C500 Project Final Report

Regioselective Rhodium-Catalyzed Allylic Etherfication

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June 5, 2005

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1. Introduction:

The transition metal-catalyzed allylic substitution reaction represents an important method for the construction of carbon-carbon (alkylation) or carbon-hetroatom bonds (amination or etherfication).[1] The basic mechanism for this type of transformation is one that proceeds *via* an η^3-allyl intermediate. The transition-metal can be palladium,[2] iridium,[3] rhodium,[4] and others, in which number of leaving groups such as esters, phosphates may also be employed.
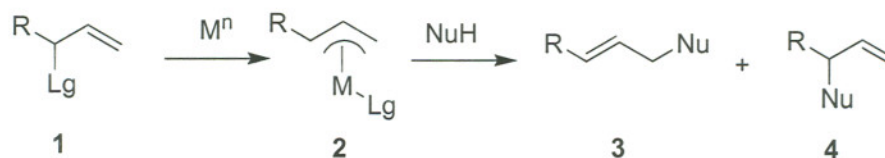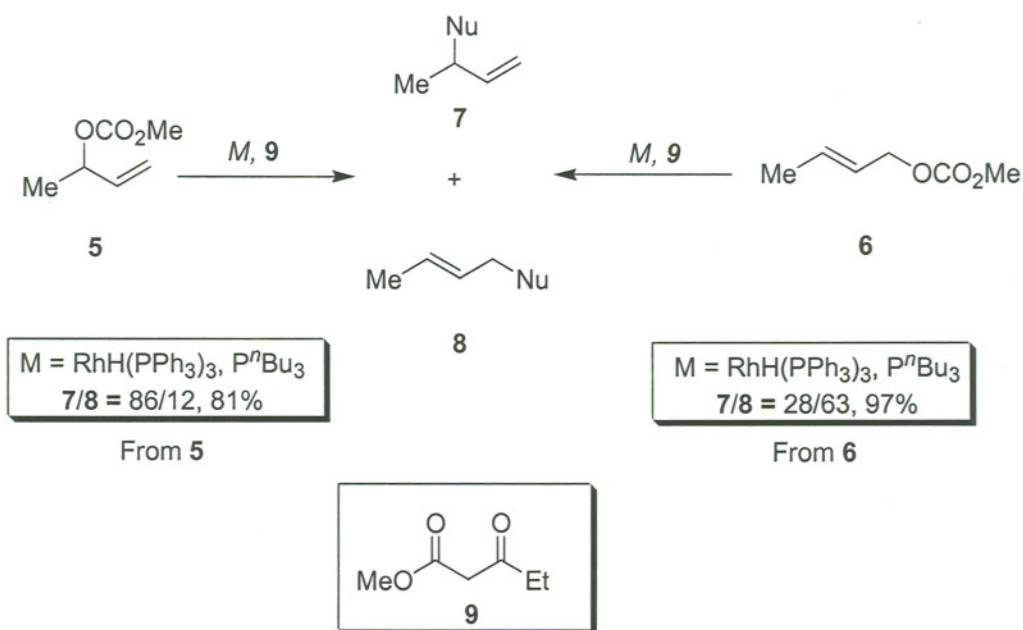

Scheme 1

A significant limitation with the formation of the unsymmetrical η^3-allyl intermediates is that the resulting alkylation can lead to the formation of two regioisomers, as shown in Scheme 1. Although a wide array of metals have been applied to this problem, rhodium has emerged as the metal of choice for controlling regioselectivity.

It has now been demonstrated that the combination of ligand and metal can be used to increase the regioselectivity, by promoting alkylation at the more hindered site of η^3-allyl intermediate. This was attributed to the positive charge build up in the intermediate at the more substituted terminus.

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2. Background:.

The first regioselective rhodium-catalyzed allylic alkylation was reported by Tsuji (Scheme **2**),[5] in which it was demonstrated that the rhodium catalyst has a memory effect with respect to the position of the leaving group. This result was attributed to the formation of an σ-allylrhodium complex rather than a π-allyl complex.
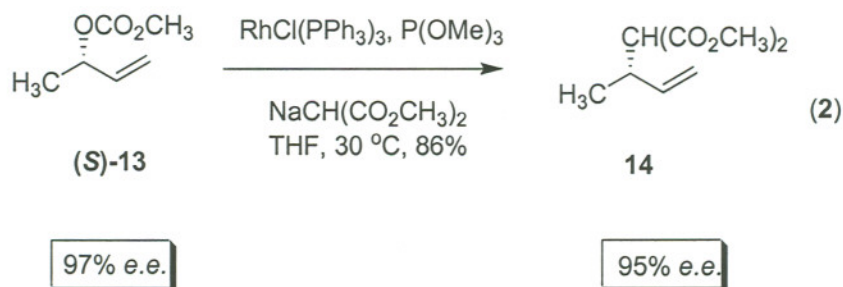

Scheme **2**

In 1998, Evans and Nelson reported the alkylation of secondary and tertiary carbonates using modified-Wilkinson's catalyst.[6] They demonstrated that the enhanced regioselectivity is due to the π-accepting nature of the trioganophosphite ligands, which increases the propensity for alkylation at of the more substituted site (eq **1**).

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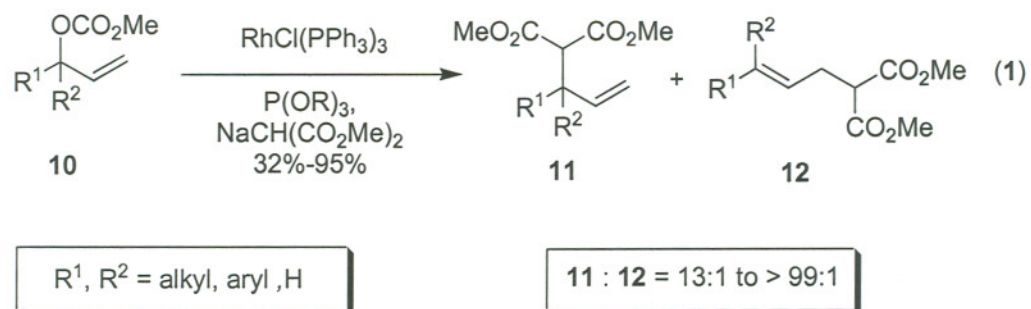
In order to examine the stereospecificity of the rhodium-catalyzed allylic alkylation, they examined an enantiomerically enriched allylic carbonate (*S*)-13. Interestingly, the reaction provides the enantioenriched product **14** with almost complete conservation of enantiomeric excess (eq **2**).

This somewhat surprising the result was attributed to the formation of a configurationally stable *eny*l or (σ+π) allyl intermediate. This type of intermediate provides a model for reactivity as outlined in Scheme **3**.
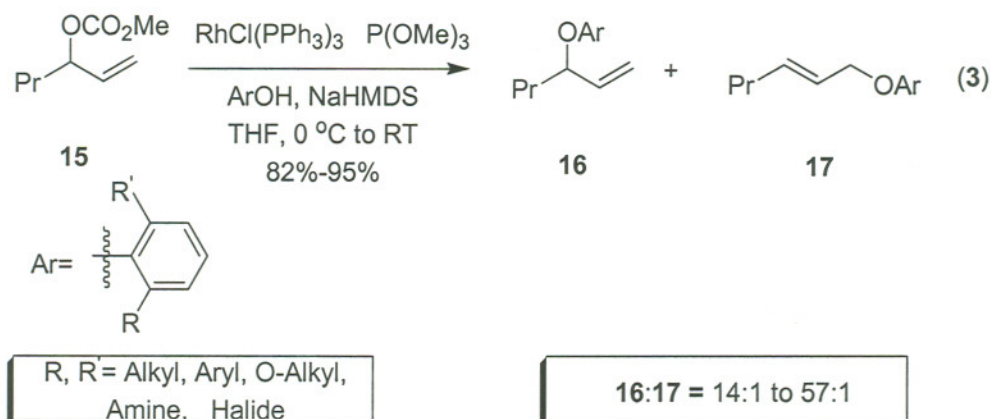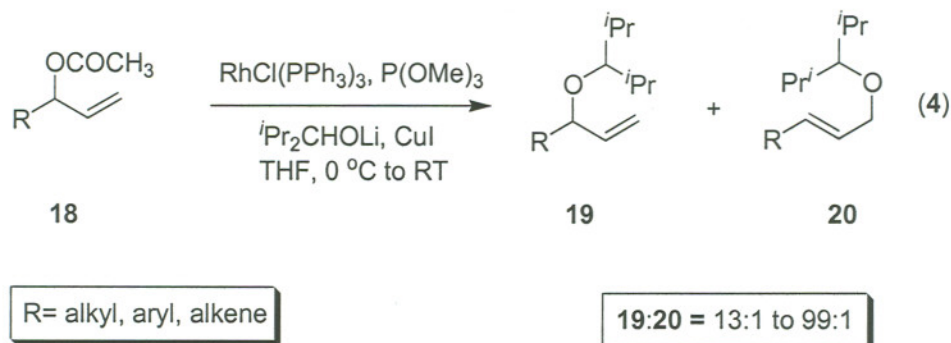
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Scheme 3
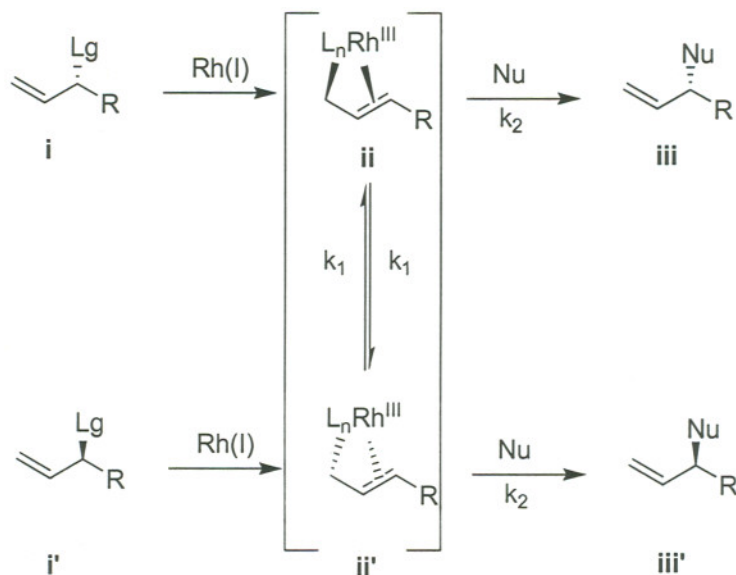
For example, the enyl intermediates **ii** and **ii'** result from a S_N2 type reaction of starting allylic compounds **i** and **i'**, which undergo another S_N2 type reaction affording **iii** and **iii'** with net retention of configuration, provided the alkylation (k_2) is faster than equilibrium (k_1 / k_{-1}) of the specific enantiomers.

Evans and Leahy later described the first rhodium-catalyzed allylic etherfication with *ortho*-substituted phenols which demonstrate relatively hindered *ortho*- and *ortho*-disubstituted derivatives undergo regioselective alkylation (eq **3**)[7]. Although this study demonstrates the reactions tolerance to substituents within the nucleophiles, it did not examine the effect of substituents within the allylic carbonate derivative.

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OCO$_2$Me → RhCl(PPh$_3$)$_3$ P(OMe)$_3$ / ArOH, NaHMDS / THF, 0 °C to RT / 82%-95% → OAr (**16**) + Pr~~~OAr (**17**)   (**3**)

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Ar= [2,6-disubstituted aryl with R' and R]

| R, R'= Alkyl, Aryl, O-Alkyl, Amine, Halide | | **16:17 = 14:1 to 57:1** |

Further studies demonstrate that the rhodium-catalyzed allylic etherfication reaction was not applicable to hard alkali metal alkoxides. In order to overcome this problem, the metal alkoxide was transmetallated with copper(I) salts to soften the nucleophilic character of the alkoxide.[8,9] This protocol provide a general approach to a series of allylic carbonates using copper(I) salts (eq **4**).

OCOCH$_3$ → RhCl(PPh$_3$)$_3$, P(OMe)$_3$ / ^{i}Pr$_2$CHOLi, CuI / THF, 0 °C to RT → **19** + **20**   (**4**)

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| R= alkyl, aryl, alkene | | **19:20 = 13:1 to 99:1** |

3. Results and discussions:

Preliminary studies demonstrate that the application of the phenols as nucleophiles to other carbonates was problematic. We envisioned that the combination of the rhodium-catalyzed allylic etherfication with phenols could be improved using a copper phenoxide in an analogue manner to the alcohols (eq **5**). A series of recemic secondary allylic carbonates were submitted to the

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regioselective allylic etherfication under the optimized reaction conditions as outlined in **Table 1**.
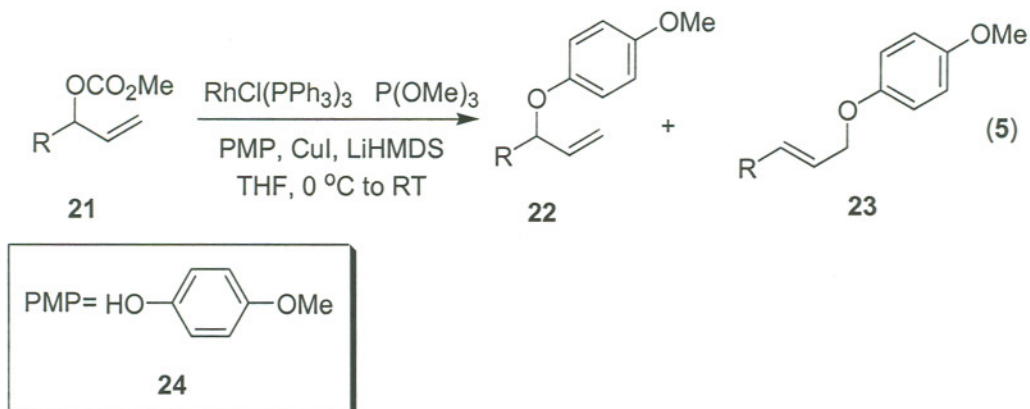
Table 1 *Scope of the Regioselective Rhodium-Catalyzed Allylic Etherfication Reaction.*

Entry[a]		R=	22:23[b,c]	Yield (%)[d]
1	a	CH_3	>99:1	88
2	b	*n*-Pr	>99:1	90
3	c	$CH_2=CH(CH_2)_3$	>99:1	87
4	d	*i*-Bu	8:1	74
5	e	$Ph(CH_2)_2$	>99:1	93
6	f	Ph	10:1	90
7	g	Naph	16:1	85
8	h	Bn	>99:1	70
9	i	$TBSOCH_2$	52:1	73
10	j	$TBSO(CH_2)_2$	>99:1	83
11	k	$BnOCH_2$	>99:1	89
12	l	$BnO(CH_2)_2$	>99:1	85
13	m	cyclohexyl	NA	50
14	n	*i*-propyl	NA	41

[a] All reactions were carried out on a 0.25mmol reaction scale. [b] Regioselectivity was dermined by GC analysis on the crude reaction mixtures. [c] The primary products were prepared using palladium-catalyzed reactions. [d] Isolated yields.

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Table 1 summarizes the application of the optimized reaction conditions to a series of *secondary* carbonates. The regioselectivity of the allylic alkylation is clearly tolerant of a wide array of linear and branched alkyl substituents (entries 1-5), providing the good selectivity and yields. The allylic alkylation is also feasible for aryl, benzyl substituents (entries 6-8) with affording synthetic useful regioselective control. The benzyl-protected hydroxyalkyl substituents and *tert*-butyldimethylsilyl-protected hydroxyalkyl substituents afforded excellent regioselectivity and yields (entries 9-12). Other α-substitute carbonates were also examined under the same optimized reaction condition (entries 13, 14). However, these entries afforded low yields, due to steric hindrance. More detailed studies may be done including catalyst loading to further probe the cause of the low yields.
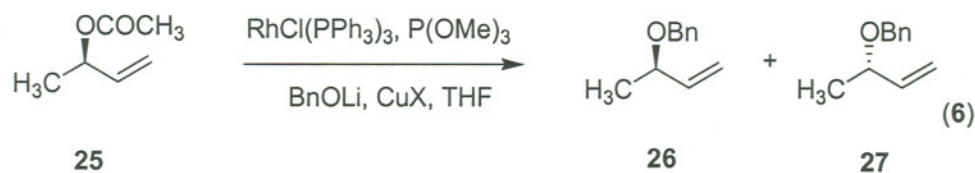
In summary, the rhodium-catalyzed allylic etherfication with copper(I) phenoxide was applied in the reactions using *p*-methoxyphenol as a nucleophile. The study demonstrates that the allylic etherfication is tolerant of alkyl, aryl and alkene groups with good regioselectivity and yields. However, branched carbonates afford lower yields.

4. Future works:

In light of the ability to accomplish stereospecificity with related nucleophiles,[8,10] we plan to examine the stereospecificity of the allylic etherfication with copper phenoxides. The enantiomerically enriched allylic carbonate **25** will be utilized with a range of different copper (I) halides (eq **6**).

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OCOCH$_3$ ... RhCl(PPh$_3$)$_3$, P(OMe)$_3$ / BnOLi, CuX, THF ... OBn + OBn (6)

25 ... 26 ... 27

X= I, Br, Cl

26:27 = 91:1 to 99:1

cee = 41% to 96%

5. Conclusion:

In conclusion, the rhodium-catalyzed allylic etherfication condition with a phenol nucleophile was accomplished using copper(I) iodide as an additive . The copper phenoxides demonstrate good regioselectivties with different allylic carbonates, however the branched allylic carbonates afford lower yield. The future work will focus on the stereospecificity of the allylic etherfication and the application to new nucleophiles

6. Experimental

General

All the experiments were using flame-dried round-bottom flasks furnished with Argon balloon. All syringes were dried in oven (150 °C) then cooled in a desiccator. The tetrahydrofuran was distilled from activated benzophenone ketyl. Trimethylphosphite was freshly distilled and stored over molecular sieves. *Para*-methoxyphenol was recrystallized from PhH then stored in a desiccator. The dry air-tight syringe were used in the experiment. All starting materials were

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purchased from Aldrich, Acros, Fluka or Lancaster chemical companies and used without any further purification.

All alcohols and carbonates were prepared using literature procedures and predicated by either flash chromatography or distillation. Wilkinson's catalyst was prepared using literature procedure and stored under vacuum. Thin layer chromatography was used Merck 60 F_{254} precoated silica plates. Flash chromatography was used Merck Silica Gel 60. All spectra were obtained by VXR400 or I-400 NMR machine. The solvent is $CDCl_3$ for every NMR sample. For the ^1H NMR was set to 7.26 ppm ($CHCl_3$, singlet). The HP 6890 gas chromatograph was used to obtain the gas chromatograms. MS data were obtained by using EI or CI spectrometer.

General Experimental Procedure for the rhodium-catalyzed allylic etherfication using ρ-methoxyphenol:

Thrimethylphosphite (12 μl) was added into the Wilkinson's catalyst suspended in THF (1.5 ml) under atmosphere of argon. After stirring for 10 minutes, the light-yellow homogenous solution was formed. To another flask, LiHMDS (490 μl/ 0.49 mmol) was added into the suspension of copper(I) iodide (95 mg/ 0.5 mmol) and ρ-methoxyphenol (62 mg/ 0.5 mmol) in anhydrous THF (1.5 ml). The flask was cooled to 0 °C, then the catalyst was added into the c alkoxide solution by Teflon® cannula. The allylic carbonates (0.25 mmol) in a gastight syringe were added into the catalyst/alkoxide mixture. The reaction solution was slowly warmed to room temperature and stirred overnight. 2 M sodium hydroxide was added into the reaction solution in order to remove the excess phenol and copper(I) iodide. Purification by flash chromatography (8/100, v/v, Dichloromethane/Hexane) furnished the products (41%-93%) as colorless oil.

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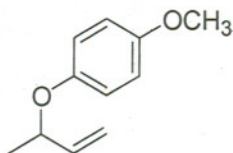
22a

1-(but-3-en-2-yloxy)-4-methoxybenzene 22a. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.87- 9.79 (m, 4H), 5.90 (ddd, J = 16.7, 10.6, 6.1 Hz, 1H), 5.24 (dt, J = 17.2, 1.3 Hz, 1H), 5.15 (dt, J = 10.5, 1.3 Hz, 1H), 4.67 (m, 1H), 3.76 (s, 3H), 1.41 (d, J = 9.4Hz, 3H).

HRMS (CI, M$^+$) calcd for C$_{11}$H$_{14}$O$_2$ 178.0994, found 178.0995.
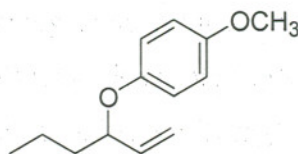
22b

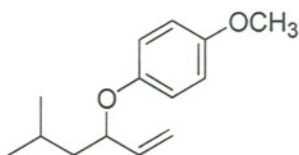**1-(hex-1-en-3-yloxy)-4-methoxybenzene 22b.** ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.86-6.77 (m, 4H), 5.84 (ddd, J = 17.2, 10.6, 6.5 Hz, 1H), 5.25- 5.15 (m, 2H), 4.50-4.44 (m, 1H), 3.75 (s, 3H), 1.82-1.38 (m, 4H), 0.95 (t, J = 7.4 Hz, 3H).

HRMS (CI, M$^+$) calcd for C$_{13}$H$_{18}$O$_2$ 206.307, found 206.1310.
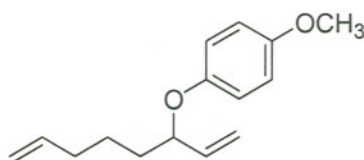
22c

1-methoxy-4-(octa-1,7-dien-3-yloxy)benzene 22c. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.87-6.80 (m, 4H), 5.86-5.78 (m, 2H), 5.26-5.18 (m, 2H), 5.03 (dt, J = 17.2, 1.7 Hz, 1H), 4.97 (dt, J =10.2, 1.1 Hz, 1H), 4.48 (m, 1H), 3.77 (s, 3H), 2.11 (tt, J = 7.1, 6.9 Hz, 2H), 1.85-1.49 (m, 4H).

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22d

1(hex-1-en-3-yloxy)-4-methoxybenzene 22d. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.86-6.78 (m, 4H), 5.83 (ddd, J = 17.2, 10.6, 6.4 Hz, 1H), 5.23-5.14 (m, 2H), 4.55-4.50 (m, 1H), 3.76 (s, 3H), 1.85-1.70 (m, 2H), 1.46-1.41 (m, 1H), .095 (t, J = 6.6Hz, 6H).

HRMS (CI, M$^+$) calcd for C$_{14}$H$_{20}$O$_2$ 220.1463, found 220.1465.
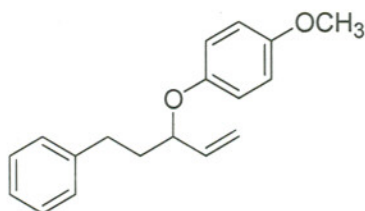
22e

1-[3-(4-methoxyphenoxy)pent-4-enyl]benzene 22e. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22 (m, 5H), 6.82 (dd, J = 9.4, 13.7 Hz, 4H), 5.78 (ddd, J = 13.1, 10.5, 6.6 Hz, 1H), 5.27 (dt, J = 13.1, 1.3 Hz, 1H), 5.20 (dt, J = 10.5, 1.1 Hz, 1H), 4.49 (dq, J = 6.5, 1Hz, 1H), 3.77 (s, 3H), 2.88-2.72 (m, 2H), 1.91-2.18 (m, 2H).
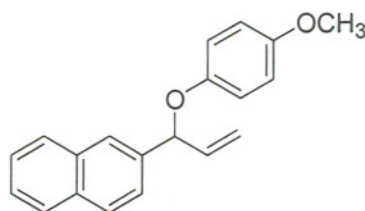
HRMS (CI, M$^+$) calcd for C$_{18}$H$_{20}$O$_2$ 268.1463, found 268.1458.
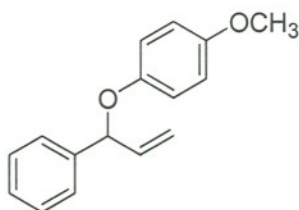
22f

1-[1-(4-methoxyphenoxy)allyl]benzene 22f. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44-7.29 (m, 5H), 6.85(m, 4H), 6.12 (ddd, J = 16.8, 10.4, 6.4 Hz, 1H), 5.55 (d, 6.0 Hz, 1H), 5.35 (dt, J = 17.1, 1.4 Hz, 1H), 5.27 (dt, J = 10.4, 1.4Hz, 1H), 3.76 (s, 3H).
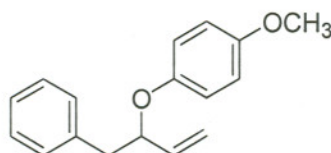
HRMS (EI, M$^+$) calcd for C$_{16}$H$_{16}$O$_2$ 240.1157, found 240.1151.

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22g

2-[1-(4-methoxyphenoxy)allyl]naphthalene 22g. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88-7.49 (m, 7H), 6.96-6.77 (m, 4H), 6.19 (ddd, J = 16.9, 10.3, 5.9 Hz, 1H), 5.71 (d, J = 6 Hz, 1H), 5.44-5.29 (m, 4H), 3.74 (s, 3H).

HRMS (CI, M$^+$) calcd for C$_{20}$H$_{18}$O$_2$ 290.1307, found 290.1294.

22h

1-(1-phenylbut-3-en-2-yloxy)-4-methoxybenzene 22h. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28-7.26 (m, 5H), 6.81-6.74 (m, 4H), 6.08 (ddd, J = 17.0, 10.8, 6.3 Hz, 1H), 5.41-5.36 (m, 2H), 4.87 (m, 1H), 3.94 (s, 3H).

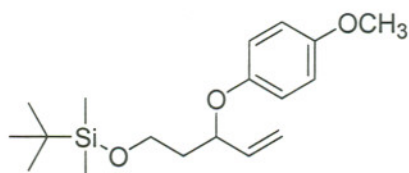HRMS (CI, M$^+$) calcd for C$_{17}$H$_{18}$O$_2$ 254.1307, found 254.1305.
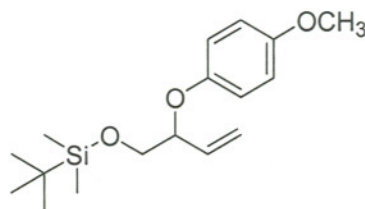
22i

[2-(4-methoxyphenoxy)but-3-enyloxy](*tert*-butyl)dimethyl silane 22i. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.88-6.77 (m, 4H), 5.87 (ddd, J = 16.7, 10.8, 5.8 Hz, 1H), 5.34 (dt, J = 17.4, 1.3 Hz, 1H), 5.25 (dt, J =10.8, 1.3 Hz), 4.57 (m, 1H), 3.85-3.70 (m, 5H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).
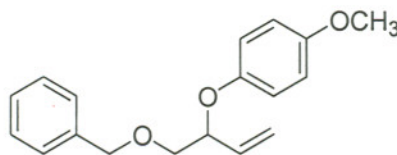
HRMS (CI, M$^+$) calcd for C$_{17}$H$_{28}$O$_3$Si 308.1808, found 308.1794.

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22j

[3-(4-methoxyphenoxy)pent-4-enyloxy](*tert*-butyl)dimethylsilane **22j.** ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.87-6.77 (m, 4H), 5.86 (ddd, $J =$ 17.2, 10.6, 6.3 Hz, 1H), 5.26-5.15(m, 2H), 4.71(m, 1H), 3.84-3.69 (m, 5H), 2.03-1.77 (m, 2H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

HRMS (CI, M$^+$) calcd for C$_{18}$H$_{30}$O$_3$Si 322.1964, found 322.1949.

22k

1-{[2-(4-methoxyphenoxy)but-3-enyloxy]methyl}benzene 22k. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55-7.46 (m, 5H), 7.05 (m, 4H), 6.09 (ddd, $J =$ 17.0, 12.5, 5.9 Hz, 1H), 5.56 (dt, $J =$ 17.3, 1.4 Hz, 1H), 5.47 (dt, $J =$ 10.6, 1.3 Hz, 1H), 4.94 (m, 1H), 4.82(d, $J =$ 3.0 Hz, 2H), 3.96 (s, 3H), 3.81-3.90 (s, 2H).
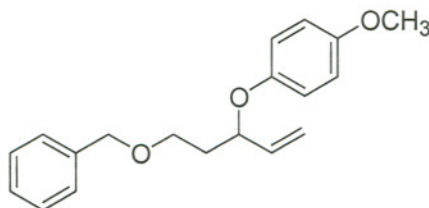
22l

1-(5-phenoxypent-1-en-yloxy)-4-methoxybenzene 22l. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33-7.28 (m, 5H), 6.88-6.80 (m, 4H), 5.87 (ddd, $J =$ 17.2, 10.6, 6.4 Hz, 1H), 5.26 (dt, $J =$ 17.4, 1.2 Hz, 1H), 5.19 (dt, $J =$ 10.7, 1.1 Hz, 1H), 4.74 (m, 1H), 4.51 (s, 2H), 3.78 (s, 3H), 3.72-3.59 (m, 2H), 2.12-1.93 (m, 2H).

HRMS (CI, M$^+$) calcd for C$_{19}$H$_{22}$O$_3$ 298.1569, found 298.1570.

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