quint., *J* = 7.0 Hz, 1H), 2.13 (s, 3H), 3.53 (t, *J* = 7.0 Hz, 1H), 5.34 (s, 1H), 5.56 (s, 1H), 7.45–7.48 (m, 2H), 7.62–7.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.28, 22.85, 27.83, 28.55, 29.48, 29.56, 29.71, 29.74 (Two signals merge.), 30.90, 32.07, 58.76, 117.74, 118.33, 118.81, 127.31, 132.54, 145.73, 145.82, 207.97; Found: C, 81.26; H, 9.78%. Calcd for $C_{22}H_{31}ON$: C, 81.18; H, 9.60%.

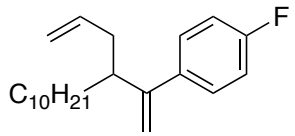
3-decyl-2-phenyl-1,5-hexadiene (5a)



oil. IR (neat) 2924, 2854, 2361, 1636, 995, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.23–1.36 (m, 16H), 1.47 (q, *J* = 7.0 Hz, 2H), 2.14–2.29 (m, 2H), 2.61 (quint., *J* = 7.0 Hz, 1H), 4.96–5.02 (m, 2H), 5.02 (d, *J* = 1.5 Hz, 1H), 5.24 (d, *J* = 1.5 Hz, 1H), 5.78 (m, 1H), 7.23–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.31, 22.88, 27.19, 29.53, 29.76, 29.80, 29.82, 30.01, 32.11, 33.89, 38.97, 44.06, 112.66, 115.97, 126.97, 127.21, 128.28, 137.31, 143.54, 152.61; Found: C, 88.30;

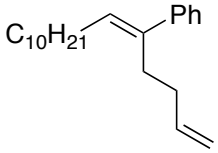
H, 11.71%. Calcd for $C_{22}H_{34}$: C, 88.52; H, 11.48%.

3-decyl-2-(4-fluorophenyl)-1,5-hexadiene (5b)



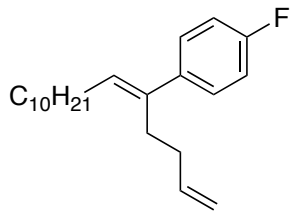
oil. IR (neat) 3086, 2924, 2854, 1605, 1512, 995, 841 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.23–1.34 (m, 16H), 1.41–1.48 (m, 2H), 2.13–2.27 (m, 2H), 2.56 (quint., *J* = 7.0 Hz, 1H), 4.96–5.01 (m, 2H), 5.01 (d, *J* = 1.0 Hz, 1H), 5.20 (d, *J* = 1.0 Hz, 1H), 5.72–5.80 (m, 1H), 6.97–7.02 (m, 2H), 7.26–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.88, 27.18, 29.53, 29.75, 29.80, 29.81, 29.98, 32.11, 33.89, 38.90, 44.29, 112.81, 115.08 (d, *J* = 21 Hz), 116.09, 128.52 (d, *J* = 8.0 Hz), 137.14, 139.52, 151.65, 162.30 (d, *J* = 243 Hz); Found: C, 83.74; H, 10.76%. Calcd for $C_{22}H_{33}F$: C, 83.49; H, 10.51%.

(*E*)-5-phenyl-1,5-hexadecadiene (6a)



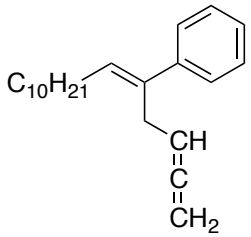
oil. IR (neat) 2924, 2854, 1643, 1597, 995, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.27–1.36 (m, 14H), 1.44 (quint., *J* = 7.0 Hz, 2H), 2.05–2.11 (m, 2H), 2.18 (q, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 4.92–5.00 (m, 2H), 5.67 (t, *J* = 7.5 Hz, 1H), 5.81 (m, 1H), 7.21 (m, 1H), 7.28–7.34 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.31, 22.89, 28.79, 29.44, 29.55, 29.63, 29.79, 29.84 (Two signals merge.), 30.07, 32.12, 33.02, 114.67, 126.57, 126.65, 128.36, 129.95, 138.61, 139.34, 143.37; Found: C, 88.70; H, 11.77%. Calcd for $C_{22}H_{34}$: C, 88.52; H, 11.48%.

(*E*)-5-(4-fluorophenyl)-1,5-hexadecadiene (6b)



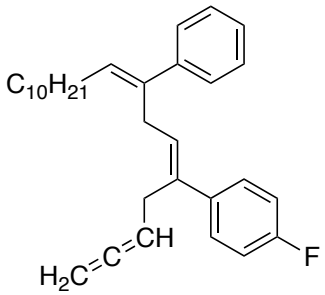
oil. IR (neat) 3077, 2925, 2854, 1641, 1603, 1158, 832 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.27–1.36 (m, 14H), 1.43 (quint., *J* = 7.5 Hz, 2H), 2.06 (q, *J* = 7.5 Hz, 2H), 2.16 (q, *J* = 7.5 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 4.92–4.99 (m, 2H), 5.60 (t, *J* = 7.5 Hz, 1H), 5.75–5.83 (m, 1H), 6.95–7.00 (m, 2H), 7.25–7.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.29, 22.88, 28.77, 29.54, 29.58, 29.62, 29.77, 29.83 (Two signals merge.), 30.05, 32.11, 32.89, 114.81, 115.09 (d, *J* = 21 Hz), 128.05 (d, *J* = 7.7 Hz), 129.96, 138.40, 138.45, 139.43 (d, *J* = 3.4 Hz), 161.97 (d, *J* = 243 Hz) ; Found: C, 83.30; H, 10.47%. Calcd for $C_{22}H_{33}F$: C, 83.49; H, 10.51%.

(*E*)-5-phenyl-1,2,5-hexadecatriene (7)



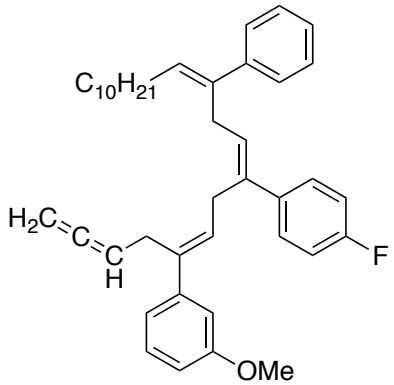
oil. IR (neat) 2924, 2854, 1952, 1597, 1458, 841, 756, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.27–1.36 (m, 14H), 1.45 (quint., *J* = 7.5 Hz, 2H), 2.20 (q, *J* = 7.5 Hz, 2H), 3.20 (dt, *J* = 3.5 Hz, 7.0 Hz, 2H), 4.63 (dt, *J* = 3.5 Hz, 7.0 Hz, 2H), 5.10 (quint., *J* = 7.0 Hz, 1H), 5.80 (t, *J* = 7.5 Hz, 1H), 7.21 (m, 1H), 7.26–7.31 (m, 2H), 7.36–7.38 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 14.30, 22.88, 28.92, 29.49, 29.54, 29.65, 29.79, 29.83, 29.84, 29.93, 32.11, 75.46, 88.91, 126.36, 126.70, 128.32, 130.73, 137.24, 143.09, 209.15; Found: C, 89.27; H, 10.96%. Calcd for $C_{22}H_{32}$: C, 89.12; H, 10.88%.

(5*E*,8*E*)-5-(4-fluorophenyl)-8-phenyl-1,2,5,8-nonadecatetraene (8)



oil. IR (neat) 3024, 2924, 2854, 1952, 1597, 1504, 1458, 1227, 1157, 841, 756, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88–0.90 (m, 3H), 1.26–1.38 (m, 14H), 1.43–1.49 (m, 2H), 2.23 (q, *J* = 7.5 Hz, 2H), 3.24 (dt, *J* = 3.5 Hz, 7.0 Hz, 2H), 3.39 (d, *J* = 6.5 Hz, 2H), 4.63 (dt, *J* = 3.5 Hz, 7.0 Hz, 2H), 5.08 (quint., *J* = 6.5 Hz, 1H), 5.62 (t, *J* = 6.5 Hz, 1H), 5.79 (t, *J* = 7.5 Hz, 1H), 6.91–6.96 (m, 2H), 7.20–7.26 (m, 3H), 7.27–7.31 (m, 2H), 7.36–7.38 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 14.29, 22.88, 28.97, 29.54, 29.67, 29.80, 29.83, 29.86, 29.99, 32.11, 75.74, 88.23, 115.04 (d, *J* = 21 Hz), 126.42, 126.80, 127.93 (d, *J* = 7.6 Hz), 128.39, 128.63, 130.29, 136.76, 138.20, 138.71, 143.28, 162.06 (d, *J* = 244 Hz), 209.21. (Three signals merge.); HRMS Found: 430.3029 (Δ = –1.7 ppm), Calcd for $C_{31}H_{39}F$: 430.3036.

(5*E*,8*E*,11*E*)-8-(4-fluorophenyl)-5-(3-methoxyphenyl)-11-phenyl-1,2,5,8,11-docosapentaene (9)



oil. IR (neat) 3441, 2924, 2854, 1952, 1682, 1597, 1504, 1234, 1142, 841, 702, 617 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.25–1.32 (m, 14H), 1.46 (m, 2H), 2.23 (q, *J* = 7.5 Hz, 2H), 3.26 (dt, *J* = 3.5 Hz, 6.5 Hz, 2H), 3.43 (m, 4H), 3.78 (s, 3H), 4.60 (dt, *J* = 3.5 Hz, 6.5 Hz,

2H), 5.12 (quint., J = 6.5 Hz, 1H), 5.61 (t, J = 6.5 Hz, 1H), 5.65 (t, J = 6.5 Hz, 1H), 5.79 (t, J = 7.5 Hz, 1H), 6.77 (m, 1H), 6.83 (m, 1H), 6.88 (m, 1H), 6.90–6.95 (m, 2H), 7.18–7.29 (m, 6H), 7.35–7.38 (m, 2H) ; ^{13}C NMR ($CDCl_3$) δ 14.30, 22.88, 29.03, 29.55, 29.69, 29.82, 29.83, 29.85, 29.93, 29.97, 30.01, 30.25, 32.20, 55.83, 75.79, 88.33, 112.12, 112.51, 115.10 (d, J = 21 Hz), 118.98, 126.44, 126.83, 127.94 (d, J = 7.6 Hz), 128.04, 128.16, 128.42, 129.28, 130.34, 137.70, 138.18, 138.21, 138.98, 143.26, 144.04, 159.69, 162.08 (d, J = 244 Hz), 209.17.; HRMS Found: 576.3760 (Δ = –1.3 ppm), Calcd for $C_{41}H_{49}FO$: 576.3767.

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19. The stereochemistry of **4f** was assigned by comparison with known compounds that have an analogous structure, see: Ref 2a.

Publication List

I. Parts of the present thesis have been published in the following journals.

Chapter 1. Chromium-Catalyzed Arylmagnesiation of Alkynes
Kei Murakami, Hirohisa Ohmiya, Hideki Yorimitsu, and Koichiro Oshima
Organic Letters **2007**, *9*, 1569–1571.

Chapter 2. Cobalt-Catalyzed Arylzincation of Alkynes
Kei Murakami, Hideki Yorimitsu, and Koichiro Oshima
Organic Letters **2009**, *11*, 2373–2375.

Chapter 3. Cobalt-Catalyzed Benzylzincation of Alkynes
Kei Murakami, Hideki Yorimitsu, and Koichiro Oshima
Chemistry – A European Journal **2010**, *16*, 7688–7691.

Chapter 4. Nickel-Catalyzed Carbometalation Reaction of [2-(1-Propynyl)phenyl]methanol with 1-Alkenylmagnesium Reagents
Kei Murakami, Hirohisa Ohmiya, Hideki Yorimitsu, and Koichiro Oshima
Chemistry Letters **2007**, *36*, 1066–1067.

Chapter 5. Silver-Catalyzed Transmetalation between Chlorosilanes and Aryl and Alkenyl Grignard Reagents for Synthesis of Tetraorganosilanes
Kei Murakami, Koji Hirano, Hideki Yorimitsu, and Koichiro Oshima
Angewandte Chemie International Edition **2008**, *47*, 5833–5835.

Chapter 6. Zinc-Catalyzed Nucleophilic Substitution Reaction of Chlorosilanes with Organomagnesium Reagents
Kei Murakami, Hideki Yorimitsu, and Koichiro Oshima
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Synthesis of Tetraorganosilanes: (Chloromethyl)dimethylphenylsilane
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Appendix. Rhodium-Catalyzed Arylzincation of Terminal Allenes Providing Allylzinc Reagents and Its Application to Versatile Three-component Coupling Reaction
Yuji Yoshida, Kei Murakami, Hideki Yorimitsu, and Koichiro Oshima
Journal of the American Chemical Society **2010**, *132*, 8878–8879.

II. Other publication not included in this thesis.

(1). Generation of Rhodium Enolates via Retro-Aldol Reaction and Its Application to Regioselective Aldol Reaction
Kei Murakami, Hirohisa Ohmiya, Hideki Yorimitsu, and Koichiro Oshima
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(2). Copper-Catalyzed Arylation of Chlorosilanes with Grignard Reagents
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(3). Silver-Catalyzed Benzylation and Allylation of Tertiary Alkyl Bromides with Organozinc Reagents
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(4). A General Approach to the Basiliolide/Transtaganolide Natural Products: The Total Synthesis of Basiliolide B, *epi*-8-Basiliolide B, Transtaganolide C, and Transtaganolide D
Hosea M. Nelson, Kei Murakami, Scott C. Virgil, and Brian M. Stoltz
Angewandte Chemie International Edition, **2011**, *50*, 3688–3691.

Acknowledgment

The studies described in this thesis were carried out at Kyoto University under the direction of Professor Koichiro Oshima (April 2006 to March 2010) and Professor Seijiro Matsubara (April 2010 to March 2012).

To begin, the author would like to thank Professor Koichiro Oshima for his unwavering support. Prof. Oshima is a role model and a great mentor. The author wishes to express his grateful acknowledgment to Prof. Oshima. Associate Professor Hideki Yorimitsu gave practical suggestions and cared for the author with a generous heart. Prof. Yorimitsu's valuable suggestions and interesting ideas are always inspiring. The author is deeply thankful to him. The author would like to show his gratitude to Professor Seijiro Matsubara for helpful suggestions and discussions.

The author wishes to express his gratitude to Professor Tamejiro Hiyama, Professor Michinori Suginome, and Professor Yasushi Tsuji for their informative suggestions. The author is also thankful to Associate Professor Masaki Shimizu, Dr. Yoshiaki Nakao, and Dr. Takuya Kurahashi for their generous help.

The author would like to express appreciation to Dr. Hirohisa Ohmiya for his teaching on the basics of organic chemistry. Learning chemistry from Dr. Ohmiya in the author's early years was one of the most valuable experiences that the author had in graduate school. The author also wishes to thank Dr. Koji Hirano for fruitful discussions. The author is indebted to Dr. Akinori Sato, Dr. Suguru Yoshida, Dr. Takashi Niwa, Dr. Sayuri Hirano, Dr. Azusa Kondoh, Dr. Shigeo Yasuda, Dr. Yuto Sumida, Dr. Masayuki Iwasaki, and Dr. Hidenori Someya for their generous help. The author feels grateful for Mr. Shigenari Kanemura, Mr. Masahiro Sai, Mr. Kosuke Motoshima, Mr. Jang Minsul, and Mr. Yoshihiro Asada for their friendship. The author appreciates Mr. Yuji Yoshida's willingness to collaborate on carbometalation chemistry. He is also indebted to Ms. Mika Ogishi for her support. It is the author's great pleasure to express his appreciation to all the members of the Oshima Group for their active and helpful discussions.

Professor Brian M. Stoltz gave the author the precious opportunity to study in his laboratory. The author wishes to express his grateful acknowledgment to Prof. Stoltz. He is also thankful to

Mr. Hosea M. Nelson for his support and friendship.

The author wishes to show his deep gratitude to Professor Atsuhiro Osuka and Dr. Naoki Aratani for practical guidance and helpful suggestions. The author is also thankful for Mr. Eiji Tsurumaki, Mr. Takayuki Tanaka, Mr. Taro Koide, and Mr. Daishi Fujino for their friendship. He would like to thank all the members of the Osuka Group.

Financial support from the Japan Society for the Promotion of Science and the Research Fellowship for Young Scientists was indispensable. The author sincerely appreciates the support.

This thesis certainly would not have been possible without unwavering support and encouragement of his family. The author wants to give his deepest thanks to his wife Chinatsu. She has been his best friend for many years and, without her, making it through graduate school would have been tough for the author. To his son Hinata, the author cannot tell him how much his smile meant to him every day. The author also would like to thank Mr. Masayoshi Tarui, Ms. Takako Tarui, Ms. Chihiro Fukuya, and Mr. Masahiro Fukuya for their generous support. Finally, the author would like to express his sincere appreciation to his father, Hironori Murakami and his mother, Mizuko Murakami for their encouragement and continuous support.

Kei Murakami