Development and Synthesis Applications of Olefin Isomerization-Claisen Rearrangement Reactions

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Development and Synthesis Applications of Olefin Isomerization-Claisen

Rearrangement Reactions

Kan Wang, PhD

University of Pittsburgh, 2007

Iridium(I)-catalyzed olefin isomerization in bis(allyl) ethers was integrated into a generally applicable strategy for affecting highly stereoselective Claisen rearrangements. Catalyzed alkene isomerization afforded allyl vinyl ethers from easily prepared di(allyl) ethers; direct thermolysis of these reaction mixtures led to highly diastereoselective [3,3] sigmatropic rearrangements affording *syn*-2,3-dialkyl-4-pentenal derivatives.
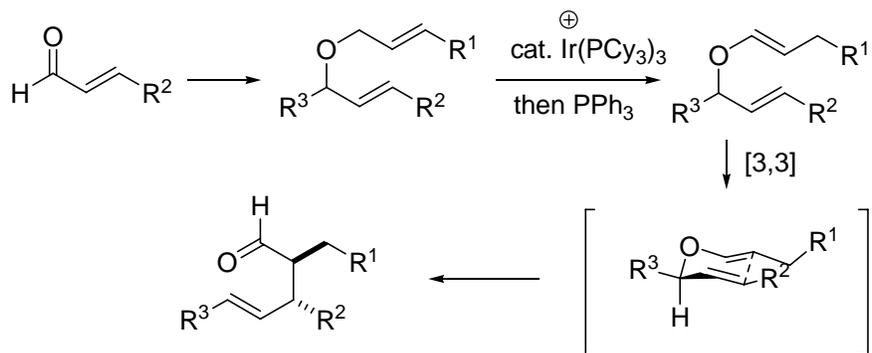
Merging the catalytic asymmetric synthesis of di(allyl) ethers with ensuing olefin isomerization-Claisen rearrangement (ICR) reactions provided a convenient, two-step route to asymmetric aliphatic Claisen rearrangements from easily obtained starting materials. These reactions delivered the 2,3-disubstituted 4-pentenal derivatives characteristic of aliphatic Claisen rearrangements with excellent relative and absolute stereocontrol. A catalytic enantioselective synthesis of the (+)-calopin dimethyl ether demonstrated the utility of this reaction technology in asymmetric synthesis enterprises.

(+)-calopin dimethyl ether
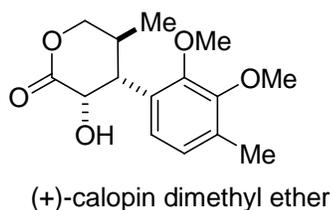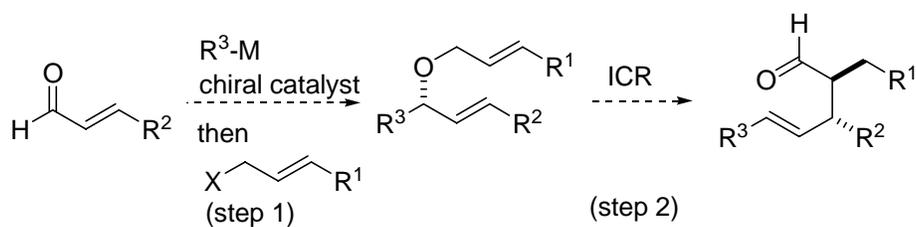
Stereoselective quaternary all-carbon stereocenter construction was often not easily achieved from methodologies developed primarily for accessing less substituted stereogenic carbons. Olefin isomerization-Claisen rearrangement (ICR) reactions offered a strategy for recruiting the Claisen rearrangement for asymmetric quaternary carbon construction. Several complementary strategies for enantioselective quaternary carbon synthesis derived directly from the ICR reaction design.
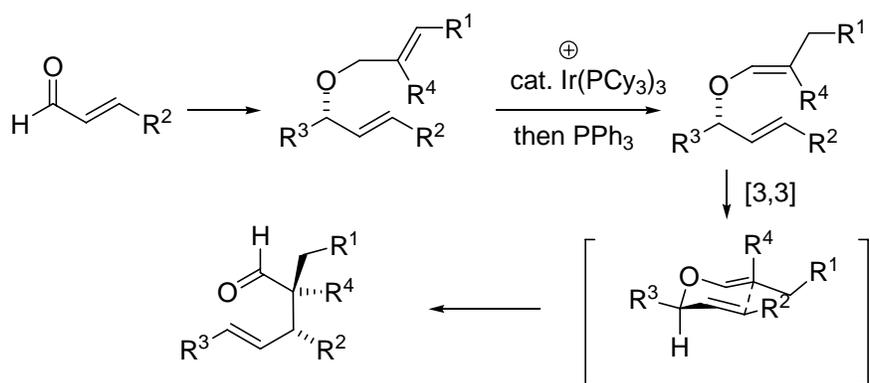
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LIST OF ABBRVIATIONS

COD   1,5-cyclooctodiene

COE   cyclooctene

DIBAL-H   di-*iso*-butylaluminum hydride

DMF   *N,N*-dimethylformamide

DMP   2,6-dimethylphenol

DMSO   methylsulfinylmethane

DTBMP   2,6-di-*tert*-butyl-4-methylpyridine

ICR   isomerization Claisen rearrangement

LAH   lithium alumninum hydride

MIB   1,7,7-trimethyl-3-morpholinobicyclo[2.2.1]heptan-2-ol

NIS   1-iodopyrrolidine-2,5-dione

NMO   *N*-methyl-morpholine oxide

TASF   tris(dimethylamino)sulfonium difluorotrimethylsilicate

TBAF   tetrabutylammonium fluoride

TBDPS   *tert*-butyldiphenylsilyl

TBS   *tert*-butyldimethylsilyl

THF   tetrahydrofuran

TMS   trimethylsilyl

TPAP   tripropylamino perruthenate

1.0   CLAISEN REARRANGEMENT-INTRODUCTION

The Claisen rearrangement stands as one of the most powerful methods for introducing molecular complexity from easily obtained starting materials.[1] Originally disclosed as the [3,3]-sigmatropic reorganization of allyl-aryl or allyl-vinyl ethers, the term Claisen rearrangement has subsequently expanded to include any such process involving a 1,5-diene possessing a heteroatom in the 3-position (Figure 1). Thus, in addition to the traditional formulation in which X = O, aza-Claisen (X = N),[2] thio-Claisen (X = S),[3] and even metallo-Claisen (X = metal)[4] rearrangements are well known.

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[1] Recent reviews of Claisen rearrangement, see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Nubbemeyer, U. *Synthesis* **2003**, 961. (c) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461-1471. (d) Wipf, P. In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 827-873. (e) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939-3002.

[2] (a) Tsunoda, T.; Sasaki, O.; Ito, S. *Tetrahedron Lett.* **1990,** *31*, 727. (b) Kurth, M. J.; Brown, E. J. *Synthesis* **1988**, 362. (c) Kurth, M. J.; Soares, C. J. *Tetrahedron Lett.* **1987**, *28*, 1031. (d) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1986**, *51*, 1377. (e) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443. (f) Hill, R. K.; Khatri, H. N. *Tetrahedron Lett.* **1978**, *19*, 4337. (g) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978.

[3] (a) Tubery, F.; Grierson, D. S.; Husson, H. P. *Tetrahedron Lett.* **1990**, *31*, 523. (b) Beslin, P.; Perrio, S. *J. Chem. Soc., Chem. Comm.* **1989**, 414. (c) Plate, R.; Theunisse, A. W. G.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 370. (d) Takahata, H.; Banba, Y.; Mozumi, M.; Yamazaki, T. *Heterocycles* **1986**, *24*, 3347. (e) Kwart, H.; Miles, W. H.; Horgan, A. G.; Kwart, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 1757. (f) Kwart, H.; Johnson, N. A.; Eggersichs, T.; George, T. *J. Org. Chem.* **1977**, *42*, 172. (g) Kwart, H.; Schwartz, J. L. *J. Org. Chem.* **1974**, *39*, 1575.

[4] (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1039, 1043, 4427, 4431. (b) Dewar, M. J. S.; Merz, K. M. *J. Am. Chem. Soc.* **1987**, *109*, 6553. (c) Normant, J. F.; Quirion, J. C. *Tetrahedron Lett.* **1989**, *30*, 3959.
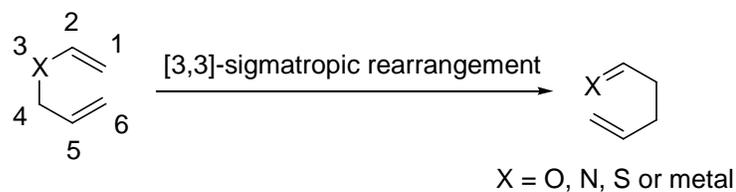
Figure 1. The Claisen rearrangement

1.1 CLAISEN VARIANTS

1.1.1 Preparation of allyl vinyl ether

One of the earliest reported methods for preparing of allyl vinyl ether Claisen substrates was the mercury(II) ion[5] or acid-catalyzed[6] interchange of allylic alcohols with alkyl vinyl ethers (Scheme 1). The formed allyl vinyl ethers typically required elVated temperatures for the [3,3] sigmatropic rearrangement. Though it allowed for a straightforward method to the preparation of allyl vinyl ethers, the toxicity and low yields associated with the mercury transetherification have limited the use of this procedure.
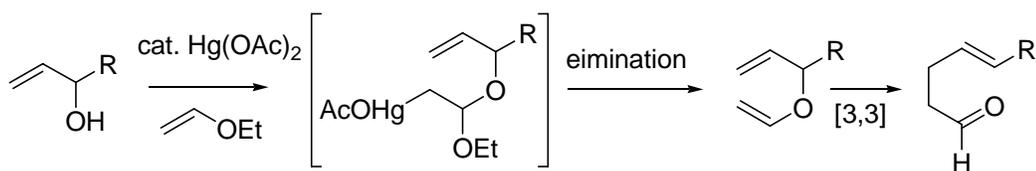
Scheme 1. Mercury (II)-catalyzed preparation of Claisen substrate

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[5] Hg^{2+} catalyzed: Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc*. **1957**, *79*, 2828-2833.
[6] H$^+$ catalyzed: (a) Marbet, R.; Saucy, G. *Helv. Chim. Acta.* **1967**, *50*, 2091-2095. (b) Marbet, R.; Saucy, G. *Helv. Chim. Acta.* **1967**, *50*, 2095.

Nakai has reported a new version of the transetherification catalyzed by 2,6-dimethylphenol (DMP)- or palladium(II). [7] The Pd(II)-catalyzed cascade transetherification followed by Claisen rearrangement at ambient temperature gave a high *syn-* diastereoselectivity, while the DMP-catalyzed transetherification followed by thermal Claisen rearrangement afforded *anti-* diastereomers (Scheme 2).

PdCl$_2$(PhCN)$_2$ 23 °C *anti : syn* = < 2 : > 98
DMP   100 °C *anti : syn* = > 98 : < 2
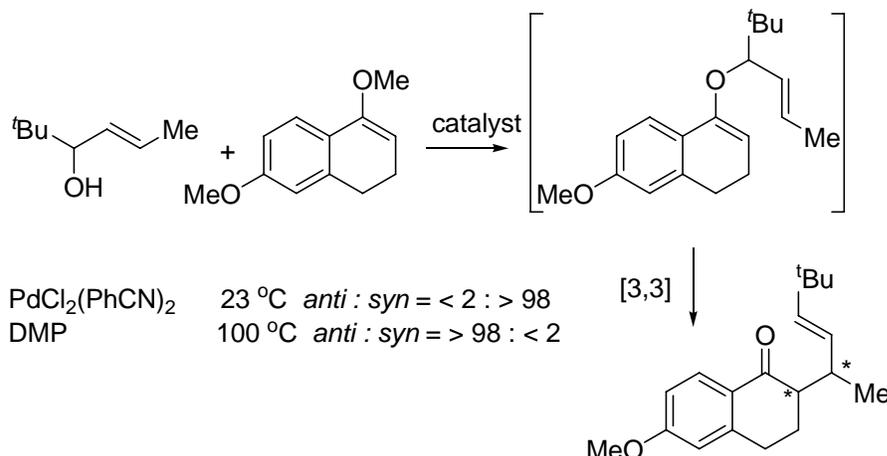
Scheme 2. Palladium (II) or DMP-catalyzed transetherfication followed by Claisen rearrangement

A methylidenation of allyl esters to allyl vinyl ethers was a useful protocol to prepare vinyl ethers. The Tebbe's reagent and similar reagents were used widely in the methylidenation (Scheme 3). [8] However the strong Lewis acidic residue had limited its application.
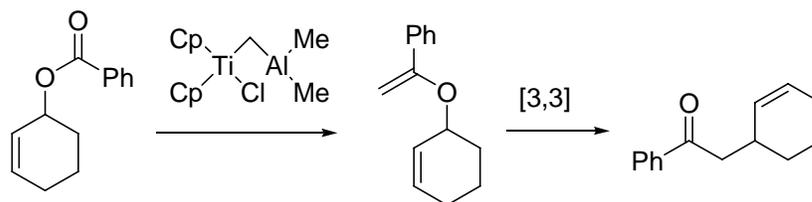
Scheme 3. Tebbe's reaction for Claisen substrates

[7] (a) Mikami, K.; Takahasi, K.; Nakai, T. *Tetrahedron Lett.* **1987,** *47*, 5879. For a most recent example of Pd(II)-catalyzed tandem vinyl ether exchange-Claisen rearrangement, see: (b) Wei, X.; Lorenz, J. C.; Kapadia, S.; Saha, A.; Haddad, N.; Busacca, C. A.; Senanayake, C. H. *J. Org, Chem.* **2007,** *72*, 4250-4253.
[8] (a) Pine, S. H.; Zahler, R.; Vans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980,** *102*, 3270. (b) Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans.* 1, **2002**, 2763 and references therein.

An elimination reaction was a common protocol to prepare vinyl ethers. Many elimination precedents have been reported. Two examples are described here: the first reaction is a selenium oxidative elimination (Scheme 4);[9] the second example is a NIS-assisted allyl alcohol attacking vinyl silyl ether following base-mediated elimination (Scheme 5).[10]
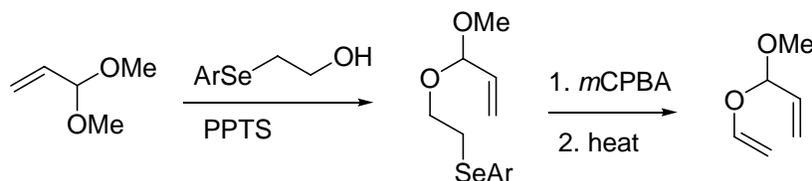
Scheme 4. Selenium oxidative elimination
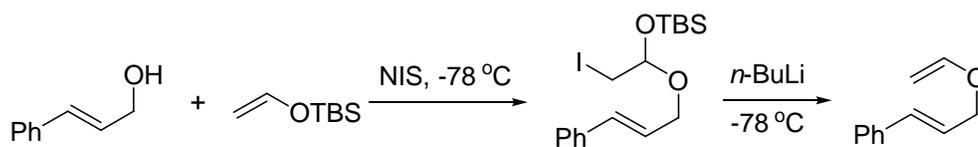
Scheme 5. NIS-assisted allyl alcohol attacking vinyl silyl ether following elimination

A novel protocol for preparing vinyl ethers reported by Stoltz was a tandem Rh-catalyzed Bamford-Stevens/Clasien rearrangement sequence (Scheme 6).[11] The protocol entailed a tandem process in which α-allyloxy *N*-aziridinyl imines **1** were converted *via* rhodium-catalyzed Bamford-Stevens reaction to allyl vinyl ethers **2**, which subsequently underwent the thermal Claisen rearrangement to furnish aldehyde products **3**. Importantly, the Bamford-Stevens reaction provided an access for (*Z*)-enol ethers, which were not easily afforded from other source, with high stereoselectivity.

[9] Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am Chem. Soc.* **1987**, *109*, 1160
[10] Maeda, K.; Shinokubo, H.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1996**, *61*, 2262.
[11] May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426-12427.
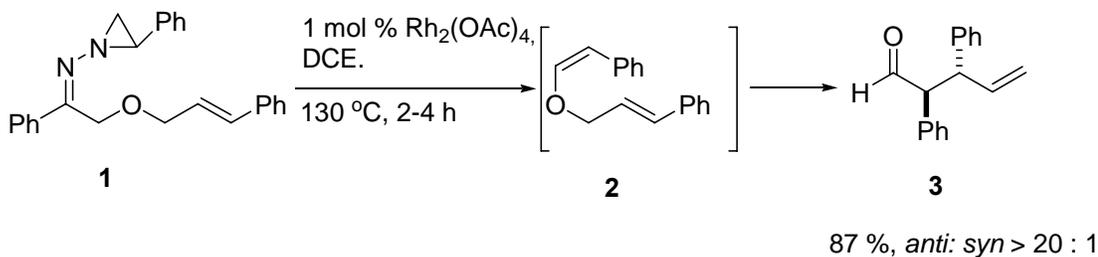
Scheme 6. Tandem Rh-catalyzed Bamford-Stevens/Clasien rearrangement

Ullmann coupling reaction is a straightforward idea to prepare allyl vinyl ethers from allyl alcohols and vinyl halides. Recently, Buchwald has reported a copper (I) iodide and tetramethyl-1,10-phenanthroline-catalyzed domino C-O coupling/Claisen rearrangement process with moderate yield and high diastereoselection (Scheme 7).[12] To avoid the strong epimerization of the formed aldehyde (**4**) under basic reaction conditions, one limitation of this protocol was that the starting material vinyl iodide was 2,2-disubstituted-1-iodoethenes. As a result, an all carbon α-quaternary center was introduced into the Claisen adduct.
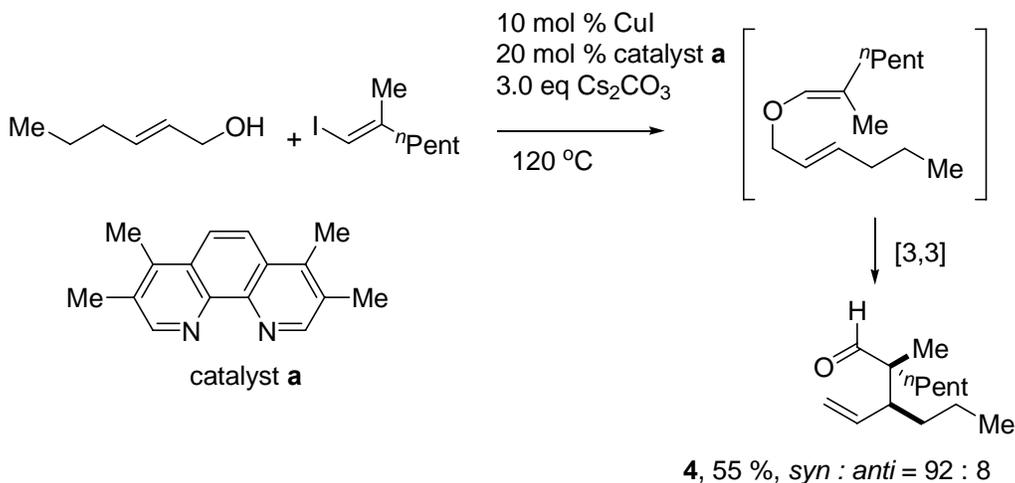
Scheme 7. Domino Cu(I)-catalyzed coupling/Claisen rearrangement

[12] (a) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978. A Ir-catalyzed etherification of allyl alcohols with vinyl or isopropenyl acetates has been reported recently, see: (b) Morita, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2006**, *71*, 6285-6286.

1.1.2 Activated Claisen variants

Although the parent aliphatic Claisen rearrangement is a very useful reaction, a common feature of these simple allyl vinyl ether Claisen rearrangements is the relatively high temperatures required. This fact, coupled with the difficulty in accessing these substrates has led to a less widespread reliance on these traditional Claisen variants as compared to certain other activated protocols.

Most of organic synthesis contributions of the Claisen rearrangement were obtained from a series of activated variants, including the Carroll's allyic β-ketoesters rearrangement (Scheme 8),[13] the Eschenmoser's *N,O*-ketene acetals rearrangement from amide acetals (Scheme 9)[14] and Johnson's ketene acetals rearrangement from ortho ester (Scheme 10).[15] In these processes, the preparation of vinyl components of the Claisen rearrangement was simplified.
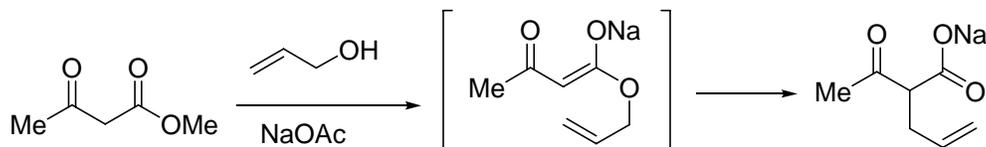
Scheme 8. Carroll's Claisen rearrangement
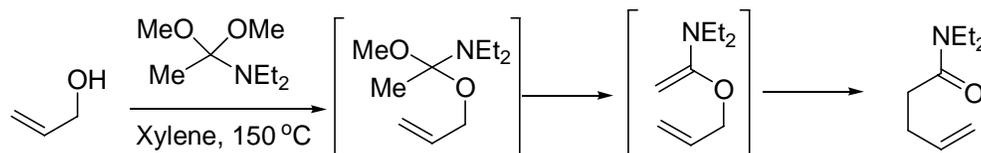
Scheme 9. Eschenmoser's Claisen rearrangement

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[13] (a) Carroll, M. F.; *J. Chem. Soc.* **1940**, 704; (b) Carroll, M. F.; *J. Chem. Soc.* **1940**, 1266. (c) Carroll, M. F.; *J. Chem. Soc.* **1941**, 507. (d) Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992.

[14] (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A.; *Helv. Chim. Acta.* **1964,** *47*, 2425. (b) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A.; *Helv. Chim. Acta.* **1969,** *52*, 1030.

[15] Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. –T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
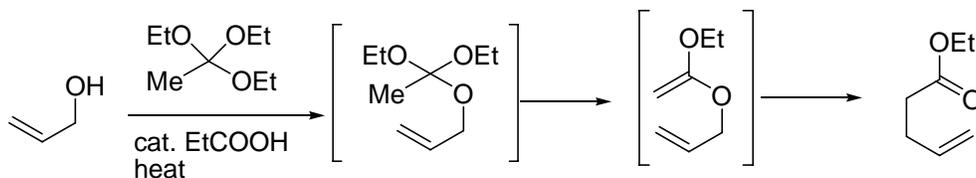
Scheme 10. Johnson's Claisen rearrangement

The most significant advancement in the field of the activated Claisen rearrangement has been reported by Ireland, in which silyl ketene acetals readily rearranged at or below room temperature (Scheme 11).[16] The silyl ketene acetals are typically generated at low temperatures (–78 °C) by enolization of allylic esters with amide bases followed by silyl trapping. A simple warming of these intermediates to ambient temperature was often enough to facilitate rearrangement. The utility of this protocol lied in the fact that silyl ketene acetal olefin geometry, and thus relative product stereochemistry, was dictated by judicious choice of enolization conditions.

syn: anti = 87: 13
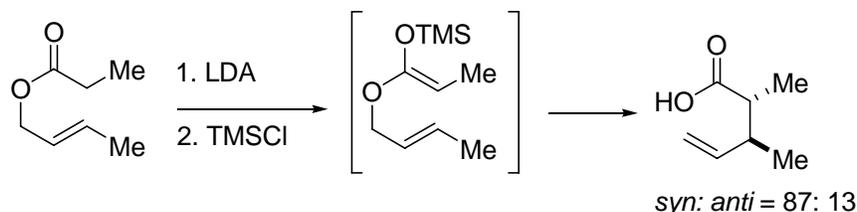
Scheme 11. Ireland's enolate Claisen rearrangement

---

[16] Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am Chem. Soc.* **1976,** *98*, 2868.

1.2   TRANSITION METAL-CATALYZED ALLYL ETHER ISOMERIZATION REACTION

Although activated Claisen variants are broadly used, they produce carboxylic acids, esters or amides. The original Claisen rearrangement affords aldehydes, which have more transformations in organic synthesis. But methods for preparing allyl vinyl ethers lack substrate generality or operational simplicity. As a result, the discovery of new protocols for making allyl vinyl ethers with both substrate generality and operational simplicity is desired.

Analysed from the structure, the allyl vinyl ether can be derived from the di(allyl) ether with a selective olefin isomerization process (Figure 2). Discovery of a useful olefin isomerization methodology followed by Claisen rearrangement with substrate generality and operational simplicity is a specific aim of my research. In this dissertation, we describe an isomerization procedure from allyl ethers to vinyl ethers that enable the Claisen rearrangement with substrate generality and operational simplicities. We named the procedure ICR (**I**somerization **C**laisen **R**earrangement) reaction. For this specific aim, a stereoselective allyl ether isomerization reaction was desired.
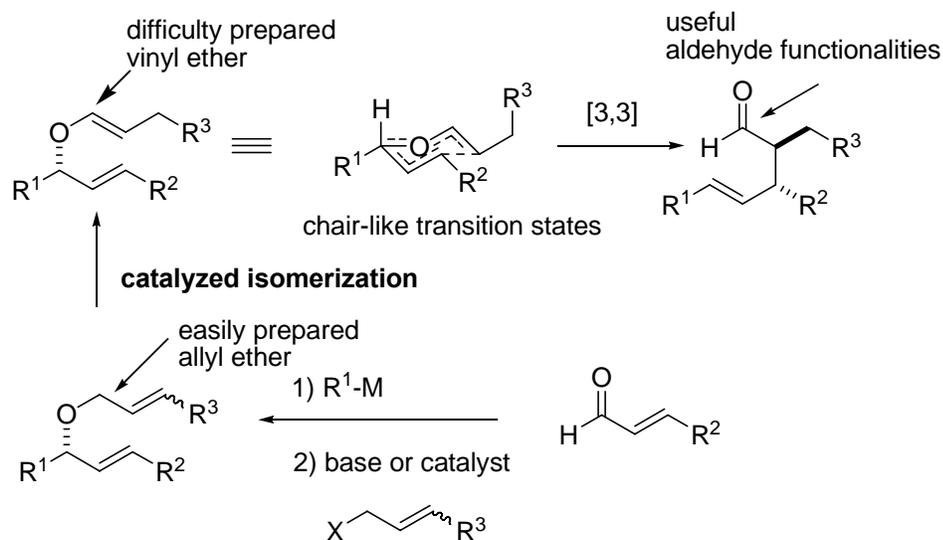
Figure 2. Olefin isomerization-Claisen rearrangement (ICR) reactions

Several kinds of chemical compounds have been reported with ability to isomerize olefins. One example is strong bases (e. g. sodium, potassium hydroxide, potassium amide/liquid ammonia, sodium methoxide and lithium diethylamide),[17] which had been used as catalysts for the allyl ether isomerization at high temperatures. The base-induced isomerization afforded highly stereoselective *cis*-propenyl ethers *via* a five-member ring transition state (95-100 %, Figure 3).
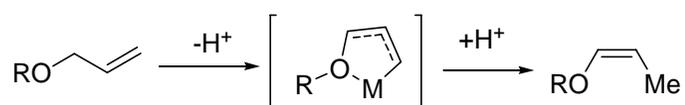
Figure 3. Base-catalyzed olefin isomerization reaction

In the base-promoted ICR reaction, which has been rarely reported,[18] the isomerization of the 3,3-disubstituted allyl ether is more favorable (Scheme 12). Its chemoselectivity is different from that of the transition metal-catalyzed ICR reaction, in which the unsubstituted allyl ether

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[17] (a) Prosser, T. J.; Price, C. C.; Snyder, W. M. *J. Am. Chem. Soc.* **1961**, *83*, 1701-1704. (b) Price, C. C.; Snyder, W. M. *J. Am. Chem. Soc.* **1961**, *83*, 1773-1774.

[18] Vyglazov, O. G.; Chuiko, V. A.; Izotova, L. V. *Russ. J. Gen. Chem.* **2003**, *73*, 933-939.

was more favorable for isomerization. These base-promoted ICR reactions are of narrow utility, limited by strongly basic conditions, tedious workups and moderate yields. As a result, most useful isomerization catalysts are transition metal complexes.
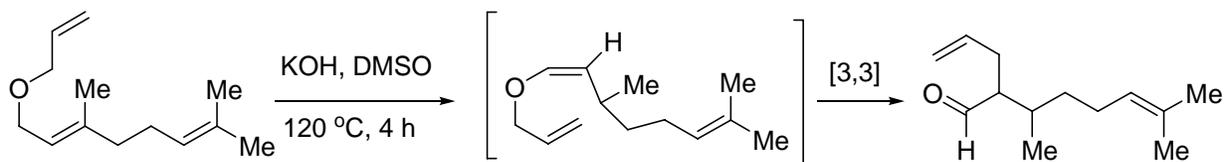
Scheme 12. Strong base-promoted ICR reaction

The transition metal-catalyzed allyl ether isomerization process involves three steps: 1) an oxidative addition (or C-H insertion); 2) an allyl migration and 3) a reductive elimination. The overall reaction affords vinyl ether from an allyl ether. First, the transition metal complex [M] coordinates an olefin (**5**); then the complex [M] insertes into the allyl C-H bond to form a new C-M-H bond intermediate (**6**); next, the allyl M-H bond isomerizes to the other allyl position to form a vinyl ether (**7**); finally, the reductive elimination of complex **7** affordes a more stable vinyl double bond (**8**) and startes a new catalytic cycle (Figure 4).
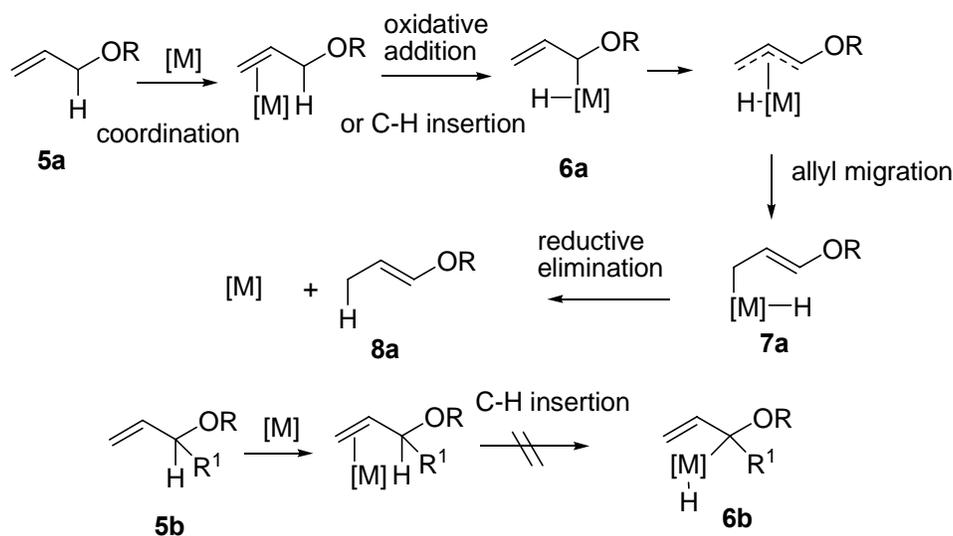
Figure 4. Transition metal-catalyzed allyl ether isomerization reactions

There is good chemoselectivity for the isomerization of di(allyl) ethers (**9**, Figure 5). Both kinetic and thermodynamic factors lead to the formation of the least sterically hindered C-M σ bond intermediate: The intermediate **c** is more favorable than intermediates **a, b** and **d**. The kinetic preference is caused by the activation barrier to the σ-complex (**6**) formation is lower for the less sterically hindered C-H bond. So in di(allyl) ether **9**, The **Ha** is more favable to be inserted than **Hb.** The thermodynamic preference is the stronger C-M bond formation, because the more substituents (**6b**) formed the weaker C-M bond.[19] As a result, it is difficult to isomerize 1-substituted allyl ethers (**5b,** Figure 4) because it is difficult to insert a metal complex into a $3^{\circ}sp^3$ C-H bond, especially for those complexes with large cone angle ligands.[20] This chemoselectivity ensures that the Claisen rearrangement precursor allyl vinyl ether (**10**) is obtained through only one isomerization process from the monosubstituted di(allyl) ether (**9**). The analysis also suggests that the kineticallyl favorable *E*-vinyl ether is formed from isomerization of the allyl ether.

[19] Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.
[20] The Complexes with small cone angle can insert the secondary allyl ethers, see: Ohmura, T.; Yamamoto Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413.
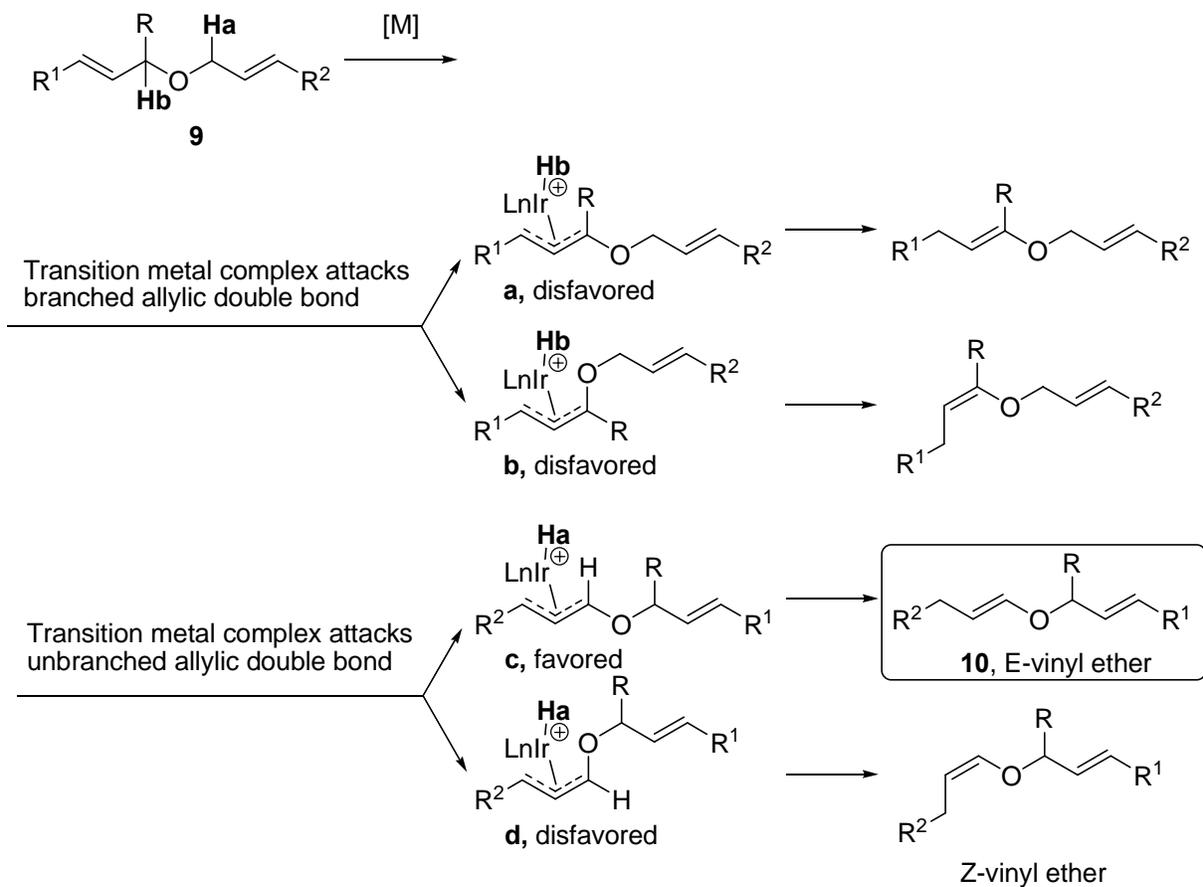
Figure 5. Chemoselectivity of isomerizatioon

The transition metal-catalyzed isomerization of allyl ethers is a convenient and straightforward method for preparing enol ethers, which are useful in synthetic transformations. In one application, allyl or but-3-en-2-yl moieties were introduced as stable protecting groups for carbohydrates. They were easily removed *via* a transition metal-catalyzed isomerization following an acid-promoted hydrolysis (Scheme 13).[21]

---

[21] (a) Boons, G.-J.; Burton, A.; Isles, S. *J. Chem. Soc., Chem. Comm.* **1996**, 141. (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.
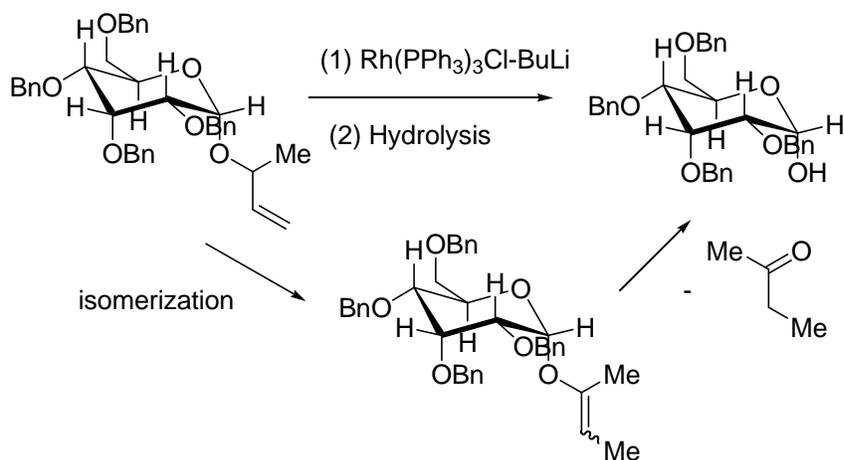
Scheme 13. Transition metal-catalyzed deprotection of allyl or but-3-en-2-yl ether

Recently, many metal complexes have been reported to be effective catalysts for the isomerization of allyl ethers. For example, a complex $H_2Ru(PPh_3)_4$ catalyzed isomerization gave an equbrium mixture with the (Z)-enol ether predominating ($Z = 55$-68%).[22] The complex $NiCl_2(dppb)/LiBHEt_3$ catalyzed isomerization of allyl ethers yielded (Z)-enol ethers under mild condition ($Z > 95$-99%).[23] In contrast, various cationic iridium(I) complexes stereospecifically produced (E)-enol ethers ($E = 88$-99%). The iridium(I) complex $[Ir(PR_3)_2Sol_2]PF_6$ prepared *in situ* by treating $[Ir(COD)(PMePh_2)_2]PF_6$ or $[Ir(COD)_2]PF_6/2PR_3$ with hydrogen or metal hydrides was found to be an excellent catalyst for achieving high yields and high stereoselectivity in the isomerization of various allyl ethers under mild conditions (Figure 6).[24]

[22] Suzuki, H.; Koyama, Y.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1979**, *20*, 1415.

[23] Wille, A.; Tomm, S.; Frauenrath, H. *Synthesis* **1998**, 305.

[24] (a) Baudry, D.; Ephritikhine, M.; Felkin, H. *J. Chem. Soc., Chem. Commun.* **1978**, 694. (b) Ohmura, T.; Yamamoto Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413. (c) Ohmura, T.; Shirai, Y.; Yamamoto Y.; Miyaura, N. *Chem. Commun.* **1998**, 1337. (d) Yamamoto, Y.; Miyairi, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem.* **1999**, *64*, 296. (e) Swenton, J. S.; Bradin, D.; Gates, B. D. *J. Org. Chem.* **1991**, *56*, 6156. Solid-supported catalyst, see: (f) Baxendale, I. R.; Lee, A. –L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1,* **2002,** 1850.
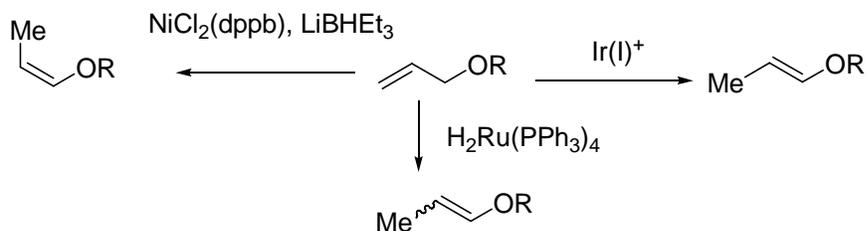
Figure 6. Different transition metal-catalyzed isomerization of allyl ethers

1.3   OLEFIN ISOMERIZATION-CLAISEN REARRANGEMENT

1.3.1 Precedents of ICR reaction

The chemoselective isomerization of the di(allyl) ether (**9**) would afford the allyl vinyl ether (**10**), the precursor of the Claisen rearrangement. Miyaura has reported the iridium complex **11** (R = PMePh$_2$) as a stereoselective catalyst for a series of isomerizations of di(allyl) ethers (Figure 7).[25] The order of isomerization reactivity was allyl > methallyl > crotyl > cinnamyl >> prenyl > 2-cyclohexenyl, which experimentally indicated that the less substituted allyl group had more tendency to be isomerized.

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[25] Yamamoto, Y.; Fujikawa, R.; Miyaura, N. *Synth. Comm.* **2000**, *30*, 2383.
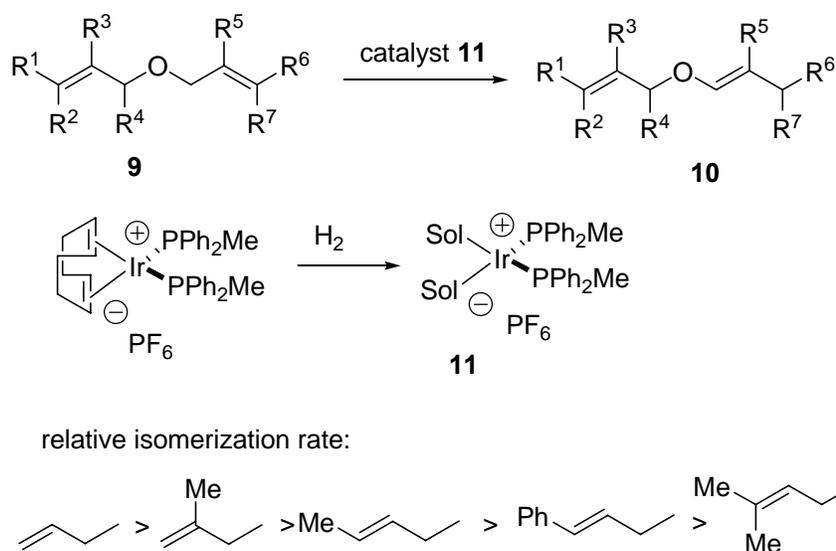
Figure 7. Relative isomerization rate of different allyl ether

Some cascade allyl ether isomerization/Claisen rearrangement reaction precedents have been reported. Salomon found that 0.1 mol% $RuCl_2(PPh_3)_3$ catalyzed the rearrangement of di(allyl) ethers bearing cycle for a synthesis of γ, δ -unsaturated aldehydes and ketones at 200 $^{\circ}$C without solvent in sealed Pyrex tubes in 1-4 h. No diastereoselectivity was reported in this reaction (eq 1). [26] It is believed that this high temperature was required for the Claisen rearrangement.
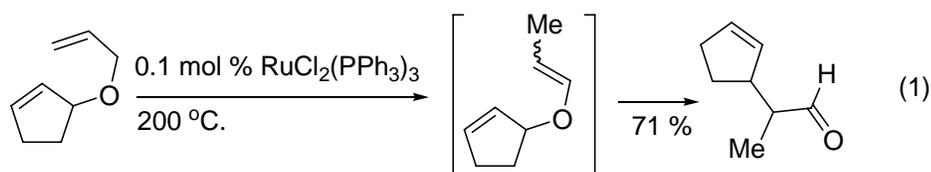
Ishii has reported that a catalyst system containing $[Ir(COD)Cl]_2$, tricyclohexanephosphine (PCy_3) and cesium carbonate, isomerized an allyl homoallyl ether to afford an allyl vinyl ether. The reaction was performed at 100 $^{\circ}$C to yield a 1: 1 diastereomeric

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[26] Salomon, R. G.; Reuter, J. M. *J. Org. Chem.* **1977**, *42*, 3360.

mixture (eq 2).[27] It is suggested that this iridium-catalyzed isomerization reaction is difficult or impossible at ambient temperature because the Claisen rearrangement of the allyl vinyl ether (**12**) did not require high temperature. Another factor eroding the reaction was that the isomerization of the homoallyl ether was much more difficult than that of the allyl ether.

$$\text{(eq 2)}$$
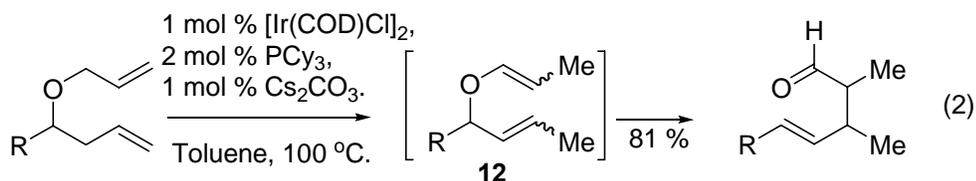
Olefin isomerization with ruthenium carbene catalysts in conjunction with RCM reactions has been reported by several groups.[28] Dixneuf has reported a three component catalyst $Ru_3(CO)_{12}$/1,3-bis(2,6-diisopropylphenyl) imidazolinium chloride/Cs_2CO_3 (molar ratio $1:3:6$) successively promotes both isomerization from the allyl ether to the vinyl ether and the Claisen rearrangement to afford the γ,δ-unsaturated aldehyde.[29] Schmidt utilized a combination of the first generation Grubbs catalyst and ethyl vinyl ether to perform tandem isomerization-Claisen rearrangements (eq 3).[30] Better diastereoselective products were obtained as a mixture of 2: 1 diastereomers. All these reports indicated that the allyl ether isomerization leading to the Claisen rearrangement. Unfortunately, very poor diastereoselections were observed in all of these precedents, so their applications in organic synthesis were rarely reported.[31]

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[27] Higashino, T.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2000,** *2*, 4193-4196.
[28] (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4732-4734. (b) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481-5484.
[29] (a) Notre, J. L.; Brissieux, L.; Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Chem. Chemmun.* **2002**, 1772-1773. (b) Ammar, H. B.; Le Notre, J.; Salem, M.; Kaddachi, M. T.; Dixneuf, P. H. *J. Organomet. Chem.* **2002**, *662*, 63-69.
[30] (a) Schmidt, B. *Synlett* **2004**, 1541-1544. The second generation Grubbs catalyst was used in Nelson group for isomerization of allyl amines, see: (b) Nihar, S.; Nelson, S. G. unpublished result.
[31] One application is a synthesis of pyrrole derives, see: Iyer, R. S.; Kobierski, M. E.; Salomon, R. G. *J. Org. Chem.* **1994,** *59*, 6038.

5 mol % catalyst
4 eq ethyl vinyl ether.

Toluene, 110 °C.
91 %, dr = 2: 1.

(3)

PCy₃ ... Ru ... Cl ... Ph ... PCy₃

catalyst
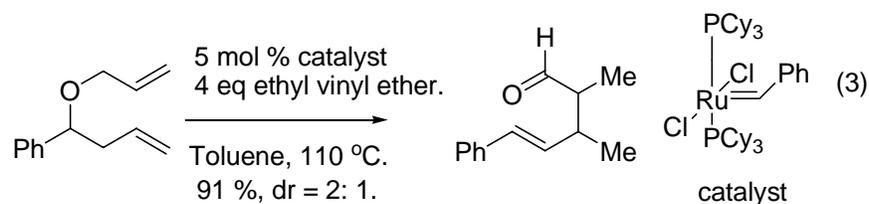
1.3.2 Requirements for good ICR reaction

Some factors are beliVed to cause poor chemoselectivity. First, the *E/Z* ratio of the vinyl ether perhaps is poor. As noted earlier, the Claisen rearrangements proceed *via* a highly ordered six-member chair like transition state to produce two stereocenters, often with high lVels of stereoselectivity. The *E* isomer afforded the 2,3-*syn* adduct and the *Z* isomer afforded the 2,3-*anti* adduct after [3,3] sigmatropic rearrangement. So the poor *E/Z* ratio causes poor diastereoselectivity (Figure 8).

isomerization

E

chair T. S.

2,3-*syn*

Z

2,3-*anti*
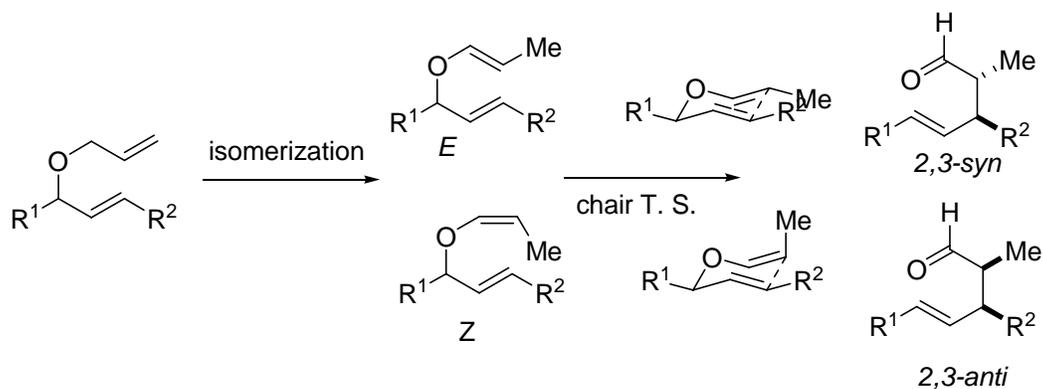
Figure 8. Stereochemical consequence of ICR reaction

Second, the epimerization of the formed aldehydes (**13,** except an α-quaternary aldehyde) sometimes is the most essential reason for the poor diastereoselectivity. The aldehyde generated from the ICR process contains an α-chiral center, which is easily epimerized under basic or Lewis acidic conditions *via* enol or enolate intermediates (Figure 9). As a result, bases, acids or Lewis acids should be avoided in good ICR reaction.
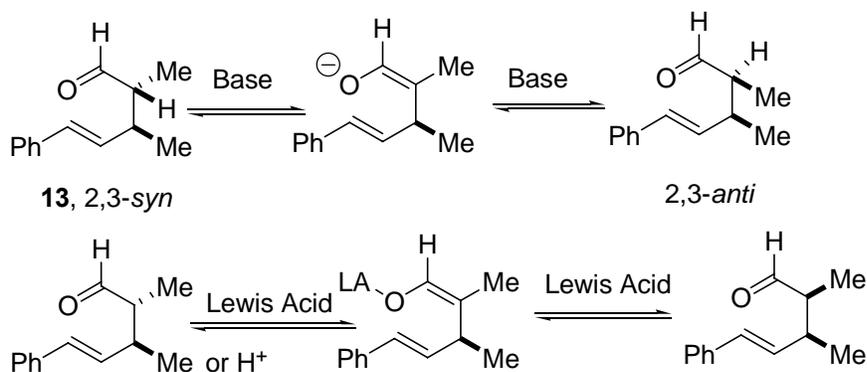
Figure 9. Epimerization of α-chiral aldehyde under base or Lewis acid

Finally, high reaction temperatures erode stereoselectivity. The [3,3] sigmatropic rearrangement of the good stereodefined allyl vinyl ether *via* different transition states affords different enantiomers, diastereomers and *E/Z* isomers. The (*E,E*)-allyl vinyl ether affords the 2,3-*syn*-4-*E* Claisen adduct *via* the chair transition state with the R^1 in a pseudo equatorial position, which is the most favorable transition state with the lowest energy. Three other isomers, 2,3-*syn*-4-*Z*, 2,3-*anti*-4-*E* and 2,3-*anti*-4-*Z* are afforded as minor products in other transition states, in which boat transition state and/or R^1 in a pseudo axial position are taken (Figure 10). The lower temperature favors the better stereoselectivity according to the Bolzman rule. So the higher temperature will afford poorer chemoselectivity in the Claisen rearrangement. Moreover, the high temperature promotes many side reactions. For example, the epimerization is accelerated significantly in high temperatures.
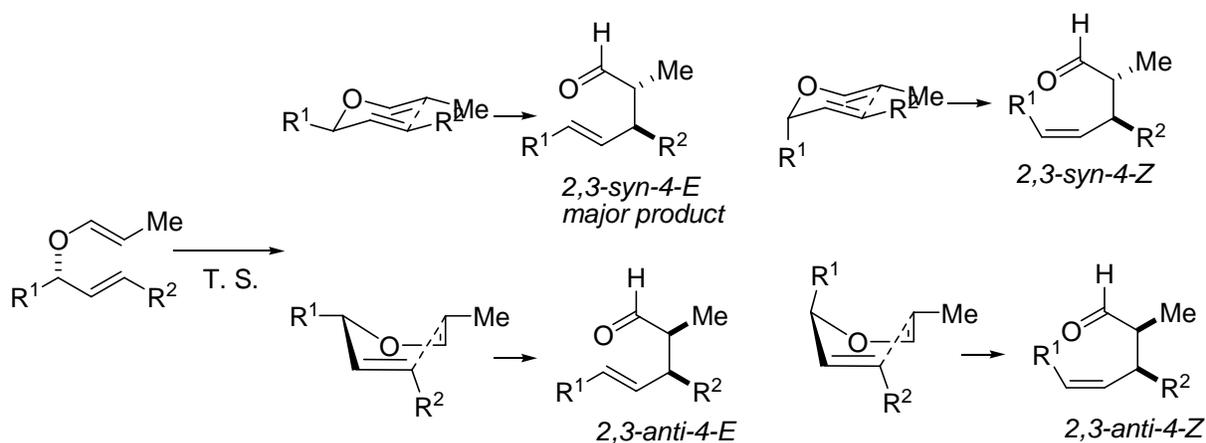
Figure 10. Stereochemical consequence for different transition states

Based on the above discussion, our research focused on the discovery of a convenient and highly stereoselective process concerning the cascade olefin isomerization/Claisen rearrangement (ICR reactions, Figure 11). Our requirements for a good ICR reaction were good isomerization regio- and stereoselectivities, neutral reaction conditions, relatively low reaction temperatures, substrate generality and operational simplicity. This transformation from simple starting materials to complex, important functionality is a main goal of synthetic chemistry.
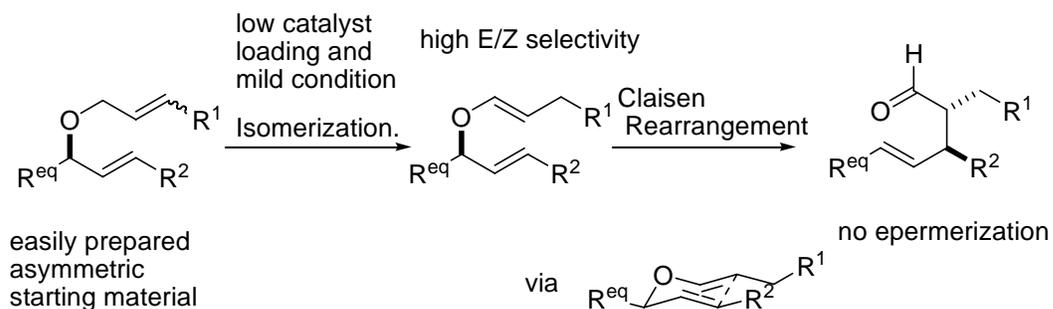
Figure 11. Requirements for good ICR protocol

2.0 IRIDIUM-CATALYZED OLEFIN ISOMERIZATION LEADING TO HIGHLY STEREOSELECTIVE CLAISEN REARRANGEMENTS OF ALIPHATIC ALLYL VINYL ETHERS

2.1 REACTION DEVELOPMENT

One major focus in developing successful ICR reactions is an olefin isomerization catalyst that would render di(allyl) ethers (**9**) effective precursors to highly stereoselective Claisen rearrangement. The catalyst would necessarily achieve both chemo- and stereoselective isomerization of one of the allyl residues and would not interfere with the ensuing thermal Claisen rearrangement nor accelerate epimerization of the aldehyde (**13**) product. Successfully developing catalysts satisfying these criteria would allow thermolysis of allyl vinyl ethers (**10**) in the presence of the catalyst complex to afford direct access to diastereomerically enriched 2,3-dialkyl-4-pentenal derivatives (**13**) (Figure 12).
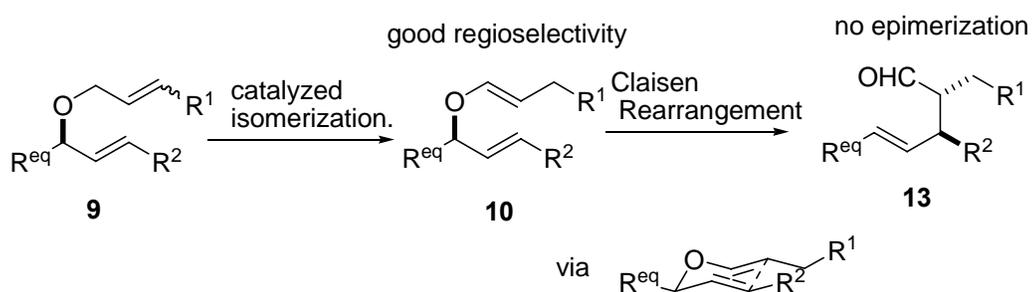
Figure 12. Olefin isomerization-Claisen rearrangement (ICR) reaction

2.1.1 Selection of precatalyst

Many cationic iridium(I) complexes used as isomerization catalysts are prepared from one equivalent of commercially available precatalyst [Ir(COD)Cl]$_2$ (COD: 1,5-cyclooctadiene), four equivalents of phosphine ligand and two equivalents of halide abstractor. These catalysts are activated *via* hydrogenation or hydrometalation by molecular hydrogen or metallic (aluminum or boron) hydride to remove the COD ligand before they become catalytically active (Figure 13). These aluminum or boron residues generated from metallic hydrides are strong Lewis acids, which were harmful for the ICR.
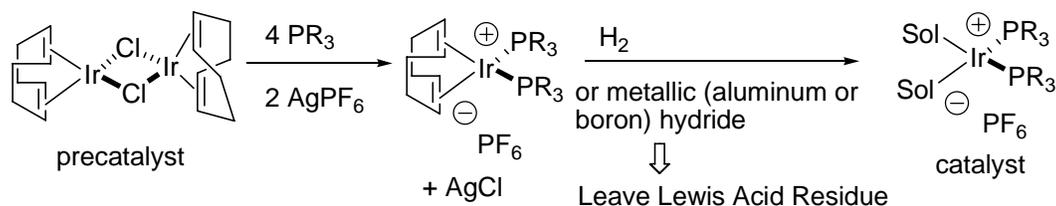
Figure 13. Activation of precatalyst [Ir(COD)Cl]$_2$

Based on the above discussion, a novel iridium-based olefin isomerization catalyst without metallic hydride activation should be discovered. The desired catalyst should not produce Lewis acid. Complexes of Ir(I) with cycloctene (COE) instead of COD are potential good precatalysts in the olefin isomerizaion. The cycloctene is easily displaced by phosphine ligand or solvent. This advantage makes the easily prepared dimer [Ir(COE)$_2$Cl]$_2$ (**14**) a useful potential olefin isomerization precatalyst. [32] Treatment of the iridium dimer complex **14** with 4, 6 or 8 equivalents of phosphine ligand and 2 equivalents of halide abstractor afforded di-, tri- or

[32] Onderdelinden, A. L.; Ent der Ent A. *Inorg. Chim. Acta.* **1972,** *6,* 420.

tetra- coordination iridium complexes (Figure 14).[33] These complexes were investigated for the ICR reaction of di(allyl) ether.
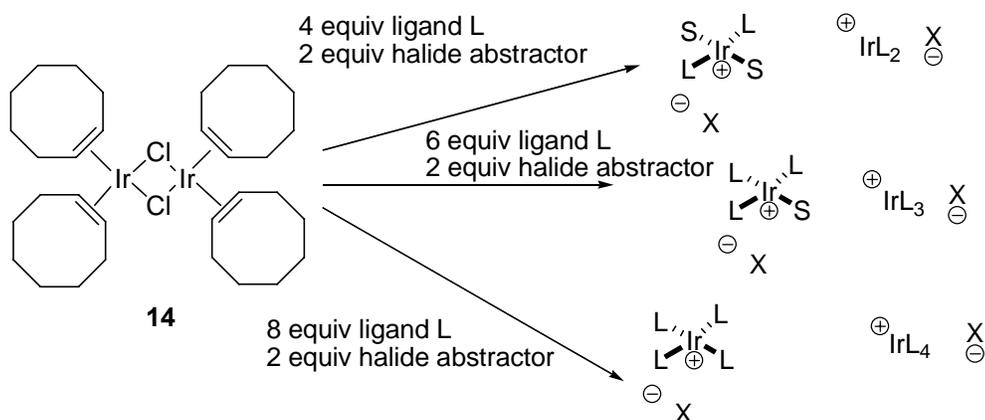
Figure 14. Isomerization catalyst based on iridium complex with COE ligand

2.1.2 Results and discussions

Choosing a suitable ligand is very important for reactivity. The isomerization of di(allyl) ether **9a** was investigated to screen the reactivity of different iridium complexes. Treated the **9a** to the 10 mol% complexes Ir(Ligand)$_2$SbF$_6$ (**15a-c**), which were prepared from 1 equivalent of [Ir(COE)$_2$Cl]$_2$ (**14**), 4 equivalents of phosphine ligands (Ligand = PCy$_3$, PPh$_3$ and PPh$_2$Me) and 2 equivalents of halide abstractor AgSbF$_6$, at ambient temperature for 12 h. The result indicated that the reaction with ligand PCy$_3$ (**5a**) gave the superior result: a mixture of aldehydes (**13a** and **13a′**. Both of them had poor diastereoselectivity) was obtained. The other two complexes (**15b,c**) afforded poorer yields of the isomerization-Claisen rearrangement products (Scheme 14). The ligand PCy$_3$ is a σ-basic phosphorus ligand that accelerates oxidative addition by stabilizing the iridium complex. Conversely, because the larger complex has more tendencies to shift from 2°

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[33] These complexes are formulated on the basis of reaction stoichiometry and are not necessarily intended to present the reactive catalyst complex that may be accessed by revrsible phosphine dissociation.

sp^3 C-Ir bond to 1° sp^3 C-Ir bond to avoid steric bulk, the steric bulk of PCy$_3$ accelerates the isomerization and the reductive elimination. In conclusion, the PCy$_3$ is the superior ligand for olefin isomerization.
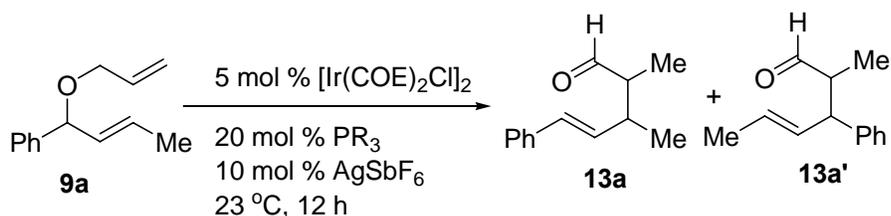
PR$_3$: PCy$_3$ (Ir complex **15a**) 50: 50 (both *dr* = 50: 50)
PPh$_3$ and PPh$_2$Me (Ir complex **15b,c**) starting material and by products

Scheme 14. Ligands of olefin isomerization catalyst

The isomerization of **9a** afforded a mixture of allyl vinyl ethers (**10a** and **10a′**) in 1 h in the presence of 10 mol% Ir(PCy$_3$)$_2$SbF$_6$ (**15a**) catalyst at 0 ^{o}C (Scheme 15). The result indicated that the reaction afforded allyl vinyl ethers first, which subsequently rearranged to the Claisen adducts at relative higher temperature. The poor diastereo- and regioslectivity suggested the complex **15a** was not suitable for ICR.
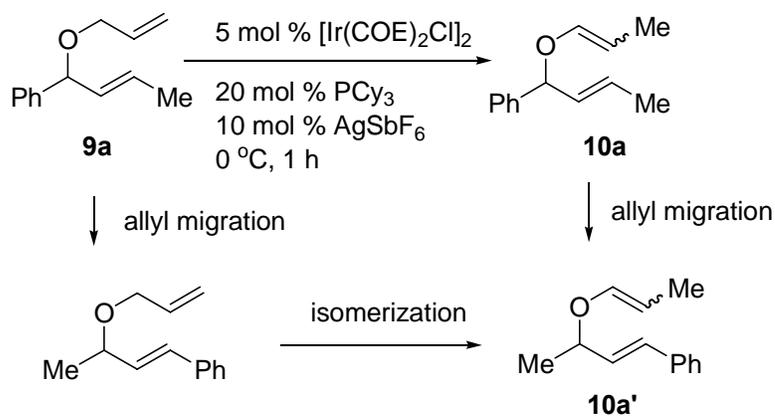
Scheme 15. Isomerization at relative lower temperature

Based on the above investigation, the ligand PCy$_3$ was chosen as the superior ligand. But the 10 mol% expensive catalyst loading is too much for a synthetic reaction. Another experiment indicated that 1 mol% catalyst **15a** loading afforded a mixture of **13a** and **13a′** (50: 50. Both of

23

them have poor diastereoselectivity. *syn: anti* = 50: 50). Next, we examined the effect of the

different coordination number of the ligands PCy$_3$. A triphosphine complex Ir(PCy$_3$)$_3$SbF$_6$ (**16**)

and a tetraphosphine complex Ir(PCy$_3$)$_4$SbF$_6$(**17**) are prepared *in situ* for mediating ICR reaction.

The result indicated that the 1 mol% triphosphine complex **16** is a better catalyst than the

diphosphine complex **15a** to afford a mixture of aldehydes nearly 100 % conversion. The

tetraphosphine complex **17** gave no isomerization products or aldehydes. Monitored by TLC and

GC-MS trace, the isomerization of di(allyl) ether **9a** with 1 mol% diphosphine complex (**15a**)

required 1-2 h, but required only 5-10 min with the triphosphine complex **16** (eq 4). As a result,

the tris(phosphine) complex **16** was preferred for the ICR reaction.

$$\text{(4)}$$
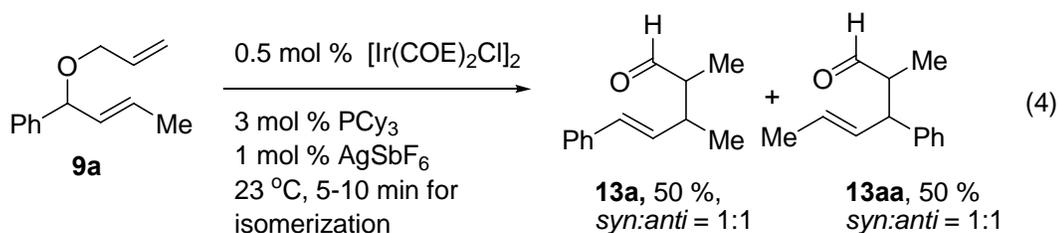
2.1.3 Halide abstractor

The iridium complex (**16)**-catalyzed ICR reaction generated a mixture of aldehydes. Besides the

desired [3,3] sigmatropic rearrangement product **13a**, a [1,3] sigmatropic rearrangement product

13a' was generated from Lewis acid-catalyzed allyl ether migration, followed by [3,3]

sigmatropic rearrangement **(**Figure 15**)**. Considering that the conjugated di(allyl) ether **9a'** was

more stable than the unconjugated di(allyl) ether **9a**; and the allyl ether migration was easily

mediated by Lewis acid. We concluded that there is some Lewis acidic character in the iridium(I)

catalyst **16**.

24
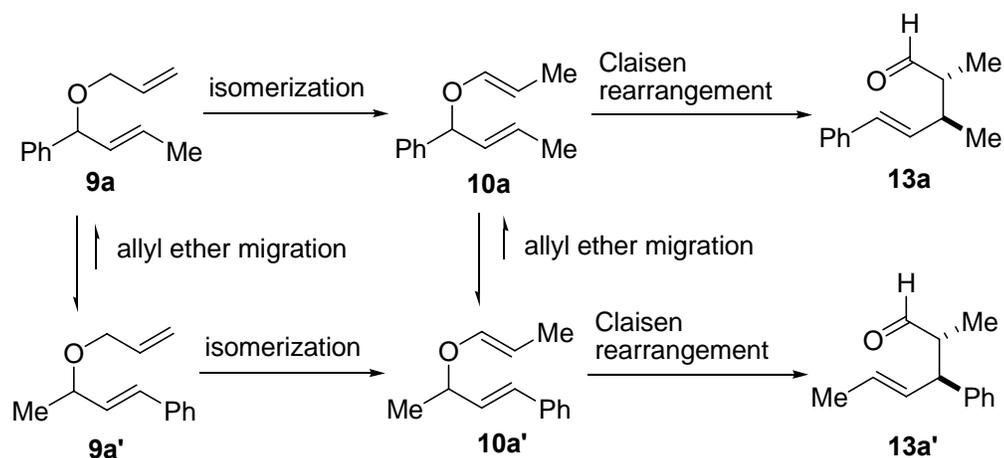
Figure 15. Lewis acid-catalyzed allyl ether migration followed by ICR reaction

A halide abstractor in the preparation of the cationic Ir(I) catalyst was critical in defining the efficiency of the reaction.[34] The complex **16** catalyzed allyl ether isomerization. However, the reaction generated poor regio- and stereoselectivity products. In general, Lewis acidic contaminants presented during the thermal Claisen rearrangements, whether they were derived from Lewis acidic Ir(I)-phosphine sepecies or Ag(I) salt by-products, led to poor diastereoselection in the putative Claisen adducts. The catalyst preparation employing $AgSbF_6$ is harmful for the ICR reaction because Ag^+ contaminants mediated side reactions. For example, the competing allyl ether migration and the epimerization of the Claisen adduct. Upon treatment of di(allyl) ether **9a** with 1 mol% $AgSbF_6$ in CH_2Cl_2 at ambient temperature overnight, a very complex mixture was observed. Among non-silver halide abstractors, both $NaSbF_6$ and $NaBPh_4$ afforded Claisen adduct with good diastereoselection (93 : 7 and 95 : 5 respective, Table 1) and high conversion when 1 mol% catalyst was used in 50/1 CH_2Cl_2/acetone, where acetone was used for increasing solubility of the sodium salt and stabilizing the Ir(I) catalyst by coordination.

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[34] Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2897.

These results indicated that the complex [Ir(PCy$_3$)$_3$]BPh$_4$ (**18**) was the optimized catalyst for the ICR reaction.

Table 1. Effect of different halide abstractor and solvent
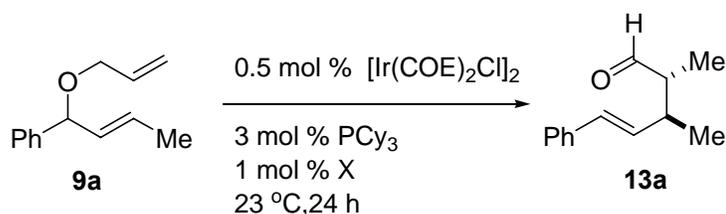
entry	halide abstractor (X)	solvent	*syn: anti*
a	AgSbF$_6$	CH$_2$Cl$_2$	50:50
b	NaSbF$_6$	CH$_2$Cl$_2$	no reaction
c	NaSbF$_6$	CH$_2$Cl$_2$/acetone = 50/1	93:7
d	NaBPh$_4$	CH$_2$Cl$_2$/acetone = 50/1	95:5

2.1.4 Optimization of ICR reaction

The [3,3] sigmatropic rearrangement of allyl vinyl ether **10a** was slow at ambient temperature, so high reaction temperatures were required for most thermal Claisen rearrangements. In the ICR of **9a**, the isomerization step was completed in 30 min with 1 mol% Ir(PCy$_3$)$_3$BPh$_4$ (**18**) from GC-MS trace and TLC, but the Claisen rearrangement required 24 h or longer at ambient temperature. Refluxing the crude isomerization reaction mixture in CH$_2$Cl$_2$ accelerated the rate; but the diastereoselection was eroded to *syn : anti* = 85 : 15. Refluxing the purified allyl vinyl ether (*E*)-**10a** in CH$_2$Cl$_2$ (The allyl vinyl ether was purified with short silica gel column chromatography using pentane as an eluent. The yield is 78 %) afforded 95: 5 diastereoselection. The result indicated that the iridium's Lewis acidic character eroded the diastereoselection.

Considering that the tetraphosphine complex $[Ir(PCy)_4]SbF_6$ (**17**) had no isomerization reactivity, so additional phosphine ligand would saturate the metal's coordination sphere prior to thermolysis. The inactivated complex **18** will passivate any residual Lewis acidic character in the Ir catalyst (Figure 16). For realizing this idea, more 3 mol% PPh_3 or PCy_3 were added into the reaction after the isomerization. After refluxing 12 h in dichloromethane, the reaction affored product with good diastereoselection (*syn : anti* = 94 : 6) for both additives. Including these two choices, PPh_3 is more convenient than PCy_3 (Table 2).

Table 2. Conditions for ICR optimization
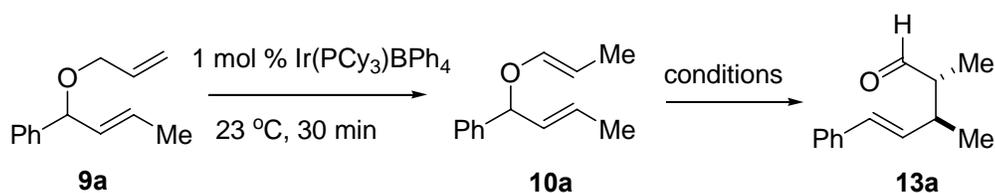
entry	conditions	temperature (^{o}C)	additive	time (h)	*syn: anti*
a	crude **10a**	23	no	24	95:5
b	crude **10a**	39	no	4	85:15
c	purified **10a**	39	no	4	95:5
d	crude **10a**	23	3 mol% PPh_3	4	94:6
e	crude **10a**	23	3 mol% PCy_3	4	94:6
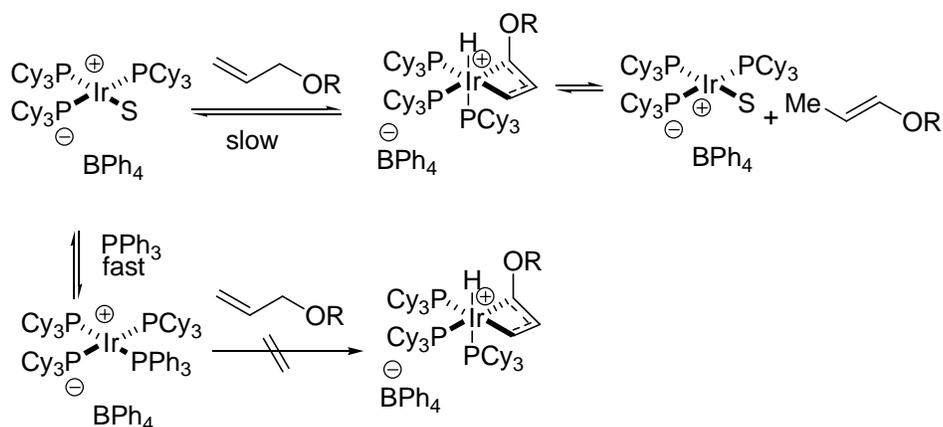
Figure 16. Additional ligands inactive the catalyst

In conclusion, an optimized ICR procedure was discovered. A series of Ir(I) complexes and conditions were investigated and found complex Ir(PCy$_3$)$_3$BPh$_4$ was the superior one. Additional 3 mol% PPh$_3$ after isomerization was necessary for obtaining product with good diastereoselectivity.

2.2 ICR REACTIONS OF SUBSTITUTED DI(ALLYL) ETHERS

2.2.1 Preparation of substrates and the summary of ICR result

Based on the good ICR result of the model di(allyl) ether, more di(allyl) ether substrates with general structures (**9**) were examined in order to determine the scope and efficiency of this novel ICR reaction. Generally, the substrates **9** were easily prepared by RM-enal 1,2-addition (M = Mg or Li), followed by *O*-allylation (Figure 17).
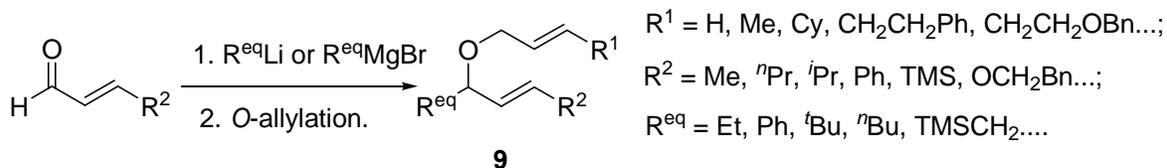
Figure 17. Preparation of di(allyl) ether substrates

Three major *O*-allylation reactions were used in this dissertation. First, a base deprontonation of the allyl alcohol followed by a S_N2 reaction with an allyl or substituted allyl bromide afforded di(allyl) ether (**9a**) (eq 5). Second, an acid-catalyzed allylation was more convenient for *(E)*-1,3-diphenylprop-2-en-1-ol (entry **e**), *(E)*-2-methyl-1,3-diphenylprop-2-en-1-ol (entry **f**) or similar structures coupling with allyl alcohols (eq 6).[35] This reaction was also useful for etherification of lots of alcohols with 1,3-diphenyl alcohols. Third, a palladium(0)-catalyzed allylic etherification of the bis(alkoxy)zinc with allyl acetate was used for alcohols containing functionalities that were not tolerated strong basic conditions, such as, *(E)*-4-phenyl-1-(trimethylsilyl)but-3-en-2-ol (eq 7).[36]

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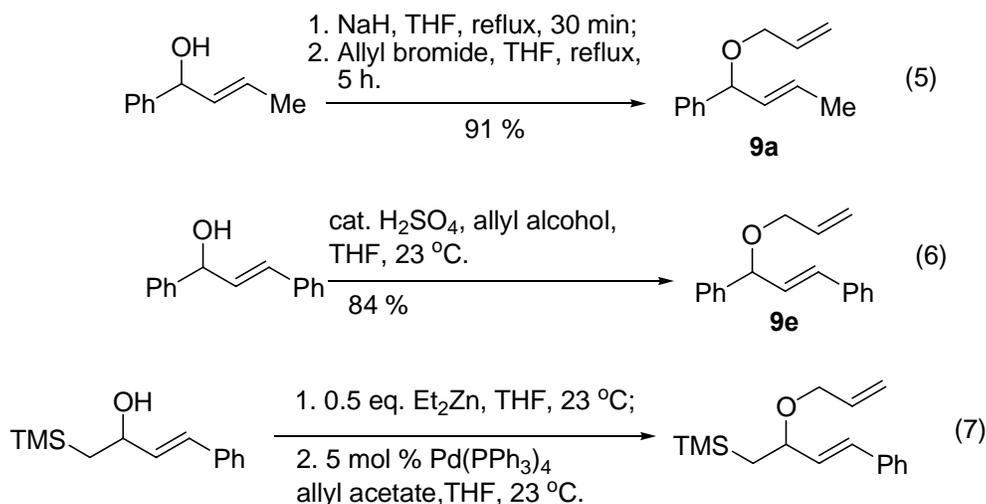
[35] Doering, W. von E.; Birladeanu, L.; Sarma, K.; Blaschke, G.; Scheidemantel, U.; Boese, R.; Benet-Bucholz, J.; Klarner, F. -G.; Gehrke, J. –S.; Zimny, B. U.; Sustmann, R.; Korth, H. –G. *J. Am. Chem. Soc.* **2000**, *122*, 193.

[36] Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369-4372. In this paper, Pd(PPh₃)₄ was used, but Pd(OAc)₂ and 5 eq PPh₃ obtain same result.

The summary of ICR results of di(allyl) ethers **9** is listed in Table 3. The di(allyl) ethers **9** were subjected to 1-2 mol% catalyst Ir(PCy$_3$)$_3$BPh$_4$ (**18**) in a solvent mixture (CH$_2$Cl$_2$ or 1,2-dichloroethane (DCE)/acetone = 50:1) at ambient temperature to afford the allyl vinyl ethers **10**. After isomerization (10-150 min), the Ir catalyst was deactivatd with 3-6 mol% PPh$_3$ following thermolysis at different conditions afforded the *syn*-2,3-disubstituted γ, δ-unsaturated pentenals **13** with good yield and diastereoselectivity.

Table 3. ICR reactions of substituted di(allyl) ethers (9)
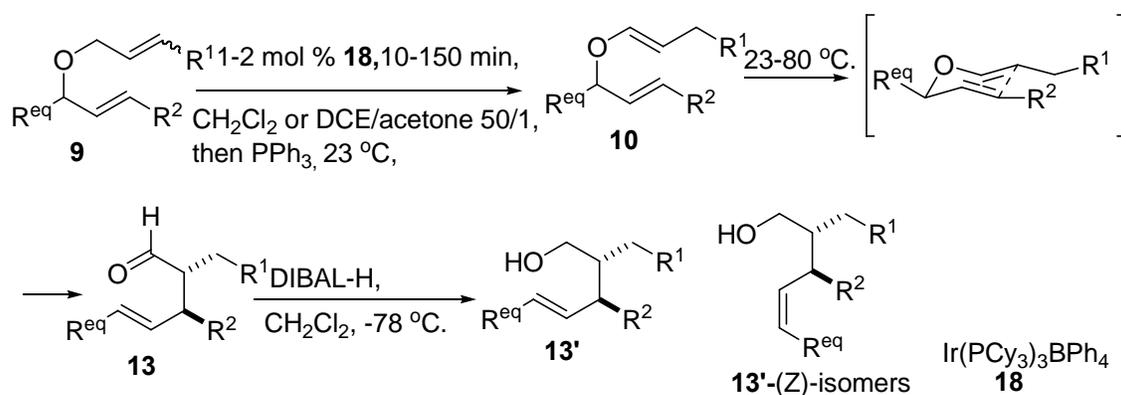
entry	R^1	R^2	R^{eq}	temp (°C)	*syn: anti* (13)	% yield (13′)	13′-(Z)-isomer (%)
a	H	Me	Ph	39	94: 6	80	0
b	H	^{n}Pr	Ph	39	97: 3	70	0
c	H	^{i}Pr	Ph	39	95: 5	93	0
d	H	TMS	Ph	39	97: 3	87	0
e	H	Ph	Ph	23	98: 2	92	0
f[a]	H	Ph	Ph	60	94: 6	92	7
g	H	^{i}Pr	^{n}Bu	80	94: 6	76	12
h	Me	Me	^{n}Bu	80	92: 8	85	12
i	H	Ph	^{n}Bu	80	96: 4	62	0
j	Me	Me	^{t}Bu	80	93: 7	62	0
k	Cy	Ph	Et	80	95: 5	61	0
l	CH$_2$CH$_2$Ph	Ph	Et	80	96: 4	77	0
m	CH$_2$CH$_2$OBn	Ph	Et	80	96: 4	74	0
n	CH$_2$CH$_2$OBn	Ph	Ph	23	97: 3	71	0

The substrate is (*E*)-3-(allyloxy)-2-methyl-1,3-diphenylprop-1-ene (**9f**, eq 8) .

(8)
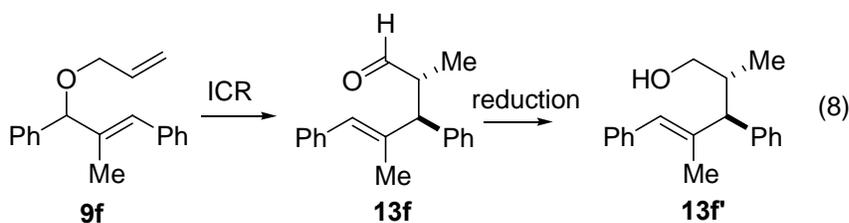
2.2.2 Isomerization reaction

In Table 3, substrates (**9**) were subjected to 1-2 mol% Ir(PCy$_3$)$_3$BPh$_4$ (**18**) in CH$_2$Cl$_2$ or 1,2-DCE /acetone 50/1 at 23 °C for 5 min to 2.5 h to afford the high yield of corresponding (*E*)-propenyl ethers (**10**). In all these entries, the isomerization of unsubstituted allyl ethers (R^1 = H, entry **a-g, i**) required 1 mol% Ir(PCy$_3$)$_3$BPh$_4$ to afford 100 % the (*E*)-propenyl ethers in 10 min at ambient temperature (eq 9). A longer reaction time afforded a mixture of (*E*)- and (*Z*)-isomers.

(9)
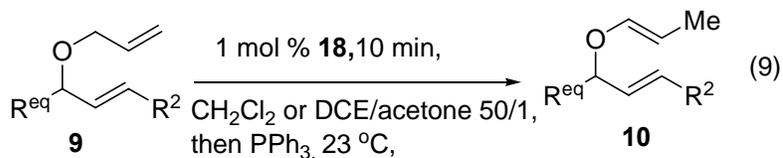
But the isomerization of the 3-substituted allyl ethers (R^1 = alkyl group, entry **h, j-n**) was more difficult than that of unsubstituted allyl ethers (R^1 = H). According the GC-MS data, the conversion of the 1 mol% Ir(PCy$_3$)$_3$BPh$_4$ catalyzed isomerization of the crotyl ether (entry **h**) was 41 % in 30 min and 59 % in 1 h. This result indicated that the isomerization of the crotyl ether was much slower than that of the allyl ether. Because methyl is a larger group than a proton to hinder the coordination of iridium complex with olefin, the isomerization was slower in the substituted allyl ether case. The slower isomerization also could be an electronic effect, the more substituted allyl metallics are less stable. Futhermore, the ratio of (*E*) : (*Z*)-vinyl ether (**10h**) is

different with time. According the data from crude proton NMR spectra, the $E : Z$ ratio was 88 : 12 in 2 h, 81 : 19 in 6 h and 74 : 26 in 12 h (eq 10).

$$\text{(eq 10)}$$
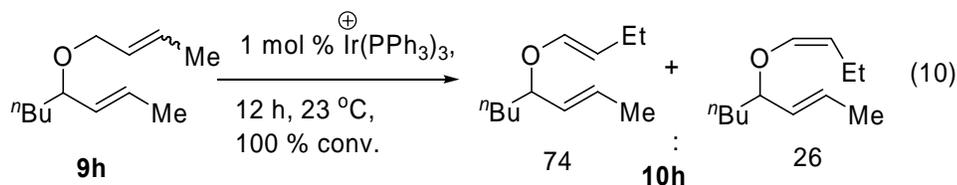
The decreased $(E) : (Z)$ ratio of vinyl ether with time suggested that there is a transformation from the *(E)*-vinyl ether to the *(Z)*-vinyl ether. This transformation is a slower process than the isomerization of the crotyl ether. So at the first step, the isomerization of the crotyl ether produced the kinetically favorable (E)-isomer. The iridium complex coordinates the olefin from the back side of the RO group to avoid the non-bonding interaction to afford the *E*-vinyl ether (Figure 18).
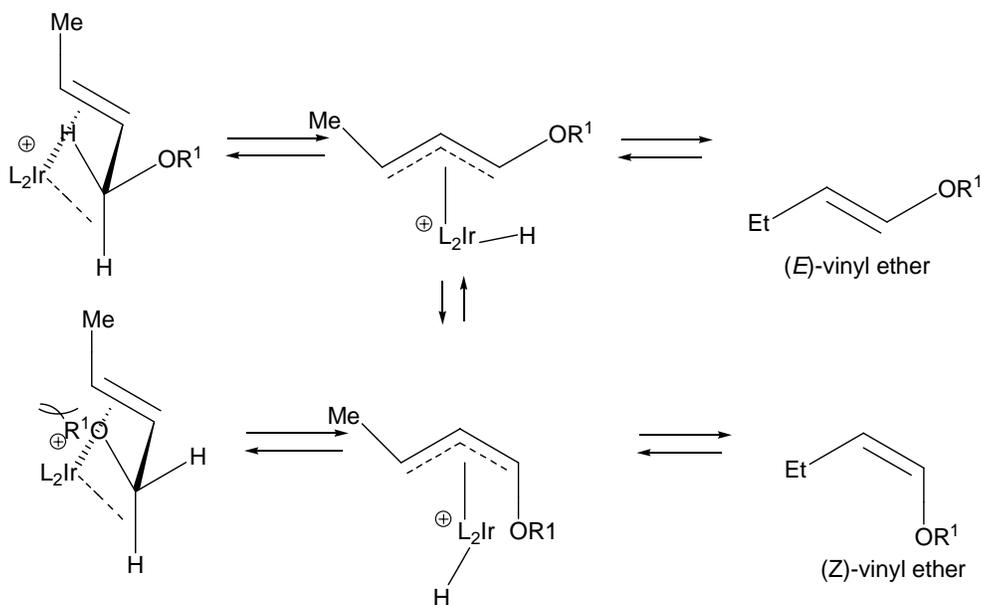
Figure 18. Formation of kinetic *E* vinyl ether

Next, the transformation from the (E)-isomer to the (Z)-isomer *via* π-allyliridium intermediate gave the (Z)-isomer as the thermodynamically favorable product, which perhaps had lower energy because of O-Ir coordination (Figure 19).

32
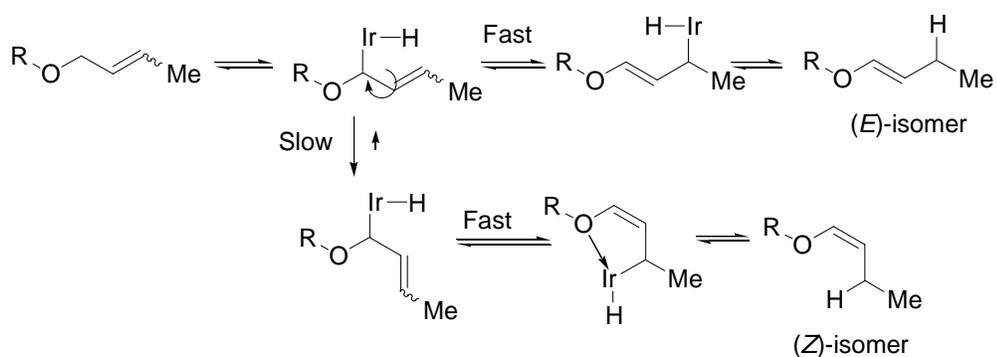
Figure 19. Transformation from (*Z*)- to (*E*)-vinyl ethers

For optimizing the isomerization of substituted allyl ether (entry **h)**, more catalyst loading was used to make the isomerization time shorter to avoid this *E-Z* transformation. When 2 mol% catalyst Ir(PCy$_3$)$_3$BPh$_4$ was used, the conversion to the allyl vinyl ether is 62 % in 30 min, 75 % in 1 h. After catalyst quenching in 1.5 h, the by-product (*Z*)-**10h** was not observed from the crude proton NMR. The desired product (*E*)-**10h** was obtained with 90 % yield after flash chromatography or was used for Claisen rearrangement directly without further purification (eq 11). When the R^1 group was larger, the isomerization reaction was more difficult and the conversion was poorer at the same reaction condition. With 2 mol% catalyst at ambient temperature followed by quenching in 150 min, the conversion for different substrates were: R^1 cyclohexyl (entry **k,** 78% conversion from crude proton NMR spectra), CH$_2$CH$_2$Ph (entry **l,** 85% conversion) and CH$_2$CH$_2$OBn (entry **m, n,** 85% conversion). These isomerization products were fine for the Claisen rearrangement without further purification.

$$\text{9h} \quad \xrightarrow[\substack{90 \text{ min, } 23\,^\circ C, \\ 90\,\%}]{2 \text{ mol }\% \ \overset{\oplus}{Ir}(PPh_3)_3,} \quad \text{10h} \qquad (11)$$
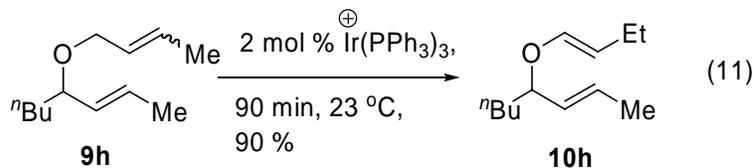
In addition to the isomerization from allyl ethers to vinyl ethers, the iridium complex Ir(PCy$_3$)$_3$BPh$_4$ (**18**) also coordinated other olefins and mediated their allyl isomerization.[37] For example, some by-products were detected from the isomerization of substrate **9b** (R^2 = ^{n}Pr). When substrate **9b** was treated with 1 mol% catalyst Ir(PCy$_3$)$_3$BPh$_4$ followed by quenching in 1 h, the crude NMR spectra indicated a mixture of products in the reaction. After thermolysis, 40 % yield of the Claisen adduct (**13b**) and 38 % yield of by-products as a mixture of 1-((3*E*)-1-((*E*)-prop-1-enyloxy)hex-3-enyl)benzene **(10ba)** and 1-((4*E*)-1-((*E*)-prop-1-enyloxy) hex-4-enyl)benzene (**10bb**) were afforded (Scheme 16). This result indicated a side reaction, in which the catalyst Ir(PCy$_3$)$_3$BPh$_4$ isomerized the double bond in nonbranched alkyl group. Because the desired isomerization reaction was faster than the side isomerization reaction, the shorter isomerization time would cut the by-products down. However, very short time (5 min) would erode the conversion of the desired product. Therefore, after screening different conditions, the optimized result indicated that the reaction with 2 mol% catalyst and quenched in 10 min afforded the best result, only trace of by-products **10ba, 10bb** and starting material **9b** were afforded.

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[37] Shen, X. in Nelson group used the catalyst **18** to transform the terminal olefin to internal olefin in the total synthesis of (-)-Pironetin. See: Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 7438-7439.
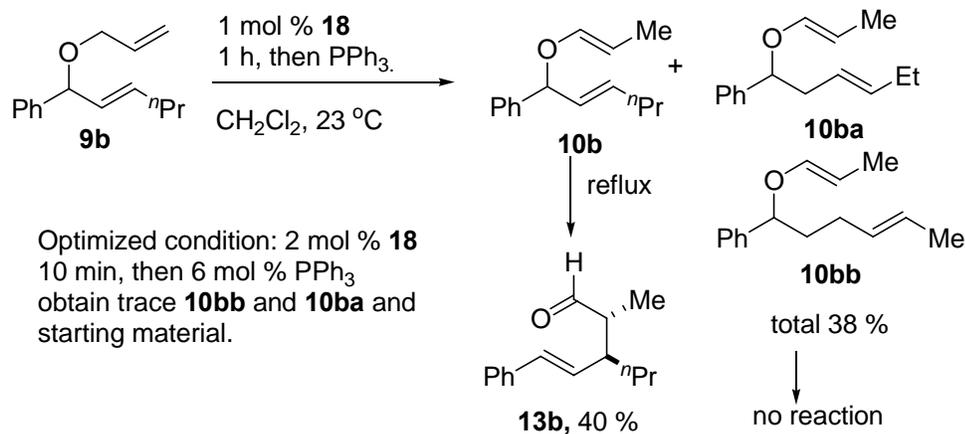
Scheme 16. ICR of di(allyl) ether 9b

2.2.3 Thermal Claisen rearrangement of different substrates

With a good isomerization procedure established to (*E*)-allyl vinyl ethers **10a-n**, we investigated the thermal Claisen rearrangement of substrates listed in Table 1 and found that the structure impacted the Claisen rearrangement rate. When R^{eq} group is ethyl, *n*-butyl or *tert*-butyl, reflux of the crude allyl vinyl ethers (entry **g-j, k-m**) in 1,2-DCE (83 ^{o}C) was recommended; when R^{eq} group is phenyl or TMSCH$_2$ and R^2 group is methyl, *n*-propyl, *iso*-propyl or TMS, reflux of the crude allyl vinyl ethers (entry **a-d**) in CH$_2$Cl$_2$ (39 ^{o}C) was good; when R^{eq} is phenyl or TMSCH$_2$ and R^2 is phenyl (entry **e,n**), stirring the allyl vinyl ethers **6e, n** at ambient temperature was sufficient. Because the phenyl and TMSCH$_2$ group stabilized the forming positive charge with conjugation or hyperconjugation, the adjacent C-O σ -bond was cleavge easily to favor the Claisen rearrangement under mild conditions (Figure 20).[38]

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[38] Wilson S. R.; Price, M. F. *J. Am. Chem. Soc,* **1982,** *104*, 1124.
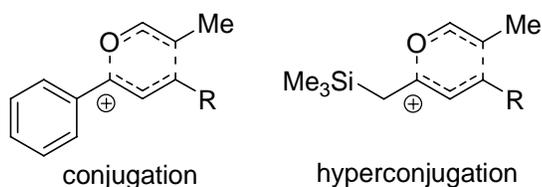
Figure 20. The Ph and TMSCH$_2$ activate the Claisen rearrangement

Claisen product α-chiral aldehyde (**13a-n**) was subjected to a significant epimerization of the α-stereocenter during the attempted general silica gel chromatographic purification because of the weak acidity of silica gel. Diastereomer ratios were determined for the crude aldehyde by intergrating the aldehyde **CHO** resonances in the ^{1}H NMR spectra. Then the aldehyde was directly reduced by DIBAL-H at -78 °C in CH$_2$Cl$_2$ to afford corresponding alcohol (**13a-n′**), the yields of ICR reactions were based on alcohol **13a-n′**. All these reactions exhibited high diastereoselection (*syn : anti* = 91 : 9 to 98 : 2) and moderate to high yields in three steps (Table 1). A neutral silica gel, Introbeads (pH = 7.0), was good enough to purify α-chiral aldehyde with little epimerization.

If the R^{eq} lies in the pseudoequatorial position in the chair-like transition state, only the (*E*)-isomer of the Claisen adduct forms. But some (Z)-isomers were observed in the ICR reaction of substrates **9g, h,** (Table 1) which had small alkyl R^{eq} and R^2 groups. These (Z)-isomers were formed *via* higher energy chair transition state with pesudoaxial R^{eq} group (Figure 21). [39]

[39] Nonoshita, K.; Maruoka, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 541.
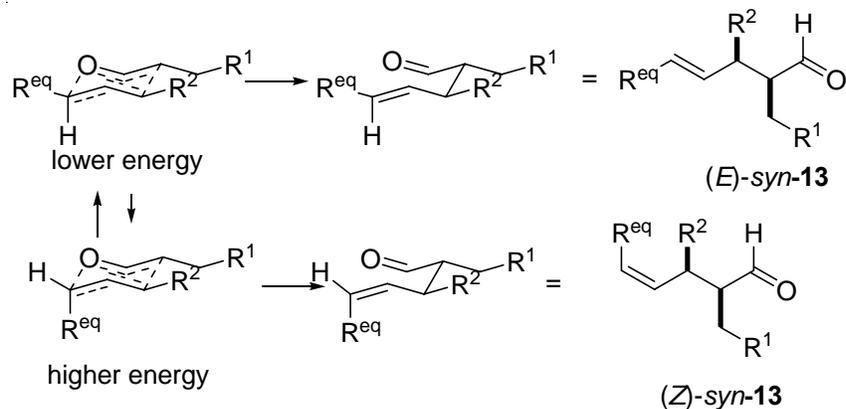
Figure 21. Formation of (*Z*)- and (*E*)-isomer of aldehydes

2.2.4 ICR of other di(allyl) ethers

Besides the good ICR result of substatres **9a-n**, some di(allyl) ethers with different structures were prepared for observing the ICR reactivity. The ICR of di(allyl) ether **9o,** which has two isomerization positions and the bulky TBDPS group as protection group of the hydroxyl, afforded no regioselective isomerization: the desired allyl vinyl ether **10o** and by-product **10o′** were observed as a 1:1 mixture from crude proton NMR spectra. After thermolysis and DIBAL-H reduction, 37 % yield of an alcohol **13o′** and 31 % by-product vinyl ether **10o′** were obtained (Scheme 17).
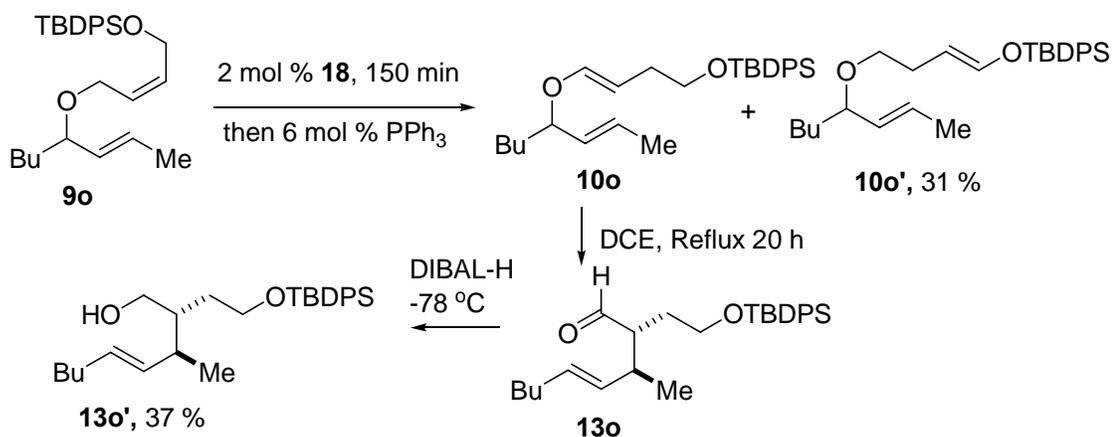
Scheme 17. Competing isomerization pathways of di(allyl) ether 9o

Treatment of a 3,3-disubstituted allyl ether (**9p**) under same conditions afforded no isomerization, even in microwave oven at 120 °C (eq 12). As a result, it is difficult to prepare Claisen adducts bearing α-*i*Pr or other branched alkyl groups with this simple ICR strategy.
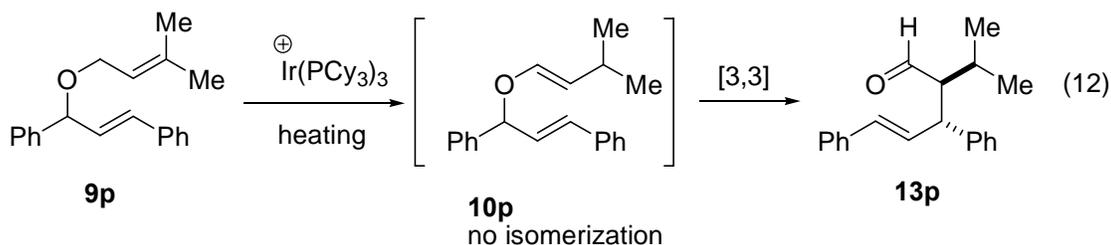
The more electron-donor alkyl substituents adjacent to the oxygen atom in the di(allyl) ethers stable the positive charge developed during the Claisen. As a result, the ICR reaction of the di(allyl) ether with quaternary carbinol center (**9q/r**) afforded trisubstituted enals (**13q/r**) with good diastereoselectivity and yields at relatively low temperatures (Scheme 18).

R	Product	Temp (°C)	yield,	*syn: anti*
Ph (**9q**)	**13q**	60	92	95: 5
Me (**9r**)	**13r**	83	81	91: 9
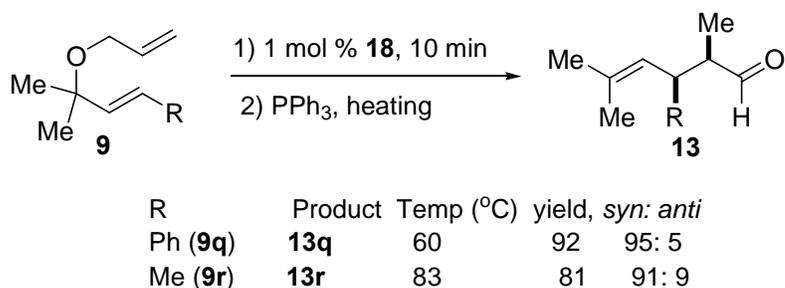
Scheme 18. ICR of di(allyl) ether with quaternary carbinol center

The ICR reaction of di(allyl) ethers (**19**) with conjugated dienes was interesting because it affords non-conjugated dienals. Substrates (**19a-d**) were treated under ICR conditions to afford Claisen products with good yields and diastereoselectivities (**20a-d**, Table 4). Diene groups activated the Claisen rearrangement at relatively low temperature. It is worthy of note that changing R and R^{eq} each other afforded a pair of diastereomers, such as, aldehydes **20a** and **20b**.

Table 4. ICR reactions of di(allyl) ethers with conjugated diene
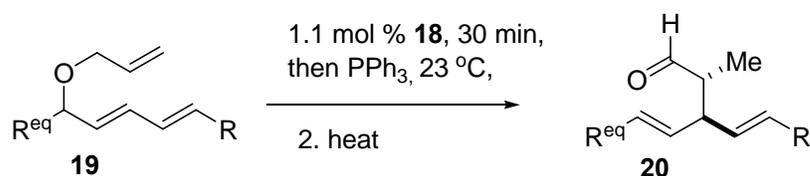
entry	R	R^{eq}	T (^{o}C)	*syn: anti*	% yield(alcohol)
a	H	Ph	23	97: 3	80
b	Ph	H	39	95: 5	70
c	H	Me, Me	39	95: 5	93
d	Ph	Et	39	95: 5	87

In conclusion, the ICR reaction of di(allyl) ethers (**9a-q** and **19a-d**) are described in this section, along with details for preparation of these substrates. The isomerization followed by the Claisen rearrangement of di(allyl) ethers affords Claisen adducts with high diastereoselection and moderate to high yields.

2.3   ICR REACTION OF ALLYL HOMOALLYL ETHERS

2.3.1 ICR reactions of allyl homoallyl ethers

Allyl-homoallyl ethers, which are easily prepared from an allyl metal (Sn, Mg, Zn) or non-metal (B, Si) reagent-aldehyde addition followed by *O*-allylation, are progenitors of allyl vinyl ethers after two isomerizations (Figure 22). The allyl-homoallyl ether 1-allyl-1-(allyloxy)cyclohexane (**21a**) was subjected to 2 mol% catalyst at ambient temperature and stirred overnight to afford 77 % of allyl vinyl ether (**22a**) and 23 % of by-product homoallyl vinyl ether (**22a′**). The result indicated that the isomerization of terminal homoallyl ether is slower than that of allyl ether. Then the thermolysis of this mixture afforded Claisen adduct (**23a**) in 64 % yield (Scheme 19).
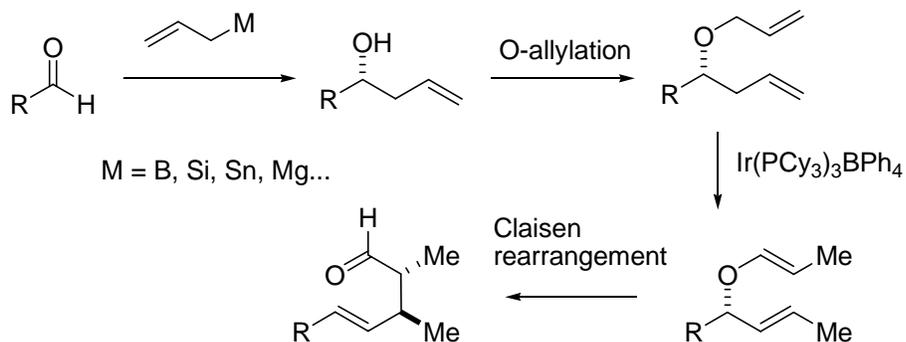
Figure 22. ICR of allyl homoallyl ether
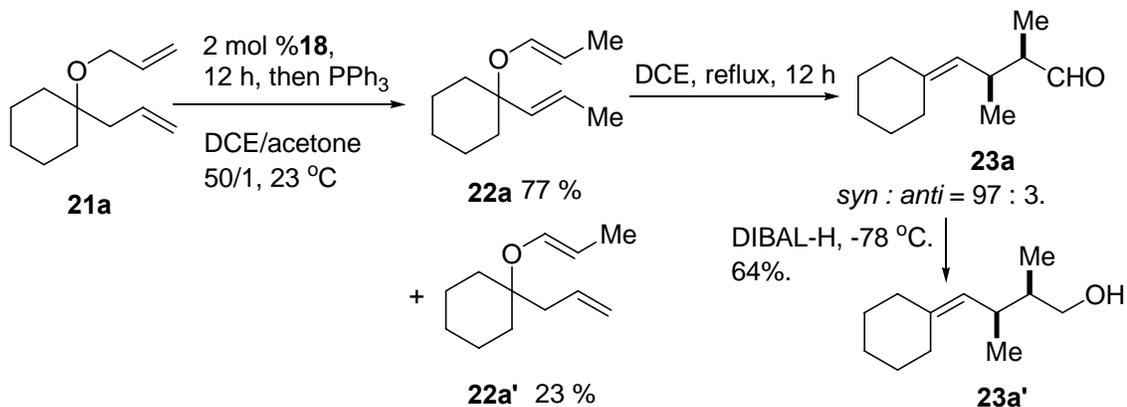
Scheme 19. ICR of quaternary allyl homoallyl ether

The ICR reaction of allyl homoallyl ethers (**21b/c**) afforded Claisen adducts (**23b/c**) with modest to good yields and good diastereoselectivity (Scheme 20). In these two reactions, no homoallyl vinyl ethers (**22b/c′**) were observed. The result indicated that the quaternary carbinol center in **21a** hindered the isomerization of the homoallyl ether. However, the ICR reaction of allyl homoallyl ethers afforded *syn*-2,3-dimethyl enals with convenience.

entry	R	yield, diastereomers
b	PhCH$_2$CH$_2$	70%, *syn : anti* : Z = 88 : 5: 7
c	TBDPSOCH$_2$	48%, *syn : anti* : Z = 92 : 4: 4
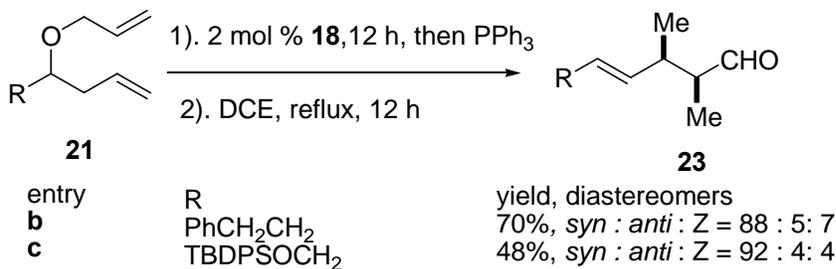
Scheme 20. ICR of allyl homoallyl ether 21b/c

2.3.2 Preparation of dienals with ICR protocol

The preparation of the 2,3-*syn*-disubstituted-4-enal with the ICR protocol from di(allyl) ether or allyl homoallyl ether was discussed in previous sections. Here we described a ICR methodology for preparing aldehydes containing a conjugated diene; then dieneophiles would be introduced into these dienals for a type I intramolecular Diels-Alder reaction (IMDA, Figure 23) to afford bicycle products.
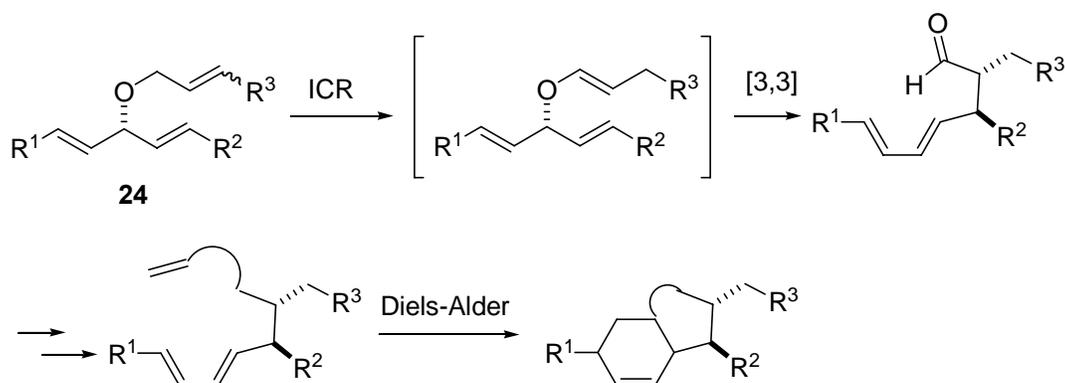
Figure 23. Design of conjugated diene from ICR following IMDA reaction

Based on the discussion in previous sections, the isomerization of terminal homoallyl ethers produces *E*-allyl ethers. So the easily prepared triene ether (*E*)-4-(allyloxy)hepta-1,5-diene (**25a**) was treated with 2 mol% catalyst **18** at ambient temperature to afford vinyl ether **26a,** which subsequently rearranged quickly to dienal **27a** with good yield and diastereoselectivity (*syn: anti* = 94: 6, Scheme 21) at ambient temperature.
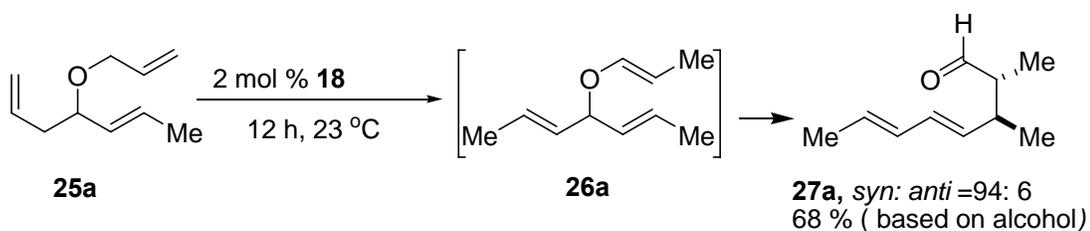
Scheme 21. ICR reaction of triene ether 25a

However, poor chemoselectivities were obtained in the ICR of similar substrates **25b** (Scheme 22) and **25c (**Scheme 23**)**. In these two reactions, two sides in triene ethers **26b/c** are different. In Scheme 22, the phenyl side is more favorable for rearrangement (to afford dienal **27ba**) than the methyl side (to afford dienal **27bb**); but in Scheme 23, due to the methyl substitution hindering the Claisen rearrangement, the phenyl side is less favorable (to afford dienal **27ca**) than the methyl side (to afford dienal **27cb**) for the Claisen rearrangement.
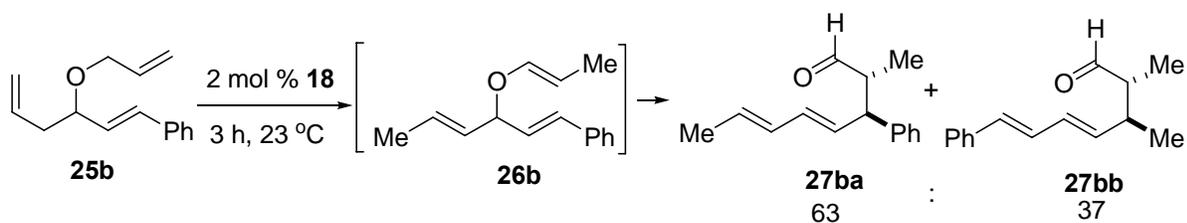
Scheme 22. ICR reaction of triene ether 25b
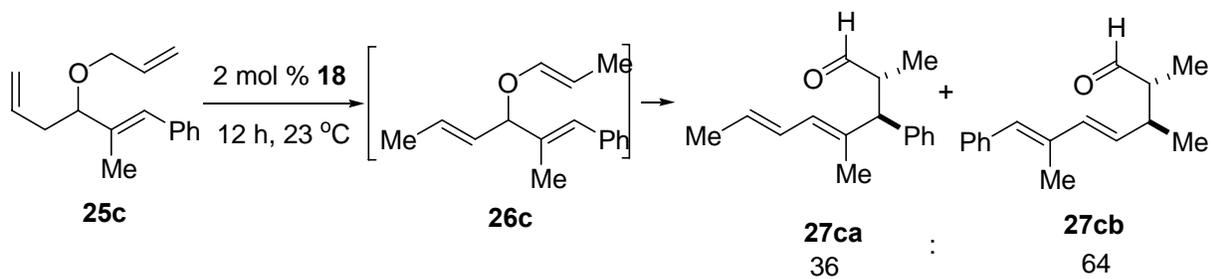
Scheme 23. ICR reaction of triene ether 25c

This double isomerization-Claisen rearrangement procedure caused some problems, such as the poor chemoselectivity in Scheme 22 and Scheme 23. For overcoming theses challenges, a new strategy, which was based on the fact that the isomerization of the homoallyl ether was much slower than that of the allyl ether, was designed. When the substrate **25b** was subjected to 2 mol% catalyst followed by quenching in 15 min, the stable allyl vinyl ether (**28b**) was obtained. After thermolysis, the Claisen adduct (**29b**) with a non-conjugated diene was obtained, which was subsequently isomerized to the conjugated dienal (**27ba**) with good diastereoselectivity after the second Ir(I)-catalyzed isomerization (Scheme 24).
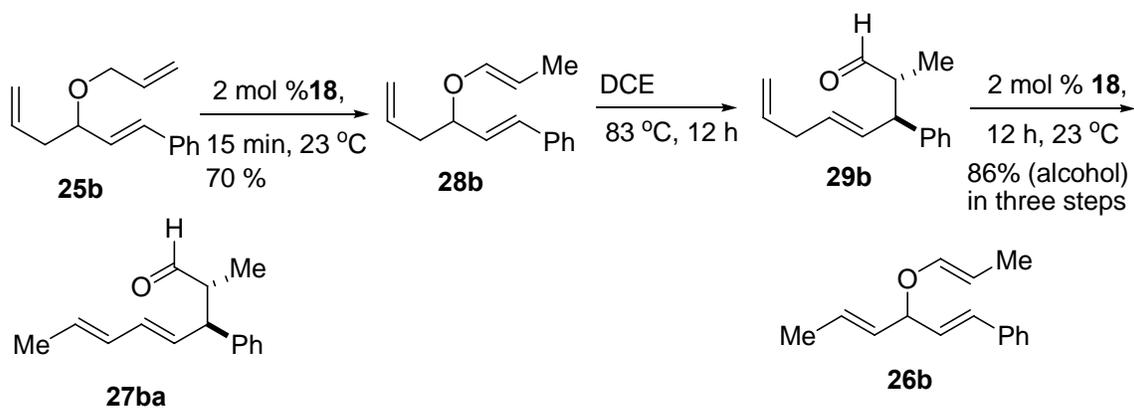
Scheme 24. Alternative route for preparing dienal

In this chapter, the iridium(I)-catalyzed olefin isomerization of di(allyl) ethers is integrated into a generally applicable strategy for affecting highly stereoselective Claisen rearrangements. Catalyzed alkene isomerization affords allyl vinyl ethers from easily prepared di(allyl) ethers; direct thermolysis of these reaction mixtures leads to highly diastereoselective [3,3] sigmatropic rearrangements affording *syn*-2,3-dialkyl-4-pentenal derivatives.

2.4   EXPERIMENTAL SECTION

General Information: Unless otherwise stated, all reactions were performed in dry glassware under an atmosphere of oxygen-free nitrogen using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous solvents were obtained by passage through successive alumina- and Q5 reagent-packed columns on a solvent purification system. Acetone was used as purchased. Sodium hydride (60 % dispersion in mineral oil) was washed with pentanes (3x) and dried under vacuum before use. Crotyl bromide, allyl bromide, and allyl

acetate were distilled form CaH_2. $[(^cC_8H_{14})_2IrCl]_2$ [40] and PCy_3 were stored and weighed out in a nitrogen filled glove box. Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. Proton and carbon NMR spectra were recorded on a Bruker DPX 301 and DPX 302 (300 MHz for proton) spectrometers with chemical shifts reported in relative to residual $CHCl_3$ (7.27 ppm) for ^1H and $CDCl_3$ (77 ppm) for ^{13}C NMR spectra. Low-resolution mass spectra were obtained on a Fiseons Autospec in EI mode at 70 V and are reported in *m/z*. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh) or Introbeads (PH = 7.0). Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using a Daicel Chiracel^{TM} OD-H column (250 x 4.6 mm) (Daicel Inc.). HPLC grade *iso*propanol and hexanes were used as the eluting solvents. Analytical gas liquid chromatography (GLC) was performed on a Varian 3900 gas chromatography with a flame ionization detector and split mode capillary injection system using Varian CP Wax 52CB column (30 m x 0.25 mm).

2.4.1 Experiment of section 2.2

Preparation of substituted di(allyl) ethers. **General Procedure A:** A solution of the alcohol (1.0 equiv.) in anhydrous THF (0.5 M) was added to a suspension of pre-washed NaH (2.0 equiv.) in anhydrous THF (1.0 M). The resulting suspension (0.25 M) was heated at reflux for 30 min whereupon allyl bromide or crotyl bromide (2.0 equiv.) was added and the resulting

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[40] Onderdelinden, A. L.; Ent der Ent A. *Inorg. Chim. Acta.***1972, 6,** 420.

suspension heated at reflux for a further 2 h. The reaction mixture was then cooled to ambient temperature and poured into ice. The THF was removed *in vacuo* and the aqueous residue was extracted with Et_2O (3x) and the combined organic extracts were dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue purified as indicated.

General Procedure B: A solution of the Et_2Zn (1.0 M in hexanes, 0.65 equiv.) was added to a solution of the allyl alcohol (1.0 equiv.) in anhydrous THF (1.8 M) at ambient temperature. The resulting solution was stirred for 30 min then added via syringe to a solution of $Pd(PPh_3)_4$ (5 mol%) and allyl acetate (1.5 equiv.) in anhydrous THF (0.09 M). The final concentration was 0.8 M. The reaction was stirred for 2 d at ambient temperature whereupon the solvent was removed *in vacuo,* and the residue purified as indicated.

General Procedure C: Five drops of concentrated H_2SO_4 were added to a solution of (*E*)-1,3-diphenyl-2-propen-1-ol (1.0 equiv.) and allyl alcohol or crotyl alcohol (1.1 equiv.) in anhydrous THF (1.0 M). The resulting solution was stirred for 1 h at ambient temperature whereupon H_2O (10 ml) was added and the resulting mixture was extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, The solvent was removed *in vacuo* and the residue purified as indicated.
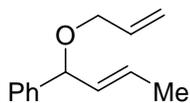
(*E*)-(1-Allyloxybut-2-enyl)benzene (9a): General Procedure **A** was followed employing 14.4 g of (*E*)-1-phenylbut-2-en-1-ol[41] (97.0 mmol), 4.7 g NaH (194.0 mmol) and 16.4 ml allyl bromide (194.0 mmol). Purification by vacuum distillation gave 16.6 g

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[41] Pocker, Y.; Hill, M. J. *J. Am. Chem. Soc.* **1969**, 91, 3243.

(91 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.16-7.27 (m, 5H), 5.80-5.93 (m, 1H), 5.49-5.68 (m, 2H), 5.20 (dd, J = 19, 1.6 Hz, 1H), 5.10 (dd, J = 10, 1.4, 1H), 4.68 (d, J = 6.7 Hz, 1H), 3.92 (ddt, J = 12.8, 5.5, 1.4 Hz, 1H), 3.86 (ddt, J = 12.8, 5.5, 1.4 Hz, 1H), 1.64 (d, J = 5.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.6, 134.9, 132.1, 128.3, 128.2, 127.3, 126.7, 116.6, 81.8, 68.9, 17.7 ppm; MS (EI, 70 V): *m/z* 187 (M$^{+\cdot}$-H), 147, 131, 115, 105, 91, 77, 69; HRMS *m/z* calcd for C$_{13}$H$_{16}$O (M$^{+\cdot}$): 188.1201; found: 188.1197.
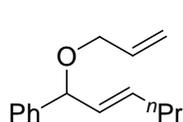
(E)-(1-Allyloxyhex-2-enyl)benzene (9b): General Procedure **A** was followed employing 5.54 g of (E)-1-phenylhex-2-en-1-ol[42] (31.0 mmol), 1.45 g NaH (62.0 mmol) and 5.3 ml allyl bromide (62.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes) gave 5.96 g (90 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.16-7.27 (m, 5H), 5.79-5.93 (m, 1H), 5.61 (dt, J= 15.4, 6.4 Hz, 1H), 5.48 (ddt, J= 15.4, 7.0, 0.9 Hz, 1H), 5.20 (dq, J = 17.2, 1.7 Hz, 1H), 5.09 (dq, J = 10.4, 1.4, 1H), 4.68 (d, J = 7.1 Hz, 1H), 3.92 (ddt, J = 12.8, 5.5, 1.4 Hz, 1H), 3.86 (ddt, J = 12.8, 5.5, 1.4 Hz, 1H), 1.95 (q, J = 6.8 Hz, 2H), 1.33 (hex, J = 7.4 Hz, 2H), 0.81 (t, J = 7.4 Hz, 3H), ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.7, 134.9, 133.3, 130.8, 128.2, 127.2, 126.6, 116.5, 81.7, 68.8, 34.2, 22.2, 13.6 ppm; MS (EI, 70 V): *m/z* 216 (M$^{+\cdot}$), 173, 159, 145, 129, 117, 105, 91, 84, 77, 71; HRMS *m/z* calcd for C$_{15}$H$_{20}$O (M$^{+\cdot}$): 216.1514; found: 216.1518.
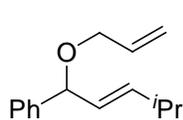
(E)-(1-Allyloxypent-4-methyl-2-enyl)benzene (9c): General Procedure **A** was followed employing 1.75 g of (E)-1-phenyl-4-methylpent-2-en-1-ol[43] (10.0 mmol), 480 mg NaH (20.0 mmol) and 1.7 ml allyl bromide (20.0 mmol). Purification by flash

[42] Wang, D.; Chen, D.; Haberman, J. X.; Li, C. *Tetrahedron* **1988**, 54, 5129-5142.
[43] Prepared in quantitative yield by addition of phenyllithium to 4-methyl-2-pentenal.

chromatography (2 % EtOAc/hexanes) gave 1.99 g (92 %) of the title compound as colorless oil. IR (liquid film): 2961, 1724, 1451, 1267, 1069, 973, 924, 739, 700 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.16-7.26 (m, 5H), 5.79-5.92 (m, 1H), 5.59 (dd, J = 15.5, 6.3 Hz, 1H), 5.45 (ddd, J = 15.5, 7.2, 1.0 Hz, 1H), 5.20 (dq, J = 17.2, 1.7 Hz, 1H), 5.09 (dq, J = 10.4, 1.5 Hz, 1H), 4.67 (d, J = 7.2 Hz, 1H), 3.90 (ddt, J = 12.8, 5.5, 1.5 Hz, 1H), 3.84 (ddt, J = 12.8, 5.5, 1.5 Hz, 1H), 2.18-2.25 (m, 1H), 0.91 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.8, 140.6, 135.0, 128.3, 127.7, 126.7, 116.7, 81.9, 68.9, 30.7, 22.2 (overlap of 2C) ppm; IR(liquid film) v_{max}: 2961, 1724, 1451, 1267, 1069, 973, 924, 739, 700 cm^{-1}; (MS (EI, 70 V): m/z 216 (M$^{+\cdot}$), 173, 159, 143, 131, 117, 105, 97, 91, 77; HRMS m/z calcd for C$_{15}$H$_{20}$O (M$^{+\cdot}$): 216.1514; found: 216.1507.
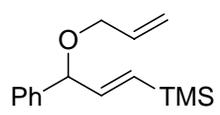
((E)-3-(Allyloxy)-3-phenylprop-1-enyl)trimethylsilane (9d): General Procedure **B** was followed employing 2.06 g of (E)-3-(trimethylsilyl)-1-phenylprop-2-en-1-ol[44] (10.0 mmol), 6.5 ml Et$_2$Zn (1.0 M in hexanes), 578 mg Pd(PPh$_3$)$_4$ (0.5 mmol) and 1.6 ml allyl acetate (15.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes) gave 1.97 g (80 %) of the title compound as colorless oil. IR (liquid film): 2955, 1617, 1452, 1248, 1070, 990, 838, 699 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.34-7.43 (m, 5H), 6.23 (dd, J = 18.6, 5.7 Hz, 1H), 6.03 (ddt, J = 17.1, 10.4, 5.4 Hz, 1H), 5.37 (d, J = 17.1, Hz, 1H), 5.26 (d, J = 10.4 Hz, 1H), 4.90 (d, J = 5.7 Hz, 1H), 4.06 (d, J = 5.4 Hz, 2H), 0.16 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 145.7, 140.8, 134.7, 131.4, 128.3, 127.4, 126.9, 116.8, 83.7, 69.1, -1.4 ppm; MS (EI, 70 V) m/z: 245 (M$^{+\cdot}$-H), 205, 189, 159, 147, 131, 115, 105. HRMS m/z calcd for C$_{15}$H$_{21}$OSi (M$^{+\cdot}$-H): 245.1362; found 245.1371.

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[44] Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* **1988**, 44, 4073.
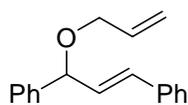
(*E*)-3-Allyloxy-1,3-diphenylpropene (9e): General Procedure **C** was followed employing 3.67 g of (*E*)-1,3-diphenyl-2-propen-1-ol[45] (17.5 mmol), 1.4 ml allyllic alcohol (20.3 mmol) and five drops of concentrated sulfuric acid. Purification by flash chromatography (5 % EtOAc/hexanes) gave 3.65 g (84 %) of the title compound as colorless oil. IR (liquid film): 3060, 3027, 2857, 1950, 1879, 1647, 1500, 1494, 1450, 1301, 1069, 967, 923, 746, 698 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20-7.41 (m, 10H), 6.61 (d, J = 15.9 Hz, 1H), 6.30 (dd, J = 15.9, 7.0 Hz, 1H), 5.97 (ddt, J = 17.1, 10.4, 5.5 Hz, 1H), 5.31 (dq, J = 17.2, 1.6 Hz, 1H), 5.20 (dq, J = 10.5, 1.3, 1H), 4.97 (d, J = 7.0 Hz, 1H), 4.06 (ddt, J = 12.8, 5.4, 1.3 Hz, 1H), 4.00 (ddt, J = 12.8, 5.6, 1.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.0, 136.4, 134.7, 131.2, 130.1, 128.3, 127.5, 126.7, 126.4, 116.7, 81.5, 69.0 ppm; MS (EI, 70 V): *m/z* 250 (M$^{+\cdot}$), 220, 207, 193, 181, 165, 145, 131, 115, 105, 91, 77, 65; HRMS *m/z* calcd for C$_{18}$H$_{18}$O (M$^{+\cdot}$): 250.1358; found: 250.1368.
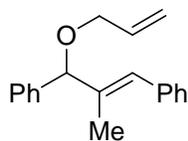
(*E*)-3-(Allyloxy)-2-methyl-1,3-diphenylprop-1-ene (9f) : General Procedure **C** was followed employing 3.15 g of (*E*)-2-methyl-1,3-diphenylprop-2-en-1-ol[46] (14.0 mmol), 1.1 ml allyllic alcohol (15.4 mmol) and five drops of concentrated sulfuric acid. Purification by flash chromatography (5 % EtOAc/hexanes) gave 3.05 g (82 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.11-7.37 (m, 10H), 6.62 (s, 1H), 5.97 (ddt, J = 17.1, 10.6, 5.4 Hz, 1H), 5.27 (dq, J = 17.2, 1.7 Hz, 1H), 5.13 (dq, J = 10.4, 1.5, 1H), 4.83 (s, 1H), 4.02 (ddt, J = 13.0, 5.2, 1.5 Hz, 1H), 3.93 (ddt, J = 13.0, 5.6, 1.5 Hz, 1H), 1.64 (d, J = 1.3 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 140.8, 138.0, 137.5, 134.9, 129.1, 128.2,

[45] Huang, W. –S.; Hu, Q. –S.; Pu, L. *J. Org. Chem.* **1999,** 64, 7940.
[46] Nudelman, N. S.; Garcia, G. V. *J. Org. Chem.* **2001,** 66, 1387.

128.1, 127.7, 126.6, 126.5, 116.6, 86.1, 69.2, 13.5 ppm. MS (EI, 70 V): *m/z* 264 (M[+·]), 249, 234, 223, 206, 191, 178, 158, 129, 105, 91, 77. HRMS *m/z* calcd for $C_{19}H_{20}O$ (M[+·]): 264.1514; found: 264.1525.
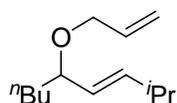
(E)-5-Allyloxy-2-methyl-non-3-ene (9g): General Procedure **A** was followed employing 4.68 g of (*E*)-2-methyl-non-3-en-5-ol[47] (30.0 mmol), 1.44 g NaH (60.0 mmol) and 5.1 ml allyl bromide (60.0 mmol).. Purification by flash chromatography (2 % EtOAc/hexanes) gave 5.09 g (87 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl₃): δ 5.90 (dddd, J = 17.2, 10.3, 6.0, 5.2 Hz, 1H), 5.55 (dd, J = 15.5, 6.5 Hz, 1H), 5.23 (dq, J = 17.2, 1.7 Hz, 1H), 5.21 (ddd, J = 15.5, 8.3, 1.3 Hz, 1H), 5.13 (dq, J = 10.3, 1.5 Hz, 1H), 4.02 (ddt, J = 12.8, 5.1, 1.5 Hz, 1H), 3.79 (ddt, J = 12.8, 6.0, 1.3 Hz, 1H), 3.61 (dt, J = 8.1, 6.6 Hz, 1H), 2.30 (m, 1H), 1.28-1.60 (m, 6H), 1.00 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl₃): δ 141.0, 135.5, 127.7, 116.3, 80.4, 68.6, 35.5, 30.8, 27.7, 22.6, 22.4 (overlap of 2C), 14.0 ppm; MS (EI, 70 V): *m/z* 195 (M[+·]-H), 179, 139, 97, 81, 69, 55; HRMS *m/z* calcd for $C_{13}H_{23}O$ (M[+·]-H): 195.1749; found: 195.1746.
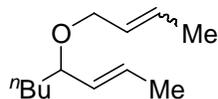
(E)-4-But-2-enyloxyoct-2-ene (9h): General Procedure **A** was followed employing 3.84 g of (*E*)-oct-2-en-4-ol[48] (30.0 mmol), 1.44 g NaH (60.0 mmol) and 6.2 ml crotyl bromide (60.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes) gave 4.63 g (85 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl₃): δ 5.50-5.71 (m, 3H), 5.27 (ddq, J = 15.3, 8.1, 1.6 Hz, 1H), 3.92 (dd, J = 11.7, 5.7 Hz, 1H), 3.68 (dd, J = 11.5, 6.4 Hz, 1H), 3.58 (q, J = 7.0 Hz, 1H), 1.66-1.69 (m, 6H), 1.48-1.63 (m,

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[47] Prepared in quantitative yield by addition of *n*-butyllithium to 4-methyl-2-pentenal.
[48] Chamberlin, A, R.; Mulholland, R. L. Jr. *Tetrahedron* **1984**, *40*, 2297-2302.

2H), 1.22-1.29 (m, 4H), 0.86 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 132.3, 128.6, 128.1, 128.0, 80.0, 68.4, 35.3, 27.6, 22.6, 17.6, 17.5, 13.9 ppm; MS (EI, 70 V): m/z 125 (M$^{+\cdot}$-^{n}Bu), 111, 97, 85, 81, 71, 69, 55; HRMS m/z calcd for C$_{12}$H$_{22}$O (M$^{+\cdot}$-^{n}Bu): 125.0966; found: 125.0970.
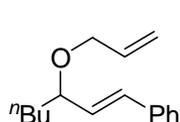
(E)-(3-Allyloxyhept-1-enyl)benzene (9i): General Procedure **A** was followed employing 5.13 g of (E)-1-phenylhept-1-en-3-ol[49] (27.0 mmol), 1.30 g NaH (54.0 mmol) and 4.6 ml allyl bromide (54.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes) gave 5.41 g (87 %) of the title compound as colorless oil. IR (liquid film): 2957, 2860, 1727, 1454, 1266, 1071, 969, 920, 739, 699 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.27-7.45 (m, 5H), 6.54 (d, J = 16.0 Hz, 1H), 6.11 (dd, J = 16.0, 8.0 Hz, 1H), 5.90-6.04 (m, 1H), 5.31 (dq, J = 17.2, 1.6 Hz, 1H), 5.20 (dm, J = 17.2 Hz, 1H), 4.13 (ddt, J = 12.8, 5.2, 1.5 Hz, 1H), 3.74-3.84 (m, 2H), 1.36-1.82 (m, 6H), 0.94 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.6, 135.2, 131.9, 130.7, 128.5, 127.5, 126.4, 116.5, 80.2, 69.1, 35.5, 27.6, 22.6, 14.0 ppm; MS (EI, 70 V): m/z 230 (M$^{+\cdot}$), 189, 173, 145, 131, 117, 105, 91; HRMS m/z calcd for C$_{16}$H$_{22}$O (M$^{+\cdot}$): 230.1671, found: 230.1670.
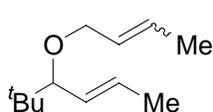
(2E)-4-(But-2-enyloxy)-5,5-dimethylhex-2-ene (9j): General Procedure **A** was followed employing 1.28 g of (E)-2,2-dimethylhex-4-en-3-ol[50] (10.0 mmol), 480 mg NaH (20.0 mmol) and 1.7 ml crotyl bromide (20.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes) gave 1.66 g (91 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.49-5.73 (m, 3H), 5.34 (dd, J = 15.3, 8.4 Hz, 1H), 3.83-4.06 (m,

[49] Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.*, **1993**, *115*, 2027.
[50] Chamberlin, A. R.; Mulholland, R. L. *Tetrahedron Lett.*, **1984**, *25*, 2297.

1H), 3.67 (dd, J = 12.2, 6.2 Hz, 1H), 3.19 (d, J = 8.4 Hz, 1H), 1.63-1.76 (m, 6H), 0.88 (s, 9H)

ppm; ^{13}C NMR[51] (75 MHz, CDCl$_3$): δ ppm; MS (EI, 70 V): m/z 182 (M$^+$), 125, 111, 95, 71, 55;

HRMS m/z calcd for C$_{12}$H$_{22}$O (M$^{+\cdot}$): 182.1671; found: 182.1670. m/z calcd for C$_8$H$_{13}$O (M$^{+\cdot}$-

^{t}Bu): 125.0966; found: 125.0967.
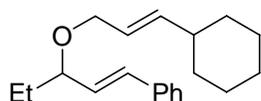
1-((S,1E)-3-((E)-3-Cyclohexylallyloxy)pent-1-enyl)benzene **(9k)**:

General procedure **A** was followed employing 1-phenyl-pent-1-en-3-ol

(162 mg, 1.0 mmol) and ((E)-3-bromoprop-1-enyl)cyclohexane [52] (306 mg, 1.5 mmol).

Purification by flash chromatograph on silical gel (2 % EtOAc in hexanes) to yield 210 mg (74

%) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.26-7.43 (m, 5H), 6.53

(d, J = 16.0 Hz, 1H), 6.09 (d, J = 16.0, 7.9 Hz, 1H), 5.66 (dd, J = 15.5, 6.2 Hz, 1H), 5.53 (dt, J =

15.5, 5.6 Hz, 1H), 4.06 (dd, J = 11.7, 5.5 Hz, 1H), 3.85 (dd, J = 11.7, 6.3 Hz, 1H), 3.80 (q, J =

7.4 Hz, 1H), 1.94-2.01 (m, 1H), 1.54-1.80 (m, 6H), 1.01-1.34 (m, 6H), 0.96 (t, J = 7.4 Hz, 3H)

ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 140.03, 136.75, 132.03, 130.72, 128.52, 127.53, 126.40,

124.02, 81.34, 69.33, 40.33, 32.73, 32,69, 28.61, 26.15, 26.00, 9.92 ppm; MS (EI, 70 V): m/z 284

(M$^{+\cdot}$), 255, 212, 162, 145, 133, 117, 104, 91, 81, 67, 57; HRMS m/z calcd for C$_{20}$H$_{28}$O (M$^{+\cdot}$):

284.2140; found 284.2136.
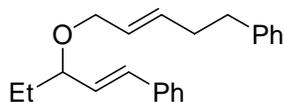
1-((3E)-5-((E)-1-Phenylpent-1-en-3-yloxy)pent-3-enyl)benzene **(9l)**:

General Procedure **A** was followed employing (E)-1-phenylpent-1-en-3-

[51] Due to a mixture of E/Z isomers, ^{13}C NMR had not been assigned clearly.
[52] Adam, J. M.; Fays, L. D.; Laguerre, M.; Ghosez, L.; *Tetrahedron* **2004**, *60*, 7325-7344.

ol (288 mg, 2.0 mmol) and a mixture of (*E*)-(5-bromopent-3-enyl) benzene and (3-bromopent-4-enyl)benzene[53] (about 4: 1, 672 mg, 3.0 mmol). Purification by flash chromatograph on silical gel (2.5 % ethyl acetate in hexanes) afford 428 mg (70 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.19-7.43 (m, 10H), 6.51 (d, J = 16.0 Hz, 1H), 6.08 (d, J = 16.0, 7.9 Hz, 1H), 5.75 (dt, J = 15.4, 6.2 Hz, 1H), 6.63 (dt, J = 15.4, 6.1 Hz, 1H), 4.06 (dd, J = 11.8, 5.4 Hz, 1H), 3.85 (dd, J = 11.8, 6.3 Hz, 1H), 3.77 (q, J = 7.0, 1H), 2.74 (t, J = 7.8 Hz, 2H), 2.40 (q, J = 7.2 Hz, 1H), 1.54-1.82 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.77, 136.68, 133.20, 132.09, 130.58, 128.53, 128.37, 128.26, 127.56, 127.30, 126.39, 125.77, 81.33, 68.88, 35.45, 34.06, 28.60, 9.88 ppm; MS (EI, 70 V): *m/z* 306 (M$^{+\cdot}$), 288, 277, 248, 234, 161, 144, 129, 115, 91; HRMS *m/z* calcd for C$_{22}$H$_{26}$O (M$^{+\cdot}$): 306.1984; found 306.1981.
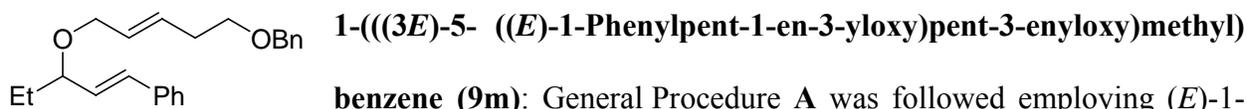
1-(((3E)-5- ((E)-1-Phenylpent-1-en-3-yloxy)pent-3-enyloxy)methyl) benzene (9m): General Procedure **A** was followed employing (*E*)-1-phenylpent-1-en-3-ol (288 mg, 2.0 mmol) and (*E*)-((5-bromopent-3-enyloxy)methyl)benzene[54] (765 mg, 3.0 mmol). Purification by flash chromatograph on silical gel (2.5 % ethyl acetate in hexanes) afford 544 mg (81 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.28-7.46 (m, 10H), 6.56 (d, J = 16.0 Hz, 1H), 6.11 (dd, J = 16.0, 7.9 Hz, 1H), 5.67-5.83 (m, 2H), 4.56 (s, 2H), 4.10 (dd, J = 11.0, 5.3 Hz, 1H), 3.90 (dd, J = 11.0, 5.8 Hz, 1H), 3.83 (q, J = 7.1 Hz, 1H), 3.57 (t, J = 6.8 Hz, 2H), 2.44 (q, J = 6.8 Hz, 2H), 1.62-1.83 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 138.32, 136.60, 132.05, 130.49, 130.10,

[53] Bandini, M.; Cozzi, P. G.; Licciulli, S.; Umani-Ronchi, A. *Synthesis* **2004**, 409-414.
[54] Tonn, C. E.; Palazon, J. M.; Ruiz-perez, C.; Rodriguez, M. L.; Martin, V. S. *Tetrahedron Lett*. **1988**, *29*, 3149-3152.

128.62, 128.46, 128.25, 127.54, 127.50, 127.44, 126.34, 81.42, 72.78, 69.58, 68.81, 32.71, 28.55, 9.83 ppm; MS (EI, 70 V): m/z 336 (M$^{+\cdot}$), 307, 264, 245, 223, 187, 175, 161, 145, 131, 117, 104, 92; HRMS m/z calcd for $C_{23}H_{28}O_2$ (M$^{+\cdot}$): 336.2089; found 336.2086.
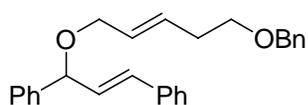
((E)-3-   ((E)-5-(Benzyloxy)pent-2-enyloxy)prop-1-ene-1,3-diyl)dibenzene (9n): General Procedure **C** was followed employing (E)-1,3-diphenylprop-2-en-1-ol (420 mg, 2.0 mmol) and (E)-5-(benzyloxy)pent-2-en-1-ol (384 mg, 2.0 mmol). Purification by flash chromatograph on silical gel (2.5 % EtOAc in hexanes) afford 691mg (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.27-7.49 (m, 15H), 6.67 (d, J = 15.9 Hz, 1H), 6.37 (dd, J = 15.9, 7.1 Hz, 1H), 5.72-5.87 (m, 2H), 5.04 (d, J = 7.1 Hz, 1H), 4.58 (s, 2H), 4.09 (dd, J = 12.6, 5.0 Hz, 1H), 4.04 (dd, J = 12.6, 3.7 Hz, 1H), 3.59 (t, J = 6.8 Hz, 2H), 2.47 (td, J = 6.8, 4.9 Hz, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.14, 138.32, 136.51, 131.29, 130.61, 130.28, 128.44, 128.31, 127.59, 127.50, 126.88, 126.51, 81.47, 72.83, 69.57, 68.86, 32.76 ppm; MS (EI, 70 V): m/z 384 (M$^{+\cdot}$), 368, 277, 293, 178, 115; HRMS m/z calcd for $C_{27}H_{30}O_2$ (M$^{+\cdot}$): 384.2089. found 384.2089.

ICR reactions of substituted di(allyl) ethers.

General Procedure D for ICR reactions: A solution of [(^{c}C$_8$H$_{14}$)$_2$IrCl]$_2$ (Ir dimmer, 0.5 mol%, 0.01 equiv Ir, or indicated amount) and PCy$_3$ (0.03 equiv, or 3 equiv per Ir) in anhydrous CH$_2$Cl$_2$ or 1,2-dichloroethane (1,2-DCE) (1.5 ml) was added to a solution of NaBPh$_4$ (0.01 equiv, or 1 equiv per Ir) in CH$_2$Cl$_2$/acetone (25:1) or 1,2-DCE/acetone (25:1) (1.5 ml, 0.67 M final concentration in substrate **1**) and the resulting yellow solution stirred for 5 min at ambient temperature. The di(allyl) ether (1.0 equiv) was added and the reaction stirred for 30 min (or

indicated time) at ambient temperature whereupon PPh$_3$ (0.03 equiv, or 3 equiv per Ir) was added and the resulting solution heated at reflux (39 $^{\circ}$C or 80 $^{\circ}$C) for the indicated time. The solvent was removed *in vacuo* and the diastereomer ratio of the aldehyde product **3** was determined by integration of the aldehyde proton resonances (-C**H**O) in the ^{1}H NMR spectrum of the crude product mixture. The crude product mixture was dissolved in anhydrous CH$_2$Cl$_2$ and cooled to – 78 $^{\circ}$C and 1 M hexanes solution of Diisobutylaluminum hydride (3.0 equiv) was added dropwise via syringe and the resulting solution was stirred for 5 min at –78 $^{\circ}$C. The reaction mixture was warmed to ambient temperature and poured into 10 ml saturated Rochelle's salt solution in water and Et$_2$O (10 ml) was added and stirred until homogeneous, the solution was extracted with Et$_2$O (3x). The combined organic extracts were dried over anhydrous MgSO$_4$ and the solvent removed *in vacuo*. The resulting residue was purified by flash chromatography on silica gel using the solvents indicated.
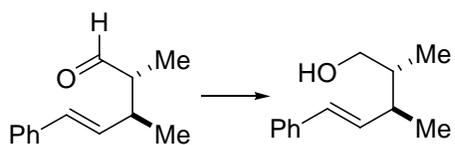
(*E*)-*syn*-2,3-Dimethyl-5-phenylpent-4-en-1-ol (13a′): General Procedure **D** (CH$_2$Cl$_2$) was followed employing 515 mg ether **9a** (2.74 mmol), 12.3 mg Ir dimer **(**0.014 mmol), 23.0 mg PCy$_3$ (0.082 mmol), 9.6 mg NaBPh$_4$ (0.028 mmol), quenched with 21.5 mg PPh$_3$ (0.082 mmol) and refluxed 6 h to afford (*E*)-*syn*-2,3-dimethyl-5-phenylpent-4-en-1-al (**13a**) (*syn: anti* = 94: 6). 5.5 ml Diisobutylaluminum hydride (1.0 M in hexanes, 5.5 mmol) reduction of **13a** followed by purification by flash chromatography (25 % EtOAc/hexanes) gave 415 mg (80 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20-7.40 (m, 5H), 6.41 (d, J = 16 Hz, 1H), 6.18 (dd, J = 16, 8.1 Hz, 1H), 3.67 (dd, J = 11, 5.7 Hz, 1H), 3.52 (dd, J = 11, 6.4 Hz, 1H), 2.39 (m, 1H), 1.72 (m, 1H), 1.10 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H)

ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 137.6, 135.3, 128.8, 128.4, 126.9, 125.9, 66.5, 40.8, 39.1, 16.6, 13.7 ppm; MS (EI, 70 V): *m/z* 190 (M$^{+\cdot}$), 131, 91; HRMS *m/z* calcd for C$_{13}$H$_{18}$O (M$^{+\cdot}$): 190.1358, found: 190.1363.
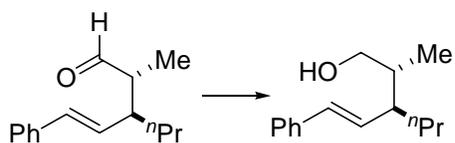
(E)-*syn*-2-   Methyl-3-*n*-propyl-5-phenylpent-4-en-1-ol (13b′): General Procedure **D** (2 mol% catalyst loading, CH$_2$Cl$_2$) was followed employing 216 mg of **9b** (1.00 mmol), 4.5 mg Ir dimer **(0.005 mmol)**, 8.4 mg PCy$_3$ (0.03 mmol), 3.4 mg NaBPh$_4$ (0.01 mmol) and an initial reaction time of 10 min (instead of 30 min) , quenched with 7.9 mg PPh$_3$ (0.03 mmol) prior to heating the reaction at reflux for 12 h to afford (E)-*syn*-2-methyl-3-^{n}propyl-5-phenylpent-4-en-1-al (**13b**) (*syn : anti* = 97 : 3). Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **13b** followed by purification by flash chromatography (20 % EtOAc/hexanes) gave 152 mg (70 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20-7.39 (m, 5H), 6.38 (d, J = 15.8 Hz, 1H), 6.04 (dd, J = 15.8, 9.5 Hz, 1H), 3.67 (dd, J = 10.7, 5.1 Hz, 1H), 3.46 (dd, J = 10.7, 6.8 Hz, 1H), 2.09-2.19 (m, 1H), 1.93 (s, 1H), 1.52-1.75 (m, 1H), 1.25-1.39 (m, 4H), 1.01 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 137.5, 133.5, 130.4, 128.4, 126.8, 125.9, 66.2, 45.9, 40.1, 33.8, 20.6, 14.7, 14.1 ppm; MS (EI, 70 V): *m/z* 218 (M$^{+\cdot}$), 159, 143, 129, 117, 104, 91; HRMS *m/z* calcd for C$_{15}$H$_{22}$O (M$^{+\cdot}$): 218.1671, found: 218.1670.
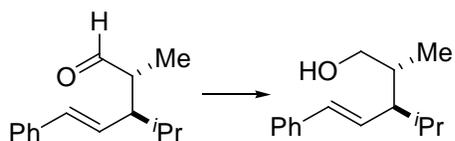
(E)-*syn*-   2-Methyl-3-*iso*-propyl-5-phenylpent-4-en-1-ol (13c′): General Procedure **D** (CH$_2$Cl$_2$) was followed employing 216 mg of **9c** (1.00 mmol), 4.5 mg Ir dimer **(0.005 mmol)**, 8.4 mg PCy$_3$ (0.03 mmol),

3.4 mg NaBPh$_4$ (0.01 mmol), quenched with 7.9 mg PPh$_3$ (0.03 mmol) and reflux 12 h to afford

(*E*)-*syn*-2-methyl-3-*iso*-propyl-5-phenylpent-4-en-1-al **13c** (*syn : anti* = 95 : 5). ^{1}H NMR (300

MHz, CDCl$_3$): δ 9.75 (d, J = 2.8 Hz, 1H), 6.47 (d, J = 15.8 Hz, 1H), 6.13 (dd, J = 15.8, 9.9 Hz,

1H), 2.69 (dqd, J = 6.9, 6.9, 2.8 Hz, 1H), 2.25 (dt, J = 9.9, 6.9 Hz, 1H), 1.99-2.05 (m, 1H), 1.18

(d, J = 6.9 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H) ppm. Diisobutylaluminum

hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **13c** followed by purification by flash

chromatography (20 % EtOAc/hexanes) gave 201 mg (93 %) of the title compound as colorless

oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.22-7.47 (m, 5H), 6.38 (d, J = 15.8 Hz, 1H), 6.06 (dd, J =

15.7, 9.4 Hz, 1H), 3.71 (dd, J = 10.7, 3.3 Hz, 1H), 3.46 (dd, J = 10.7, 6.1 Hz, 1H), 1.86-2.08 (m,

3H), 1.78 (m, 1H), 1.06 (d, J = 6.8 Hz, 3H), 0.96 (d, J= 6.7 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H)

ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 137.5, 132.0, 128.4, 126.9, 126.0, 66.6, 52.7, 37.0, 28.2,

21.9, 17.4, 15.6 ppm; IR (liquid film): 3355, 2959, 1494, 1385, 1030, 974, 747, 693 cm^{-1}. MS

(EI, 70 V): *m/z* 218 (M$^{+\cdot}$), 175, 157, 129, 117, 104, 91; HRMS *m/z* calcd for C$_{15}$H$_{22}$O (M$^{+\cdot}$):

218.1671, found: 218.1673.
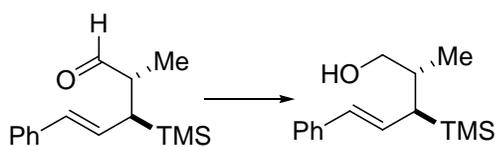
(*E*)-*syn*- 2-Methyl-3-(trimethylsilyl)-5-phenylpent-4-en-1-ol (13d′): General Procedure **D** (CH$_2$Cl$_2$) was followed employing 246 mg of **9d** (1.00 mmol), 4.5 mg

Ir dimer **(**0.005 mmol), 8.4 mg PCy$_3$ (0.03 mmol), 3.4 mg NaBPh$_4$ (0.01 mmol), quenched with

7.9 mg PPh$_3$ (0.03 mmol) and reflux 32 h to afford (*E*)-*syn*-2-methyl-3-(trimethylsilyl)-5-

phenylpent-4-en-1-al **13d** (*syn : anti* = 97 : 3). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.76 (d, J = 1.6

Hz, 1H), 7,46-7.22 (m, 5H), 6.39 (d, J = 15.7 Hz, 1H), 6.22 (dd, J = 15.7, 10.2 Hz, 1H), 2.77

(qdd, J = 7.0, 7.0, 1.8 Hz, 1H), 2.12 (dd, J = 10.2, 6.9 Hz, 1H), 1.27 (d, J = 7.0 Hz, 3H), 0.21 (s,

9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.6, 137.4, 129.7, 128.8, 128.3, 126.6, 125.6, 47.0, 36.5, 14.2, -1.7 ppm. Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **13d** followed by purification by flash chromatography (20 % EtOAc/hexanes) gave 215 mg (87 %) of the title compound as colorless oil. IR (liquid film): 3367, 2954, 1635, 1598, 1496, 1447, 1248, 1028, 967, 835, 744, 692 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.18-7.38 (m, 5H), 6.30 (d, J = 15.7 Hz, 1H), 6.16 (dd, J = 15.7, 10.6 Hz, 1H), 3.72 (dd, J = 10.6, 4.2 Hz, 1H), 3.51 (dd, J = 10.6, 7.0 Hz, 1H), 1.95-2.07 (m, 1H), 1.79 (s, 1H), 1.74 (dd, J = 10.6, 8.0 Hz, 1H), 1.11 (d, J = 6.8 Hz, 3H), 0.12 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 138.0, 131.1, 128.7, 126.4, 125.6, 67.6, 38.6, 36.8, 8.0, -1.3 ppm; MS (EI, 70 V) *m/z*: 248 (M$^{+\cdot}$), 233, 205, 194, 173, 158, 143, 129, 91, 73. HRMS *m/z* Calcd for C$_{15}$H$_{24}$OSi (M$^{+\cdot}$): 248.1596; found 248.1591.
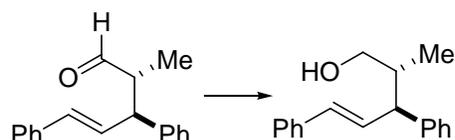
(E)-syn- **2-Methyl-3-phenyl-5-phenylpent-4-en-1-ol (13e′):** General Procedure **D** (CH$_2$Cl$_2$) was followed employing 500 mg of **9e** (2.00 mmol), 9.0 mg Ir dimer (0.01 mmol), 16.8 mg PCy$_3$ (0.06 mmol), 6.8 mg NaBPh$_4$ (0.02 mmol), quenched with 15.8 mg PPh$_3$ (0.06 mmol) and a reaction was stirred 12 h at ambient temperature (instead of reflux) to afford (E)-syn-2-methyl-3-phenyl-5-phenylpent-4-en-1-al **13e** (syn : anti = 98 : 2). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.68 (d, J = 2.8 Hz, 1H), 7.15-7.32 (m, 10H), 6.43 (d, J = 15.8 Hz, 1H), 6.35 (dd, J = 15.8, 7.3 Hz, 1H), 3.64 (t, J = 8.3 Hz, 1H), 2.84 (qdd, J = 6.8, 6.8, 2.8 Hz, 1H), 0.92 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.3, 140.9, 136.6, 131.3, 130.4, 128.6, 128.3, 127.9, 127.4, 126.7, 126.1, 50.7, 50.6, 12.5 ppm. Diisobutylaluminum hydride (4.0 ml, 1.0 M in hexanes, 4.0 mmol) reduction of **13e** followed by purification by flash chromatography (20 % EtOAc/hexanes) gave 461 mg (92 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.23-7.38

(m, 10H), 6.40-6.52 (m, 2H), 3.73 (dd, J= 10.4, 4.2 Hz, 1H), 3.59 (dd, J = 9.5, 4.9 Hz, 1H), 3.36 (dd, J = 8.3, 7.9 Hz, 1H), 2.10-2.20 (m, 1H), 1.92 (s, 1H), 0.87 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 142.9, 137.2, 132.7, 130.2, 128.5, 128.4, 128.0, 127.1, 126.2, 126.1, 66.2, 52.8, 40.4, 15.1 ppm; MS (EI, 70 V): m/z 252 (M$^{+\cdot}$), 193, 178, 165, 115, 91, 77, 65; HRMS m/z calcd for C$_{18}$H$_{20}$O (M$^{+\cdot}$): 252.1514, found: 252.1514.
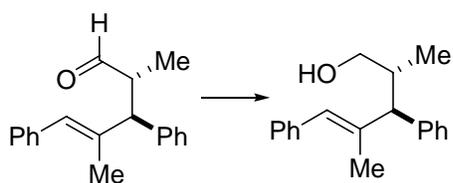
(E)-syn-2,4-Dimethyl-3,5-diphenylpent-4-en-1-ol (13f′): General Procedure **D** (1,2-DCE) was followed employing 264 mg of **9f** (1.00 mmol), 4.5 mg Ir dimer (0.005 mmol), 8.4 mg PCy$_3$ (0.03 mmol), 3.4 mg NaBPh$_4$ (0.01 mmol), quenched with 7.9 mg PPh$_3$ (0.03 mmol) and warm the reaction at 60 °C 70 h to afford (E)-syn-2,4-dimethyl-3,5-diphenylpent-4-en-1-al (**13f**) (2, 3-syn, 4E: 2,3-anti, 4E: 4Z = 87: 6: 7). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.78 (d, J = 3.7 Hz, 1H), 7.21-7.45 (m, 10H), 6.68 (s, 1H), 3.65 (d, J = 11.3 Hz, 1H), 3.10-3.26 (m, 1H), 1.86 (s, 3H), 1.05 (d, J = 6.8 Hz, 3H) ppm. Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **13f** followed by purification by flash chromatography (20 % EtOAc/hexanes) gave 230 mg (92 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.18-7.55 (m, 10H), 6.62 (s, 1H), 3.79 (dd, J= 10.7, 4.0 Hz, 1H), 3.58 (dd, J = 10.6, 6.4 Hz, 1H), 3.30 (d, J = 11.0 Hz, 1H), 2.40-2.60 (m, 1H), 1.77 (d, J= 1.2 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.7, 140.4, 137.8, 128.8, 128.4, 128.1, 127.9, 126.1, 126.0, 125.7, 66.5, 59.2, 35.5, 15.7, 15.0 ppm; MS (EI, 70 V): m/z 267 (M$^{+\cdot}$+H), 249, 234, 219, 207, 191, 175, 129, 117; HRMS m/z calcd for C$_{19}$H$_{22}$O (M$^{+\cdot}$): 266.1671; found: 266.1676.

(E)-syn-3-iso-Propyl-2-methylnon-4-en-1-ol   **(13g′):**
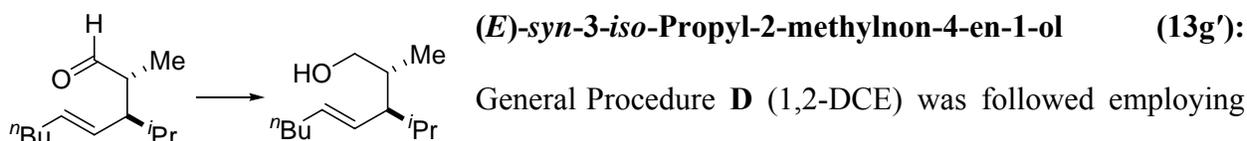
General Procedure **D** (1,2-DCE) was followed employing 377 mg of **9g** (1.92 mmol), 9.0 mg Ir dimer **(**0.01 mmol), 16.8 mg PCy$_3$ (0.06 mmol), 6.8 mg NaBPh$_4$ (0.02 mmol), quenched with 15.8 mg PPh$_3$ (0.06 mmol) and reflux 14 h to afford (*E*)-*syn*-3-*iso*-propyl-2-methylnon-4-en-1-al **13g**. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.60 (d, J = 3.0 Hz, 1H), 5.42 (dt, J = 15.3, 6.7 Hz, 1H), 5.21 (ddt, J = 15.2, 9.7, 1.2 Hz, 1H), 2.44-2.50 (m, 1H), 1.94-2.05 (m, 3H), 1.81-1.87 (m, 1H), 1.30-1.33 (m, 4H), 1.04 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H) ppm. Diisobutylaluminum hydride (4.0 mmol, 1.0 M in hexanes, 4.0 mmol) reduction of **13g** followed by purification by flash chromatography (20 % EtOAc/hexanes) gave 288 mg (76 %) of the title compound as colorless oil (13 % *Z*-isomers from NMR). Separation of the isomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 ^{o}C for 2.00 min, ramp at 5.00 ^{o}C/min to 250 ^{o}C, hold for 20 min, T$_r$ = 25.9 (*2,3-syn*, *4E*), 26.3 (*2,3-anti*, *4E*) and 26.8 (*2,3-syn*, *4Z*) min] provided the isomer ratio: 83: 5: 12. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.35 (dt, 15.3, 6.6 Hz, 1H), 5.16 (ddt, J= 15.3, 9.6, 1.1 Hz, 1H), 3.60 (dd, J= 10.7, 4.0 Hz, 1H), 3.34 (dd, J= 10.7, 6.5 Hz, 1H), 2.00 (qd, J= 6.6, 0.9 Hz, 2H), 1.90 (s, 1H), 1.73-1.86 (m, 1H), 1.63-1.71 (m, 1H), 1.53-1.61 (m, 1H), 1.29-1.32 (m, 4H), 0.93 (d, J = 6.5 Hz, 3H), 0.87 (t, J= 6.8 Hz, 3H), 0.83 (d, J= 6.7 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 132.0, 129.3, 66.6, 52.3, 36.7, 32.2, 31.8, 27.6, 22.1, 21.7, 17.1, 15.5, 13.7 ppm; MS (EI, 70 V): *m/z* 198 (M$^{+\cdot}$), 167, 155, 139, 137, 123, 111, 95, 83, 69; HRMS *m/z* calcd for C$_{13}$H$_{26}$O (M$^{+\cdot}$): 198.1984; found: 198.1976.
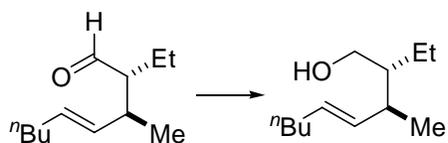
(*E*)-*syn*-2-Ethyl-3-methylnon-4-en-1-ol (13h′): General Procedure **D** (2 mol% catalyst loading, 1,2-DCE) was followed employing 182 mg of **9h** (1.00 mmol), 9.0 mg Ir dimer (0.01 mmol), 16.8 mg PCy₃ (0.06 mmol), 6.8 mg NaBPh₄ (0.02 mmol) and an initial reaction time of 90 min (instead of 30 min), then quenched with 15.8 mg PPh₃ (0.06 mmol) and reflux 14 h to afford (*E*)-*syn*-2-ethyl-3-methylnon-4-en-1-al **13h**. ¹H NMR (300 MHz, CDCl₃): δ 9.59 (d, J = 3.6 Hz, 1H), 5.46 (dt, J = 15.3, 6.3 Hz, 1H), 5.33 (dd, J = 15.3, 7.7 Hz, 1H), 2.44-2.53 (m, 1H), 1.91-2.10 (m, 3H), 1.28-1.74 (m, 6H), 0.96 (t, J = 6.9 Hz, 3H), 0.80-0.88 (m, 6H) ppm. Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **13h** followed by purification by flash chromatography (15 % EtOAc/hexanes) gave 155 mg (85 %) of the title compound as colorless oil. Separation of the isomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp at 5.00 °C/min to 250 °C, hold for 20 min, T_r = 25.1 (*2,3-anti, 4E*), 25.3 (*2,3-syn, 4E*) and 25.5 (*2,3-syn, 4Z*) min] provided the isomer ratio: 7: 80: 12. ¹H NMR (300 MHz, CDCl₃): δ 5.42 (dt, 15.4, 5.7 Hz, 1H), 5.35 (dd, J= 15.4, 6.6 Hz, 1H), 3.59 (s, 1H), 3.58 (s, 1H), 2.16-2.30 (m, 1H), 1.96 (q, J = 6.5 Hz, 2H), 1.61 (s, 1H), 1.24-1.38 (m, 6H), 0.99 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 134.4, 129.7, 63.3, 47.5, 37.2, 32.2, 31.7, 22.1, 20.9, 17.8, 13.8, 11.6; MS (EI, 70 V): *m/z* 184 (M⁺·), 166, 153, 137, 123, 111, 95, 81, 69, 55 ppm; HRMS *m/z* calcd for C₁₂H₂₄O (M⁺·): 184.1827; found: 184.1831.
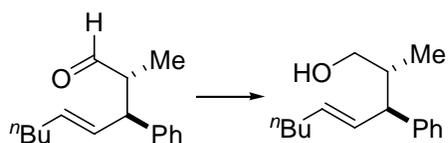
(*E*)-*syn*-2-Methyl-3-phenylnon-4-en-1-ol (13i′) General Procedure **D** (1,2-DCE) was followed employing 460 mg of **9i** (2.00 mmol), 9.0 mg Ir dimer (0.01 mmol), 16.8 mg PCy₃

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(0.06 mmol), 6.8 mg NaBPh$_4$ (0.02 mmol), quenched with 15.8 mg PPh$_3$ (0.06 mmol) and reflux 14 h to afford aldehyde **13i** (*syn : anti* = 96 : 4). Diisobutylaluminum hydride (4.0 ml, 1.0 M in hexanes, 4.0 mmol) reduction of (*E*)-*syn*-2-methyl-3-phenylnon-4-en-1-al **13i** followed by purification by flash chromatography (20 % EtOAc/hexanes) gave 284 mg (62 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.17-7.34 (m, 5H), 5.68 (ddt, J= 15.2, 9.0, 1.1 Hz), 5.54(dt, J= 15.2, 6.3 Hz), 3.70 (dd, J= 10.9, 5.0 Hz, 1H), 3.57 (dd, J= 10.9, 5.8 Hz, 2H), 3.11 (t, J= 9.1 Hz, 1H), 1.94-2.08 (m, 3H), 1.63 (s, 1H), 1.26-1.40 (m, 4H), 0.89 (t, J= 7.0 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.9, 132.6, 131.4, 128.4, 127.8, 126.0, 66.7, 53.1, 40.5, 32.2, 31.5, 22.2, 15.3, 13.9 ppm; MS (EI, 70 V): *m/z* 232 (M$^{+\cdot}$), 173, 131, 117, 105, 91, 69, 55; HRMS *m/z* calcd for C$_{16}$H$_{24}$O (M$^{+\cdot}$): 232.1827; found: 232.1833.
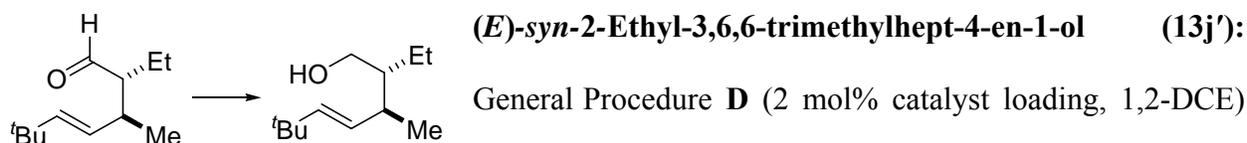
(*E*)-*syn*-2-Ethyl-3,6,6-trimethylhept-4-en-1-ol **(13j′):** General Procedure **D** (2 mol% catalyst loading, 1,2-DCE) was followed employing 127 mg of **9j** (0.70 mmol), 3.2 mg Ir dimer (0.0035 mmol), 5.9 mg PCy$_3$ (0.021 mmol), 2.4 mg NaBPh$_4$ (0.007 mmol) and an initial reaction time of 90 min (instead of 30 min) before quenched with 5.5 mg PPh$_3$ (0.021 mmol) and reflux 14 h to afford (*E*)-*syn*-2-ethyl-3,6,6-trimethylhept-4-en-1-al **13j** (*syn : anti* = 93 : 7). Diisobutylaluminum hydride (1.4 ml, 1.0 M in hexanes, 1.4 mmol) reduction of **13j** followed by purification by flash chromatography (15 % EtOAc/hexanes) gave 80 mg (62 %) of the title compound as colorless viscous oil. Separation of the diastereomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 $^{\circ}$C for 2.00 min, ramp at 5.00 $^{\circ}$C/min to 250 $^{\circ}$C, hold for 20 min, T$_r$ = 21.0 (*2,3-syn*, *4E*) and 21.3 (*2,3-anti*, *4E*) min] provided the diastereomer

ratio: 93: 7. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.47 (dd, J = 15.7, 0.6 Hz, 1H), 5.28 (dd, J = 15.7,

8.1 Hz, 1H), 3.60 (m, 2H), 2.19 (s, 1H), 1.61 (s, 1H), 1.26-1.49 (m, 3H), 1.00 (d, J = 6.8 Hz, 3H),

1.00 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 140.9, 129.1, 63.5,

47.7, 37.6, 31.6, 29.8, 21.1, 18.2, 11.6 ppm; MS (EI, 70 V): *m/z* 184 (M$^{+\cdot}$), 151, 128, 111, 97, 84,

69, 58; HRMS *m/z* calcd for C$_{12}$H$_{24}$O (M$^{+\cdot}$): 184.1827; found: 184.1829.
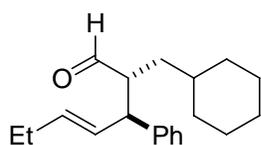
syn-(_E_)-2-(Cyclohexylmethyl)-3-phenylhept-4-enal **(13k)**: General

Procedure **D** was followed employing 1-((*S*,1*E*)-3-((*E*)-3-

cyclohexylallyloxy) pent-1-enyl)benzene (**9k**, 210 mg, 0.74 mmol) and 2 mol% catalyst (6.7 mg

Ir-dimer, 12.4 mg PCy$_3$, 5.1 mg NaBPh$_4$), stirred 6 h at dichloromethane whereupon the solvent

was removed *in vacuo*. Hexane was added and the resulting suspension was loaded onto a 6 x 2

cm plug of Florisil and eluted with hexanes. Removal of the solvent *in vacuo* afford 1-((1*E*)-3-

((*E*)-3-cyclohexylprop-1-enyloxy)pent-1-enyl)benzene (**10k**). Then added 5 ml dichloroethane

and refluxed in oil bath for 16 h. Purification by flash chromatograph on Iatrobeads neutral

(pH7) silica gel (2.5 % ethyl ether in hexanes) to yield 128 mg (61 %) of the title compound as a

colorless oil. (*syn : anti* = 95 : 5). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.53 (d, J = 4.5 Hz, 1H), 7.16-

7.37 (m, 5H), 5.53-5.60 (m, 2H), 3.40-3.48 (m, 1H), 2.72-2.81 (m, 1H), 1.95-2.11 (m, 2H), 0.96

(t, J = 7.2 Hz, 3H), 0.57-1.72 (m, 13 H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.0, 142.1, 134.2,

129.8, 127.9, 126.6, 54.0, 50.2, 35.4, 35.1, 34.1, 32.3, 26.4, 26.1, 25.9, 25.4, 13.5 ppm; MS (EI,

70 V): *m/z* 284 (M$^{+\cdot}$), 255, 226, 212, 162, 145; HRMS *m/z* calcd for C$_{20}$H$_{28}$O (M$^{+\cdot}$): 284.2140.

found 284.2144.
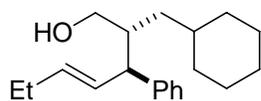
syn-(E)-2-(cyclohexylmethyl)-3-phenylhept-4-en-1-ol **(13k′)**: Diisobutylaluminum hydride (1.4 ml, 1.0 M in hexanes, 1.4 mmol) reduction of **13k** (142 mg, 0.5 mmol) followed purification by flash chromatograph on silical gel (16 % ethyl acetate in hexanes) afford 128 mg (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.17-7.33 (m, 5H), 5.68 (dd, J = 15.3, 7.9 Hz, 1H), 5.61 (dt, J = 15.3, 5.3 Hz, 1H), 3.74 (dd, J = 11.3, 3.6 Hz, 1H), 3.62 (dd, J = 11.3, 5.0 Hz, 1H), 3.23 (t, J = 8.7 Hz, 1H), 1.90-2.08 (m, 3H), 0.86-1.70 (m, 14H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.1, 133.0, 131.6, 128.4, 127.9, 126.0, 63.5, 52.2, 42.4, 36.4, 35.0, 34.4, 32.6, 26.5, 26.4, 26.2, 25.5, 13.7 ppm; MS (EI, 70 V): m/z 286 (M$^{+\cdot}$), 268, 243, 214, 199, 172, 143, 130; HRMS m/z calcd for C$_{20}$H$_{28}$O (M$^{+\cdot}$): 286.2297. found 286.2292.
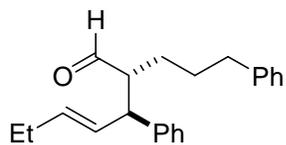
syn-(E)-3-Phenyl-2-(3-phenylpropyl)hept-4-enal **(13l)**: General Procedure **D** was followed employing 1-((3E)-5-((E)-1-phenylpent-1-en-3-yloxy)pent-3-enyl)benzene (**9l**, 306 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$, 6.8 mg NaBPh$_4$) in dichloroethane for 6 h, and then reflux 16 h. Purification by flash chromatograph on Iatrobeads neutral (pH7) silica gel (2.5 % EtOAc in hexanes) afford 236 mg (77 %) (syn : anti = 96 : 4) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.71 (d, J = 4.2 Hz, 1H), 7.19-7.50 (m, 10H), 5.68-5.72 (m, 2H), 3.60-3.66 (m, 1H), 2.52-2.84 (m, 4H), 2.09-2.17 (m, 2H), 1.41-1.72 (m, 3H), 1.08 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.84, 134.30, 141.88, 141.75, 129.48, 128.72, 128.24, 127.86, 126.66, 125.72, 56.42, 49.71, 35.52, 28.60, 27.27, 25.45, 13.50 ppm; MS (EI, 70 V): m/z 306 (M$^{+\cdot}$), 288, 277, 199, 187, 145, 91; HRMS m/z calcd for C$_{22}$H$_{26}$O (M$^{+\cdot}$): 306.1984. found 306.1982.

syn-(E)-3-Phenyl-2-(3-phenylpropyl)hept-4-en-1-ol (13l′):
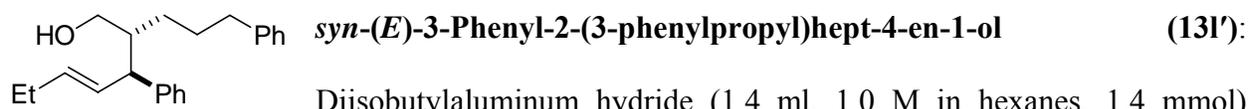
Diisobutylaluminum hydride (1.4 ml, 1.0 M in hexanes, 1.4 mmol) reduction of **13l** (236 mg, 0.77) followed purification by flash chromatograph on silical gel (16 % EtOAc in hexanes) afford 216 mg (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.08-7.34 (m, 10H), 5.66 (dd, J = 15.4, 8.3 Hz, 1H), 5.58 (dt, J = 15.4, 5.7 Hz, 1H), 3.73 (dd, J = 11.3, 4.5 Hz, 1H), 3.68 (dd, J = 11.3, 4.7 Hz, 1H), 3.25 (t, J = 8.8 Hz, 1H), 2.35-2.61 (m, 2H), 1.98-2.11 (m, 2H), 1.82-1.93 (m, 1H), 1.44-1.74 (m, 3H), 1.23-1.33 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.01, 142.48, 133.12, 131.34, 128.49, 128.26, 128.19, 127.81, 126.06, 125.58, 63.20, 51.57, 45.28, 36.01, 28.81, 28.34, 25.49, 13.68 ppm; IR(liquid film): 3373, 3026, 2931, 1601, 1494, 1453, 1030, 969, 748, 699 cm^{-1}; MS (EI, 70 V): m/z 308 (M$^{+\cdot}$), 290, 261, 233, 199, 186, 145, 117, 91; HRMS m/z calcd for C$_{22}$H$_{28}$O (M$^{+\cdot}$): 308.2140. found 308.2142.

syn-(E)-2-(3-(Benzyloxy)propyl)-3-phenylhept-4-enal (13m):
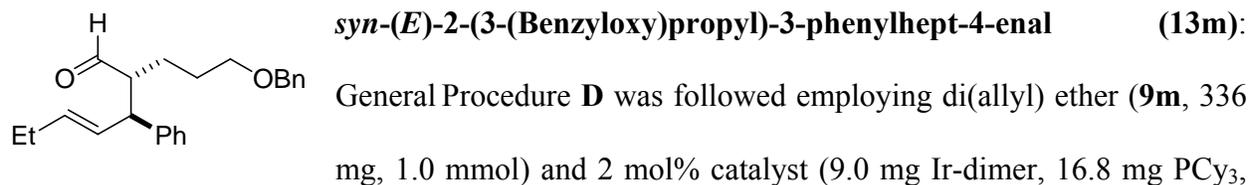
General Procedure **D** was followed employing di(allyl) ether (**9m**, 336 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$, 6.8 mg NaBPh$_4$) in dichloroethane for 6 h, then refuxed 16 h after 15.2 mg PPh$_3$ was added. Purification by flash chromatograph on Iatrobeads neutral (pH7) silica gel (2.5 % ethyl acetate in hexanes) afford 249 mg (74 %) of the title compound as colorless oil, (syn : anti = 96 : 4). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.59 (d, J = 4.1 Hz, 1H), 7.18-7.34 (m, 10H), 5.43-5.63 (m, 2H), 4.16 (s, 2H), 3.45-3.54 (m, 1H), 3.37 (t, J = 5.8 Hz, 1H), 2.64-2.72 (m, 1H), 1.97-2.13 (m, 2H), 1.28-1.72 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.75, 141.92,

138.45, 134.34, 129.49, 128.70, 128.28, 127.90, 127.53, 127.46, 126.64, 72.70, 69.67, 56.26, 49.83, 27.04, 25.45, 24.43, 13.50 ppm.
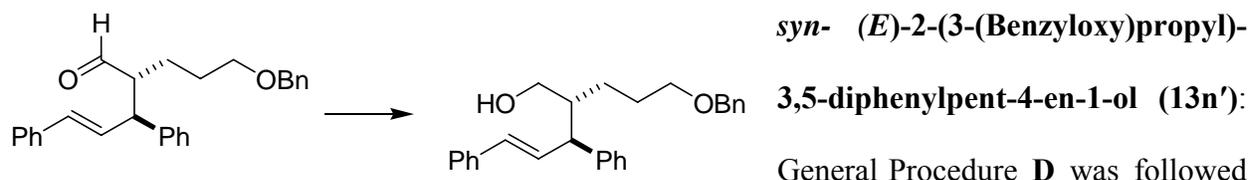
***syn-* (*E*)-2-(3-(Benzyloxy)propyl)-3,5-diphenylpent-4-en-1-ol (13n′):** General Procedure **D** was followed employing ((*E*)-3-((*E*)-5-(benzyloxy)pent-2-enyloxy)prop-1-ene-1,3-diyl)dibenzene (**9n**, 384 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$, 6.8 mg NaBPh$_4$) in dichloromethane for 6 h, and stirred overnight after 15.2 mg (0.06 mmol) PPh$_3$ was added o afford *syn-*(*E*)-2-(3-(benzyloxy)propyl)-3,5-diphenylpent-4-en-1-ol **13n** (*syn : anti* = 97 : 3). Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **13n** followed by purification by flash chromatography (16 % EtOAc/hexanes) gave 274 mg (71 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.19-7.36 (m, 15H), 6.49 (d, J = 15.6 Hz, 1H), 6.41 (dd, J = 15.6, 8.0 Hz, 1H), 4.45 (s, 2H), 3.76 (d, J = 4.5 Hz, 2H), 3.50 (t, J = 8.6 Hz, 1H), 3.39 (t, J = 6.4 Hz, 2H), 1.96-2.05 (m, 1H), 1.30-1.77 (m, 4H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.20, 138.35, 137.22, 132.53, 130.42, 128.60, 128.44, 128.30, 127.95, 127.60, 127.49, 127.16, 126.28, 126.15, 72.81, 70.45, 62.64, 51.62, 45.10, 26.81, 25.00 ppm.

***tert*-Butyl((*Z*)-4-((*E*)-oct-2-en-4-yloxy)but-2-enyloxy)diphenylsilane (9o):** General procedure **A** was followed employing (*E*)-oct-2-en-4-ol (640 mg, 5.0 mmol) and (*Z*)-(4-bromobut-2-enyloxy)(*tert*-butyl)diphenylsilane (2.910 g, 7.5

mmol)[55]. Purification by flash chromatograph on silical gel (2 % EtOAc in hexanes) to yield 1443 mg (66 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.69-7.72 (m, 4H), 7.38-7.46 (m, 6H), 5.76 (dt, J = 11.2, 6.0 Hz, 1H), 5.58 (dt, J = 11.2, 6.6 Hz, 1H), 5.51 (dq, J = 15.3, 6.4 Hz, 1H), 5.23 (dd, J = 15.3, 8.2 Hz, 1H), 4.27 (d, J = 6.0 Hz, 2H), 3.91 (dd, J = 12.7, 5.6 Hz, 1H), 3.74 (dd, J = 12.7, 6.9 Hz, 1H), 3.50 (q, J = 7.0 Hz, 1H), 1.65 (d, J = 6.3 Hz, 3H), 1.20-1.45 (m, 6H), 1.07 (s, 9H), 0.89 (t, J = 7.4 Hz, 3H) ppm.
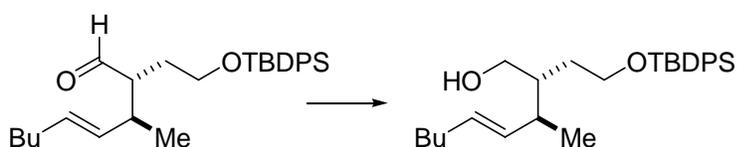
syn- (*E*)-2-(2-(*tert*-Butyldiphenlilyl oxyethyl) -3-methylnon-4-en-1-ol (13o′): General Procedure **D** was followed employing di(allyl) ether (**9o**, 436 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloroethane for 6 h, and refluxed overnight to afford *syn*-(*E*)-2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-3-methylnon-4-en-1-al **13o**. Then DIBAL-H (1.0 M in hexanes, 2.0 ml, 2.0 mmol) was added at -78 °C. Purification by flash chromatograph on silical gel (5-16 % EtOAc in hexanes) afford 162 mg (37 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.67-7.77 (m, 4H), 7.35-7.50 (m, 6H), 5.40 (dt, J = 15.2, 6.2 Hz, 1H), 5.32 (dd, J = 15.2, 6.7 Hz, 1H), 3.54-3.83 (m, 4H), 2.74 (brs, 1H), 2.14-2.38 (m, 1H), 1.97-2.01 (m, 1H), 1.45-1.72 (m, 3H), 1.31-1.35 (m, 4H), 1.08 (s, 9H), 0.97 (d, J = 6.9 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 135.56, 134.06, 133.27, 129.98, 129.73, 127.70, 64.57, 63.28, 44.36, 38.38, 32.26, 31.75, 26.77, 22.17, 19.07, 17.48, 13.92 ppm; MS (EI, 70 V): *m/z* 381 (M$^{+\cdot}$-C$_4$H$_9$), 363, 351, 303, 255, 229, 199; HRMS *m/z* calcd for C$_{24}$H$_{33}$O$_2$Si (M$^{+\cdot}$-C$_4$H$_9$): 381.2250. found 381.2255.

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[55] LeStrat, F.; Murphy, J. A.; Hughes, M. *Org. Lett.* **2004**, 4, 2735-2738.
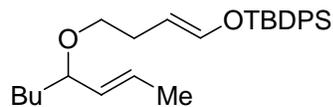
 tert- **Butyl((*E*)-4-((*E*)-oct-2-en-4-yloxy)but-1-enyloxy)diphenylsil ane (10o′)**: The compound was isolated with the **13o′** as the by product. yield 135 mg (31 %). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.67-7.77 (m, 4H), 7.35-7.50 (m, 6H), 6.34 (d, J = 11.9 Hz, 1H), 5.59 (dq, J = 15.3, 6.4 Hz, 1H), 5.28 (dd, J = 15.3, 8.1 Hz, 1H), 5.14 (dt, J = 11.9, 7.5 Hz, 1H), 3.53 (q, J = 7.0 Hz, 1H), 3.41 (dt, J = 9.3, 6.9 Hz, 1H), 3.15 (dt, J = 9.3, 7.2 Hz, 1H), 2.10 (q, J = 7.0 Hz, 2H), 1.72 (dd, J = 6.4, 1.5 Hz, 3H), 1.25-1.47 (m, 6H), 1.11 (s, 9H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ141.57, 135.46, 132.99, 132.58, 129.79, 127.68, 108.14, 80.86, 68.54, 35.38, 28.02, 27.65, 26.85, 26.55, 22.66, 19.23, 17.64, 14.05, 1.02 ppm.
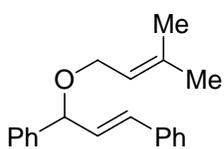
 (*E*)-3-(3-Methylbut-2-enyloxy)-1,3-diphenylprop-1-ene (9p): General Procedure **C** was followed employing 2.61 g of (*E*)-1,3-diphenyl-2-propen-1-ol (12.4 mmol) and 3-methylbut-2-en-1-ol (2.09 g, 24.8 mmol). Purification by flash chromatography (5 % EtOAc/hexanes) gave 2.58 g (75 %) of the title compound as colorless oil. IR (liquid film): 3027, 1600, 1494, 1449, 1377, 1059, 967, 745, 698. cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.27-7.54 (m, 10H), 6.70 (d, J = 15.9 Hz, 1H), 6.44 (dd, J = 15.9, 7.0 Hz, 1H), 5.54 (t, J = 6.8 Hz, 1H), 5.06 (d, J = 7.0 Hz, 1H), 4.06-4.18 (m, 2H), 1.86 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.3, 136.9, 136.5, 131.1, 130.5, 128.4, 127.5, 126.9, 126.5, 121.1, 81.5, 64.8, 25.8, 18.0 ppm; MS (EI, 70 V) *m/z*: 278 (M$^{+\cdot}$), 209, 193, 181, 158, 131, 115, 105, 91, 77, 69; HRMS *m/z* calcd for C$_{20}$H$_{22}$O (M$^{+\cdot}$): 278.1671; found 278.1683.
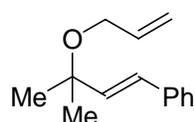
(E)-(3-(Allyloxy)-3-methylbut-1-enyl)benzene (9q): General Procedure **A** was followed employing (E)-2-methyl-4-phenylbut-3-en-2-ol[56] (810 mg, 5.0 mmol), allyl bromide (908 mg, 7.5 mmol). Purification by flash chromatograph on silical gel (2.5 % EtOAc in hexanes) afford 1008 mg (99 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.27-7.46 (m, 5H), 6.56 (d, J = 16.4 Hz, 1H), 6.29 (d, J = 16.4 Hz, 1H), 5.99 (ddt, J = 17.2, 10.4, 5.3 Hz, 1H), 5.35 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.4 Hz, 1H), 3.96 (d, J = 5.3 Hz, 2H), 1.47 (s, 6H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.76, 135.90, 135.31, 128.87, 127.43, 126.30, 115.78, 75.32, 64.08, 26.39 ppm. MS (EI, 70 V): m/z 187 (M$^{+\cdot}$-Me), 161, 145, 129, 117, 105, 91, 77, 67; HRMS m/z calcd for C$_{13}$H$_{15}$O (M$^{+\cdot}$-Me) 187.1123; found 187.1122.
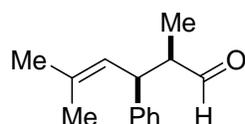
syn-2,5-Dimethyl-3-phenylhex-4-enal (13q): General Procedure **D** was followed employing (E)-(3-(Allyloxy)-3-methylbut-1-enyl)benzene (**9q**, 404 mg, 2.0mmol) and 1 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloroethane for 10 min, after 15.8 mg PPh$_3$ was added, heated the mixture to 60 $^\circ$C and stirred 6 h. Purification by flash chromatograph on Introbeads silica gel (PH = 7.0, 2.5 % ethyl acetate in hexanes) afford 372 mg (92 %) of the title compound as colorless oil, (*syn: anti* = 95: 5). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.68 (d, J = 3.0 Hz, 1H), 7.21-7.37 (m, 5H), 5.44 (d, J = 9.9 Hz, 1H), 3.70 (t, J = 9.7 Hz, 1H), 2.68-2.79 (m, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 0.94 (d, J = 6.9 Hz, 3H) ppm.
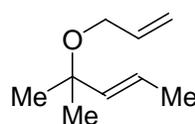
(E)-4-(Allyloxy)-4-methylpent-2-ene (9r): General Procedure **A** was followed employing (E)-2-methylpent-3-en-2-ol[57] (1.0 g, 10 mmol), allyl bromide (1.8 g,

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[56] Kohler, H.; *Am. Chem. J.* **1905**, 33, 28.

15 mmol). Purification by flash chromatograph on silical gel (2.5 % EtOAc in hexanes) afford 1.26 g (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.91 (ddt, J = 17.3, 10.4, 5.4 Hz, 1H), 5.61 (dq, J = 16.4 Hz, 6.0 Hz, 1H), 5.46 (d, J = 16.4 Hz, 1H), 5.25 (d, J = 17.3 Hz, 1H), 5.11 (d, J = 10.4 Hz, 1H), 3.83(d, J = 5.4 Hz, 1H), 1.71 (d, J = 6.0 Hz, 3H), 1.28 (s, 6H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.6, 136.0, 124.4, 115.2, 74.7, 63.6, 26.1, 17.5 ppm; MS (EI, 70 V): *m/z* 125 (M$^{+\cdot}$-Me), 109, 91; HRMS *m/z* calcd for C$_8$H$_{13}$O (M$^{+\cdot}$-Me)125.0966, found 125.0961.
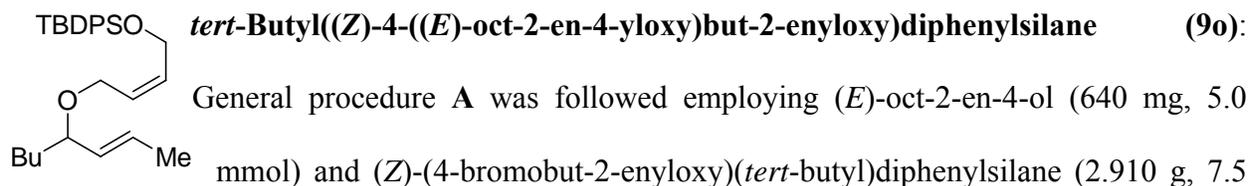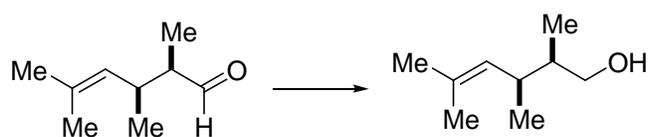

syn-2,3,5-Trimethylhex-4-en-1-ol (13r′): General Procedure **D** was followed employing di(allyl) ether (**9r**, 280 mg, 2.0mmol) and 1 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloroethane for 10 min, after 15.8 mg PPh$_3$ was added, heated the mixture to 83 °C and stirred 6 h to afford *syn*-2,3,5-trimethylhex-4-en-1-al **13r**, (*syn : anti =* 91 : 9). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.63 (d, J = 2.1 Hz, 1H), 5.02 (d, J = 9.8 Hz, 1H), 2.70 (dqd, J = 9.8, 6.9, 6.9 Hz, 1H), 2.24 (dqd, J = 6.9, 6.9, 2.1 Hz, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H) ppm. Diisobutylaluminum hydride (4.0 ml, 1.0 M in hexanes, 4.0 mmol) reduction of **13r** followed by purification by flash chromatography (16 % EtOAc/hexanes) gave 230 mg (81 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.99 (d, J = 9.7 Hz, 1H), 3.56 (dd, J = 10.7, 5.5 Hz, 1H), 3.34 (dd, J = 10.7, 6.6 Hz, 1H), 2.25 (dqd, J = 9.7, 6.7, 6.7 Hz, 1H), 2.00 (brs, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.39-1.55 (m, 1H), 0.89 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ

[57] Collins, S.; Hong, Y.; Hoover, G. J.; Veit, J. R. *J. Org. Chem*. **1990**, 55, 3565-3568.

130.5, 129.9, 67.0, 41.4, 34.8, 25.8, 18.3, 17.9, 14.2 ppm; MS (EI, 70 V): m/z 142 (M$^{+\cdot}$), 109, 96, 83, 66, 53; HRMS m/z calcd for $C_9H_{18}O$ (M$^{+\cdot}$): 142.1358. found 142.1354.
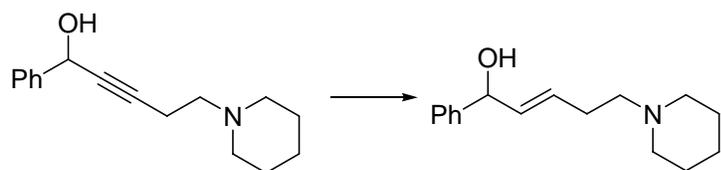
(*E*)-1-Phenyl-5-(piperidin-1-yl)pent-2-en-1-ol (19a′): A solution of 1-(but-3-ynyl)piperidine [58] (1.37 g, 10.0 mmol) in dry THF was added *n*-BuLi (1.6 M in hexanes, 6.3 ml, 10.0 mmol) at -78 °C and stirred 30 min, then benzealdehyde (1.06 g, 10.0 mmol) in THF was added dropwise, stirred overnight with warm to ambient temperature. Saturated NH_4Cl solution was added to quench the reaction, exatracted with ethyl ether. After solvent Vaporation, the crude oil was purified by column chromatography on silical gel (16 % ethyl acetate in hexanes) to yield 1.85 g (82 %) of 1-phenyl-5-(piperidin-1-yl)pent-2-yn-1-ol (**19a′′**) as light yellow oil. The compound was solved in dry THF, then sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 65 % in toluene, 3.33 M, 1.8 equiv, 4.5 ml, 14.8 mmol in 20 ml THF) was added dropwise at 0 °C, warmed to reflux for 3h, cool it to 0 °C, add water following saturated sodium tartrate solution slowly to quench the reaction and extracted with ethyl ether, After solvent Vaporation, the crude oil was purified by column chromatography on silical gel (20 % methanol in dichloromethane) to yield 1.76 g (95 %) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.23-7.40 (m, 5H), 5.66-5.79 (m, 2H), 5.15 (d, J = 5.0 Hz, 1H), 2.34-2.40 (m, 6H), 2.23-2.34 (m, 2H), 1.55-.162 (m, 4H), 1.43-1.47 (m, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.40, 133.71, 129.87, 128.36, 127.35, 126.15, 74.83, 58.60, 54.36, 29.56, 25.68, 24.30 ppm; MS (EI, 70 V): m/z 227 (M$^{+\cdot}$-

[58] Turner, S. C.; Esbenshade, T. A.; Bennani, Y. L.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2003**, 13, 2131-2136.

H$_2$O), 198, 158, 129, 115, 98, 84, 77; HRMS *m/z* calcd for C$_{16}$H$_{21}$N (M^{+}-H$_2$O): 227.1674. found 227.1673.
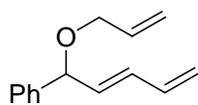
(*E*)-(1-(Allyloxy)penta-2,4-dienyl)benzene (19a): The general procedure **A** was applied to (*E*)-1-phenyl-5-(piperidin-1-yl)pent-2-en-1-ol (**19a′**, 1.76 g, 7.8 mmol). The crude product was purified by column chromatography on silical gel (2 % ethyl acetate in hexanes) to yield 1.25 g (80 %) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.29-7.40 (m, 5H), 6.23-6.42 (m, 2H), 5.90-6.02 (m, 1H), 5.83 (dd, j = 14.4, 7.0 Hz, 1H), 5.11-5.35 (m, 4H), 4.88 (d, J = 7.1 Hz, 1H), 4.02 (dd, J = 13.8, 5.5 Hz, 1H), 3.98 (dd, J = 13.8, 5.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.00, 136.28, 134.73, 134.29, 132.11, 128.46, 127.64, 126.83, 117.83, 116.91, 81.22, 69.18 ppm; MS (EI, 70 V): *m/z* 200 (M^{+}), 187, 173, 159, 143, 131, 115, 105, 91, 77, 65, 55; HRMS *m/z* calcd for C$_{14}$H$_{16}$O (M^{+}): 200.1201. found 200.1205.
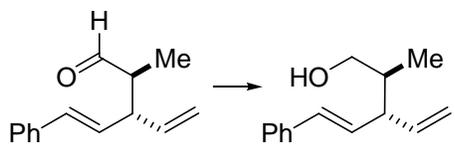
syn-(*E*)-2-Methyl-5-phenyl-3-vinylpent-4-enol (20a′): General Procedure **D** was followed employing (*E*)-(1-(allyloxy)penta-2,4-dienyl)benzene (**19a**, 200 mg, 1.0 mmol) with 1 mol% catalyst (4.5 mg Ir-dimer, 8.4 mg PCy$_3$ and 3.4 mg NaBPh$_4$) and stirred 30 min at dichloromethane. Then added PPh$_3$ (7.8 mg, 0.03 mmol) and keep ambient temperature for 12 h to afford *syn*-(*E*)-2-methyl-5-phenyl-3-vinylpent-4-enal **20a** (*syn : anti* = 94 : 6). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.73 (d, J = 2.0 Hz, 1H), 6.49 (d, J = 15.9 Hz, 1H), 6.20 (dd, J = 7.8 Hz, 1H), 5.91 (ddd, J = 16.6, 10.8, 7.4 Hz, 1H), 5.26 (ddd, J = 10.8, 1.3, 0.9 Hz, 1H), 5.25 (ddd, J = 16.6, 1.3, 1.3 Hz, 1H), 3.37 (q, J = 7.4 Hz, 1H), 2.65 (qdd, J = 7.0, 7.0, 2.0 Hz, 1H), 1.20 (d, J = 7.0 Hz, 3H) ppm.

Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **20a** followed by purification by flash chromatograph on silical gel (16 % ethyl acetate in hexanes) to yield 160 mg (80 %) of the title compound as colorless oil. IR (liquid film): 3373, 2961, 2877, 1635, 1494, 1449, 1030, 969, 915, 749, 694 cm^{-1}.^{1}H NMR (300 MHz, CDCl$_3$): δ 7.23-7.41 (m, 5H), 6.35 (d, J = 15.9 Hz, 1H), 5.98 (dd, J = 15.9, 7.9 Hz, 1H), 5.73-5.85 (m, 1H), 5.06 (d, J = 11.6 Hz, 1H), 5.05 (d, J = 15.6 Hz, 1H), 3.58 (dd, J = 10.6, 6.0 Hz, 1H), 3.46 (dd, J = 10.6, 6.0 Hz, 1H), 2.90 (q, J = 7.4 Hz, 1H), 1.62-1.85 (m, 1H), 1.73 (s, 1H), 0.90 (d, J = 6.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 138.49, 137.39, 131.55, 130.43, 128.48, 127.13, 126.07, 116.10, 66.29, 49.87, 39.88, 13.87 ppm; MS (EI, 70 V): *m/z* 202 (M[+.]), 184, 169, 155, 143, 128, 115, 91; HRMS *m/z* calcd for C$_{14}$H$_{16}$ (M[+.]-H$_2$O): 184.1252. found 184.1244.
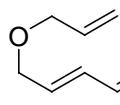
((1E,3E)-5-(Allyloxy)penta-1,3-dienyl)benzene(19b): The general procedure **A** was applied to (*2E,4E*)-5-phenylpenta-2,4-dien-1-ol[59] (1.6 g, 10.0 mmol). The crude product was purified by column chromatography on silical gel (2 % ethyl acetate in hexanes) to yield 1.91 g (95 %) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.21-7.40 (m, 5H), 6.79 (dd, J = 15.6, 10.4 Hz, 1H), 6.54 (d, J = 15.6 Hz, 1H), 6.41 (dd, J = 15.1, 10.5 Hz, 1H), 5.84-6.00 (m, 2H), 5.30 (d, J = 17.3 Hz, 1H), 5.20 (d, J = 10.4 Hz, 1H), 4.08 (d, J = 6.2 Hz, 2H), 4.01 (d, J = 5.6 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.98, 134.61, 132.61, 132.49, 129.95, 128.42, 128.08, 127.40, 126.22, 116.80, 70.89, 70.19 ppm. MS (EI, 70 V): *m/z* 200 (M[+.]), 187, 173, 159, 143, 131, 115, 105, 91, 77, 65, 55; HRMS *m/z* calcd for C$_{14}$H$_{16}$O (M[+.]): 200.1201; found 200.1205.

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[59] Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem.* **2005**, 70, 5376-5386.
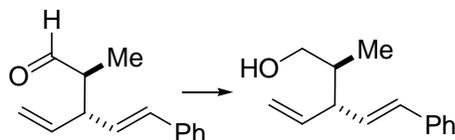
***anti*-(*E*)-2-Methyl-5-phenyl-3-vinylpent-4-enol (20b′):**

The general procedure **D** was followed employing ((*1E,3E*)-5-(Allyloxy)penta-1,3-dienyl)benzene (**19b**, 200 mg, 1.0 mmol) with 1 mol% catalyst (4.5 mg Ir-dimer, 8.4 mg PCy$_3$ and 3.4 mg NaBPh$_4$) and stirred 30 min at dichloroethane. Then added PPh$_3$ (7.8 mg, 0.03 mmol) and warm to 80 °C for 12 h to afford *anti*-(*E*)-2-methyl-5-phenyl-3-vinylpent-4-enal **20b** (*syn : anti* = 92 : 8). Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **20b** followed by purification by flash chromatograph on silical gel (16 % ethyl acetate in hexanes) to yield 160 mg (80 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.23-7.41 (m, 5H), 6.45 (d, J = 15.9 Hz, 1H), 6.19 (dd, J = 15.9, 8.5 Hz, 1H), 5.91 (ddd, J = 16.9, 10.5, 7.6 Hz, 1H), 5.14 (d, J = 16.9 Hz, 1H), 5.12 (d, J = 10.5 Hz, 1H), 3.65 (dd, J = 10.8, 6.1 Hz, 1H), 3.54 (dd, J = 10.8, 6.0 Hz, 1H), 3.00 (q, J = 7.4 Hz, 1H), 1.79-1.93 (m, 1H), 1.73 (s, 1H), 0.98 (d, J = 6.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 139.97, 137.41, 131.18, 130.03, 128.44, 127.09, 126.06, 115.31, 66.23, 49.67, 39.90, 13.76 ppm. MS (EI, 70 V): *m/z* 202 (M[+·]), 184, 169, 155, 143, 128, 115, 91; HRMS *m/z* calcd for C$_{14}$H$_{16}$ (M[+·]-H$_2$O): 184.1252; found 184.1244.
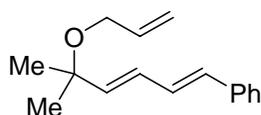
((*1E,3E*)-5-(Allyloxy)-5-methylhexa-1,3-dienyl)benzene (19c): The general procedure **A** was applied to (3*E*,5*E*)-2-methyl-6-phenylhexa-3,5-dien-2-ol[60] (1.88 g, 10.0 mmol). The crude product was purified by column chromatography on silical gel (2 % ethyl acetate in hexanes) to yield 2.17 g (95 %) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.21-7.44 (m, 5H), 6.81 (dd, J = 15.6, 10.3 Hz, 1H), 6.58 (d, J = 15.6 Hz, 1H), 6.35 (dd, J = 15.3, 10.3 Hz, 1H), 5.95 (ddt, J = 17.2. 10.3, 5.4 Hz, 1H),

[60] Gallagher, W. P.; Terstiege, I.; Maleczka, R. E. *J. Am. Chem. Soc.* **2001**, 123, 3194-3204.

5.84 (d, J = 11.6 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.15 (d, J = 10.3 Hz, 1H), 3.90 (d, J = 5.4

Hz, 2H), 1.39 (s, 6H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 139.76, 137.19, 135.99, 132.23,

129.53, 128.55, 127.45, 126.25, 115.77, 75.23, 64.12, 26.38 ppm.
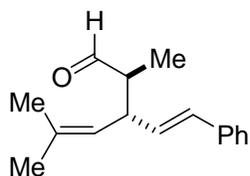
syn-(E)-2,5-Dimethyl-3-styrylhex-4-enal (20c): General Procedure **D** was followed employing di(allyl) ether (**19c**, 228 mg, 1.0 mmol) with 1 mol% catalyst (4.5 mg Ir-dimer, 8.4 mg PCy$_3$ and 3.4 mg NaBPh$_4$) and stirred 30 min at dichloroethane. Then added PPh$_3$ (7.8 mg, 0.03 mmol) and warm to 80 ^{o}C for 12 h (*syn :*

anti = 92: 8). The crude product was purified by column chromatography on Iatrobeads neutral

(pH7) silica gel (2 % ethyl acetate in hexanes) to yield 176 mg (77 %) of the title compound as

light yellow oil.^{1}H NMR (300 MHz, CDCl$_3$): δ 9.66 (d, J = 2.3 Hz, 1H), 6.40 (d, J = 15.9 Hz,

1H), 6.06 (dd, J = 15.9, 7.7 Hz, 1H), 5.15 (d, J = 8.3 Hz, 1H), 3.39 (q, J = 8.2 Hz, 1H), 2.44-2.50

(m, 1H), 1.75 (s, 3H), 1.68 (s, 3H), 1.10 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ

204.82, 137.16, 134.17, 130.61, 129.81, 128.47, 127.24, 126.12, 123.39, 50.93, 43.48, 25.88,

18.21, 11.62 ppm.

2.4.2 Experiment of section 2.3.

2.4.2.1 ICR reaction of allyl homoallyl ether
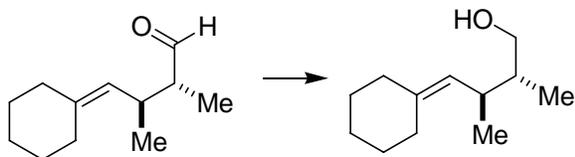
syn- 4-Cyclohexylidene-2,3-dimethylbutan-1-ol (23a′): General procedure **D** was followed employing 180 mg of 1-allyl-1-

75

(allyloxy)cyclohexane[61] (**21a**, 180 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg Ir-dimer, 0.01 mmol, 16.8 mg PCy$_3$, 0.06 mmol, 6.8 mg NaBPh$_4$, 0.02 mmol) in dichloroethane and an initial reaction time of 12 h before quenched with 15.8 mg PPh$_3$ (0.06 mmol) and reflux 12 h to afford *syn*-4-cyclohexylidene-2,3-dimethylbutan-1-al **23a** (*syn: anti* = 94: 6). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.62 (d, J = 2.3 Hz, 1H), 4.96 (d, J = 9.8 Hz, 1H), 2.72 (ddq, J = 9.8, 6.8, 6.8 Hz, 1H), 2.22 (qdd, J = 6.9, 6.9, 2.3 Hz, 1H), 2.10-2.18 (m, 2H), 2.00-2.10 (m, 2H), 1.46-1.59 (m, 6H), 1.04 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.1, 139.8, 124.0, 51.6, 37.0, 32.5, 28.8, 28.4, 27.6, 26.6, 18.1, 10.5 ppm. Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **23a** followed by purification by flash chromatography (15 % EtOAc/hexanes) gave 115 mg (64 %) of the title compound as colorless oil. IR (liquid film): 3349, 2927, 2853, 1667, 1448, 1376, 1019, 851 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 4.95 (d, 1H), 3.58 (dd, J = 10.3, 5.5 Hz, 1H), 3.39-3.41 (m, 1H), 2.24-2.36 (m, 1H), 2.06-2.17 (m, 4H), 1.41-1.65 (m, 6H), 0.91 (d, J = 6.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 138.8, 126.7, 67.2, 41.5, 37.3, 34.0, 29.1, 28.7, 27.9, 26.9, 18.6, 14.4 ppm.
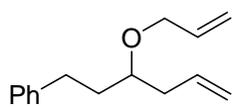
(3-(Allyloxy)hex-5-enyl)benzene (21b): General Procedure **A** was followed employing 1.76 g of 1-phenylhex-5-en-3-ol[62] (10.0 mmol), 480 mg NaH (20.0 mmol) and 1.4 ml allyl bromide (20.0 mmol). Purification by flash chromatography (2 % ethyl acetate/hexanes) gave 1.94 g (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.32-7.58 (m, 5H), 5.85-6.16 (m, 2H), 5.45 (dq, J = 17.1, 1.5 Hz, 1H), 5.20-5.33 (m, 3H), 4.21 (ddt, J = 12.6, 5.3, 1.2 Hz, 1H), 4.11 (ddt, J = 12.6, 5.6, 1.2 Hz, 1H), 3.54 (tt, J = 5.9, 5.9 Hz, 1H), 2.75-2.97 (m, 4H), 1.94-1.98 (m, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ

[61] Higashino, T.; Sakaguchi, S.; Ishii, Y. *Org. Lett*., **2000,** 2, 4193.
[62] Schmidt, B. *J. Org. Chem*. **2004**, 69, 7672-7687.

142.14, 135.10, 134.52, 128.26, 128.17, 125.57, 116.94, 116.47, 77.59, 69.83, 38.11, 35.47, 31.48 ppm.
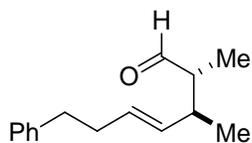
syn-(*E*)-2,3-Dimethyl-7-phenylhept-4-enal (23b): General procedure **D** was followed employing 216 mg of (3-(allyloxy)hex-5-enyl)benzene (**21b**, 1.0 mmol) and 2 mol% catalyst (9.0 mg Ir-dimer, 0.01 mmol, 16.8 mg PCy$_3$, 0.06 mmol, 6.8 mg NaBPh$_4$, 0.02 mmol) in dichloroethane and an initial reaction time of 12 h before quenched with 15.8 mg PPh$_3$ (0.06 mmol) and reflux 12 h. Purification by flash chromatograph on Iatrobeads neutral (pH7) silica gel (2.5 % EtOAc in hexanes) afford 150 mg (70 %) of the title compound as colorless oil, (*syn : anti : Z*- isomer = 88 : 5 : 7). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.75 (d, J = 2.1 Hz, 1H), 7.30-7.63 (m, 5H), 5.65 (dt, J = 15.3, 6.3 Hz, 1H), 5.30 (ddt, J = 15.3, 7.3, 1.0 Hz, 1H), 2.83 (t, J = 7.7 Hz, 2H), 2.64-2.75 (m, 1H), 2.48 (q, J = 7.6 Hz, 1H), 2.38-2.47 (m, 1H), 1.13 (d, J = 7.0 Hz, 1H), 1.13 (d, J = 6.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.45, 141.71, 133.38, 129.91, 128.43, 128.21, 125.74, 51.10, 37.36, 35.86, 34.24, 16.78, 10.06 ppm; MS (EI, 70 V): *m/z* 216 (M$^{+\cdot}$), 175, 158, 131, 117, 105, 91; HRMS *m/z* calcd for C$_{15}$H$_{20}$O (M$^{+\cdot}$): 216.1514. found 216.1518.
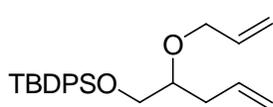
(2-(Allyloxy)pent-4-enyloxy)(*tert*-butyl)diphenylsilane (**21c**): General Procedure **A** was followed employing 1.02 g of 1-(*tert*-butyl-diphenylsiloxy)pent-4-en-2-ol [63] (3.00 mmol). Purification by flash chromatography (5 % EtOAc/hexanes) gave 841 mg (74 %) of the title compound as colorless oil. IR (liquid film): 3072, 2930, 2858, 2360, 1428, 1113, 917, 823, 702 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.72-

[63] Roush, W. R.; Hoong, L. K.; Palmer, Ma. A. J. Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, 55, 4117-4126.

7.76 (m, 4H), 7.41-7.50 (m, 6H), 5.81-6.01 (m, 2H), 5.30 (dq, J = 17.2, 1.5 Hz, 1H), 5.19 (d, J = 10.4 Hz, 1H), 5.13 (d, J = 18.0 Hz, 1H), 5.08 (d, J = 10.2 Hz, 1H), 4.15 (dd, J = 12.7, 5.5 Hz, 1H), 4.06 (dd, J = 12.7, 5.7 Hz, 1H), 3.76 (dd, J = 10.6, 5.7 Hz, 1H), 3.69 (dd, J = 10.6, 4.9 Hz, 1H), 3.50-3.58 (m, 1H), 2.30-2.48 (m, 2H), 1.12 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 135.6, 135.3, 134.8, 133.5, 129.6, 127.6, 116.9, 116.5, 79.2, 71.0, 65.4, 36.1, 26.8, 19.2 ppm; MS (EI, 70 V) *m/z*: 323 (M^{+}-^{t}Bu), 283, 267, 239, 221, 205, 177, 163, 135, 117. HRMS *m/z* calcd for C$_{20}$H$_{23}$O$_2$Si (M^{+}-^{t}Bu): 323.1467; found 323.1469.
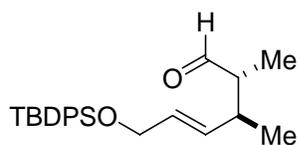
syn-(E)- 6-(*tert*-Butyl-diphenylsiloxy)-2,3-dimethylhex-4-en-1-nal (23c): General Procedure **D** (2 mol% catalyst loading, 1,2-DCE) was followed employing 380 mg of ether **21c** (1.00 mmol) and an initial reaction time of 12 h prior to heating the reaction time of 14 h to afford aldehyde (*syn: anti* = 96: 4). Purification by flash chromatography on Iatrobeads neutral (pH = 7) silica gel (5 % EtOAc/hexanes) gave 184 mg (48 %) of the title compound (*syn : anti* = 95 : 5) as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.67 (d, J = 1.8 Hz, 1H), 7.69-7.72 (m, 4H), 7.37-7.45 (m, 6H), 5.69 (dd, J = 15.4, 6.6 Hz, 1H), 5.60 (dt, J = 15.4, 4.2 Hz, 1H), 4.22 (d, J = 4.2 Hz, 2 H), 2.59-2.70 (m, 1H), 2.36 (qdd, J = 7.0, 6.9, 1.8 Hz, 1H), 1.09 (s, 9H), 1.05 (d, J = 7.1 Hz, 3H), 1.03 (d, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.1, 135.5, 133.7, 132.9, 129.6, 129.3, 127.6, 64.2, 50.9, 36.7, 26.8, 19.2, 16.3, 9.8 ppm; MS (EI, 70 V) *m/z*: 323 (M^{+}-^{t}Bu), 267, 245, 239, 199, 183, 139. HRMS *m/z* calcd for C$_{20}$H$_{23}$O$_2$Si (M^{+}-^{t}Bu): 323.1467, Found 323.1451.
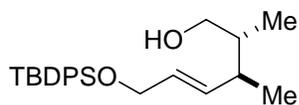
syn- (E)-6-(*tert*-Butyl-diphenylsiloxy)-2,3-dimethylhex-4-en-1-ol (23c′): Diisobutylaluminum hydride reduction of 140 mg of **23c** (0.37

mmol) followed by purification by flash chromatography (15 % EtOAc in hexanes) gave 127 mg

(91 %) of the title compound as colorless oil. IR (liquid film): 3365, 3071, 2960, 2858, 1428,

1380, 1265, 1112, 823, 739, 703 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.69-7.72 (m, 4H), 7.37-

7.46 (m, 6H), 5.65 (dd, J = 15.5, 6.9 Hz, 1H), 5.56 (dt, J = 15.5, 4.6 Hz, 1H), 4.20 (d, J = 4.6 Hz,

2 H), 3.59 (dd, J = 10.6, 5.7 Hz, 1H), 3.44 (dd, J = 10.6, 6.4 Hz, 1H), 2.14-2.26 (m, 1H), 1.51-

1.65 (m, 1H), 1.45 (s, 1H), 1.08 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ 135.6, 135.5, 133.8, 129.6, 127.9, 127.6, 66.6, 64.5, 40.6, 38.4,

26.8, 19.2, 16.4, 13.6 ppm; MS (EI, 70 V) *m/z*: 325 (M$^{+\cdot}$-^{t}Bu), 229, 199, 181, 139, 109. HRMS

m/z calcd for C$_{20}$H$_{25}$O$_2$Si (M$^{+\cdot}$-^{t}Bu): 325.1624; found 325.1627.

2.4.2.2 Preparation of dienal from ICR protocol
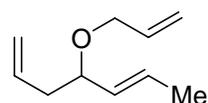
(*E*)-4-(Allyloxy)hepta-1,5-diene (25a): General Procedure **A** was followed

employing 5.41 g of (*E*)-hexa-1,5-dien-3-ol[64] (48.3 mmol) and allyl bromide

(8.7 g, 72 mmol) in THF. Purification by flash chromatography (2.5 % EtOAc/hexanes) gave

5.273 g (72 %) of the title compound as colorless oil. IR (liquid film): 3078, 2980, 2919, 2857,

1642, 1440, 1084, 969, 916 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.74-5.96 (m, 2H), 5.61 (dq, J

= 15.3, 6.4 Hz, 1H), 5.00-5.37 (m, 5H), 4.03 (ddt, J = 12.9, 5.1, 1.5 Hz, 1H), 3.82 (ddt, J = 12.9,

5.9, 1.4 Hz, 1H), 3.71 (dt, J = 8.0, 6.5 Hz, 1H), 2.38 (dtt, J = 14.1, 6.8, 1.3 Hz, 1H), 2.25 (dtt, J =

14.1, 6.6, 1.3 Hz, 1H), 1.72 (dd, J = 6.4, 1.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 135.2,

134.9, 131.4, 128.8, 116.5, 116.4, 79.6, 68.7, 40.2, 17.6 ppm; MS (EI, 70 V) *m/z*: 151 (M$^{+\cdot}$-H),

111, 95, 69, 59. HRMS *m/z* calcd for C$_{10}$H$_{15}$O (M$^{+\cdot}$-H): 151.1123; found 151.1128.

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[64] Viola, A.; Iorio, E. J.; Chen, K. K.; Glover, G. M.; Nayak, U.; Kocienski, P. J. *J. Am. Chem. Soc.*, **1967**, 3462.
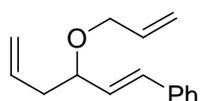
1-((*E*)-3-(Allyloxy)hexa-1,5-dienyl)benzene (25b): General Procedure **A** was followed employing 3.13 g of (*E*)-1-phenylhexa-1,5-dien-3-ol[65] (18.0 mmol) and allyl bromide (3.3 g, 27 mmol) in THF. Purification by flash chromatography (2.5 % EtOAc/hexanes) gave 3.51 g (91 %) of the title compound as colorless oil. IR (liquid film): 3078, 2856, 1642, 1494, 1072, 750, 693 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.06-7.26 (m, 5H), 6.39 (d, J = 16.0 Hz, 1H), 5.96 (dd, J = 16.0, 7.9 Hz, 1H), 5.66-5.86 (m, 2H), 4.93-5.19 (m, 4H), 3.97 (dd, J = 12.9, 4.9 Hz, 1H), 3.73-3.84 (m, 2H), 2.21-2.41 (m, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.3, 134.9, 134.3, 132.1, 129.7, 128.4, 127.5, 126.3, 116.9, 116.4, 79.5, 69.0, 40.2 ppm; MS (EI, 70 V) *m/z*: 213 (M$^{+\cdot}$-H), 181, 173, 145, 131, 115, 103, 91, 77, 63. HRMS *m/z* calcd for C$_{15}$H$_{17}$O (M$^{+\cdot}$-H): 213.1279; found 213.1276.
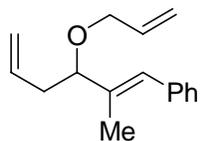
1-((*E*)-3-(Allyloxy)-2-methylhexa-1,5-dienyl)benzene (25c): General Procedure **A** was followed employing 3.38 g of (*E*)-2-methyl-1-phenylhexa-1,5-dien-3-ol[66] (18.0 mmol) and allyl bromide (3.3 g, 27 mmol). Purification by flash chromatography (2.5 % EtOAc/hexanes) gave 3.783 g (92 %) of the title compound as colorless oil. IR (liquid film): 3026, 2857, 1724, 1492, 1449, 1069, 743, 699 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.22-7.36 (m, 5H), 6.44 (s, 1H), 5.76-6.09 (m, 2H), 5.03-5.34 (m, 4H), 4.03 (ddt, J = 12.8, 5.1, 1.5 Hz, 1H), 3.81-3.89 (m, 2H), 2.46-2.58 (m, 1H), 2.32-2.42 (m, 1H), 1.85 (d, J = 1.3 Hz) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 137.3 (overlap of 2 C), 135.0, 134.9, 129.0, 128.2, 128.1, 126.5, 116.7, 116.5, 84.9, 69.0, 38.5, 12.6 ppm; MS (EI, 70 V) *m/z*: 227 (M$^{+\cdot}$-H), 187, 169, 145, 129, 117, 105, 91. HRMS *m/z* calcd for C$_{16}$H$_{19}$O (M$^{+\cdot}$-H): 227.1436; found 227.1439.

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[65] Kelly, B. G.; Giheany, *Tetrahedron Lett*., **2002,** 43, 887.
[66] Gordon, C. M.; McCluskey *Chem. Comm.*, **1999**, 1431. Prepared in quantitative yield by addition of allyl magnesium bromide to 3-phenyl-2-methyl-propenal.
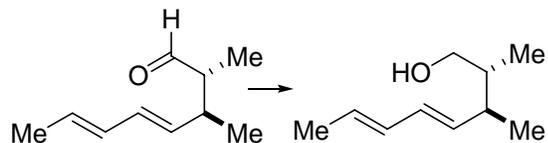
syn-(4E,6E)-2,3-Dimethylocta-4,6-dien-1-ol (27a): General Procedure **D** was followed employing 304 mg of **25a** (2.00 mmol) and 2 mol% catalyst (18 mg iridium dimmer, 33.6 mg PCy$_3$ and 13.6 mg NaBPh$_4$), the initial reaction time of 17 h (no PPh$_3$) at ambient temperature in CH$_2$Cl$_2$ to afford *syn*-(4*E*,6*E*)-2,3-dimethylocta-4,6-dien-1-al **26a** (*syn: anti* = 94: 6). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.61 (d, J = 1.9 Hz, 1H), 5.93-6.04 (m, 2H), 5.53-5.69 (m, 1H), 5.40-5.49 (m, 1H), 2.52-2.64 (m, 1H), 2.31 (m. 1H), 1.70 (d, J = 6.1 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 7.0 Hz, 3H) ppm. Diisobutylaluminum hydride reduction of **26a** followed by purification by flash chromatography (15 % EtOAc/hexanes) gave 207 mg (68 %) of the title compound as colorless oil. IR (liquid film): 3391, 2961, 1723, 1454, 1377, 1038, 989 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.95-6.08 (m, 2H), 5.56-5.66 (m, 1H), 5.46-5.55 (m, 1H), 3.59 (dd, J = 10.7, 5.8 Hz, 1H), 3.44 (dd, J = 10.7, 6.4 Hz, 1H), 2.19 (m, 1H), 1.74 (d, J = 6.1 Hz, 3H), 1.59 (m, 1H), 0.99 (d, J = 4.5 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.3, 131.6, 129.5, 127.3, 66.6, 40.9, 38.8, 17.9, 16.7, 13.7 ppm; MS (EI, 70 V) *m/z*: 154 (M$^{+\cdot}$), 125, 109, 95, 81, 67, 55. HRMS *m/z* calcd for C$_{10}$H$_{18}$O (M$^{+\cdot}$): 154.1358, found 154.1369.
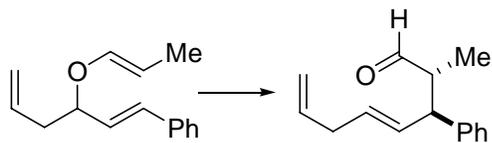
syn-(E)-2-Methyl-3-phenylocta-4,7-dienal (29b): General Procedure **D** (2 mol% catalyst loading, CH$_2$Cl$_2$) was followed employing 214 mg of **25b** (1.00 mmol) and an initial reaction time of 15 min (instead of 30 min), Purification by short column flash chromatography (2 % Et$_2$O/hexanes) gave 148 mg (70 %) of ether **28b** as colorless oil; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.25-7.41 (m, 5H),

6.56 (d, J = 16.0 Hz, 1H), 6.10-6.18 (m, 2H), 5.78-5.92 (m, 1H), 5.08-5.16 (m, 2H), 4.96 (dq, J = 12.3, 6.7 Hz, 1H), 4.25 (q, J = 6.6 Hz, 1H), 2.37-2.57 (m, 2H), 1.53 (dd, J = 6.8, 1.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 145.0, 136.4, 133.7, 131.9, 129.1, 128.5, 127.7, 126.5, 117.4, 101.3, 80.3, 39.8, 12.4 ppm. Then 3 mL 1,2-DCE was added into 148 mg of **28b** (0.70 mmol) and refluxed 12 h, remove the solvent to give aldehyde **29b** (*syn : anti* = 97 : 3) as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.70 (d, J = 3.1 Hz, 1H), 7.19-7.36 (m, 5H), 5.66-5.86 (m, 2H), 5.56 (dt, J = 15.4, 6.3 Hz, 1H), 4.98- 5.04 (m, 2H), 3.52 (t, J = 8.9 Hz, 1H), 2.72-2.84 (m, 3H), 0.92 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.7, 141.4, 136.3, 131.9, 129.9, 128.6, 127.9, 126.6, 115.4, 50.7, 36.4, 12.6 ppm; MS (EI, 70 V) *m/z*: 214 (M$^{+\cdot}$), 199, 173, 157, 141, 129, 115, 103, 91, 77, 65. HRMS *m/z* calcd for C$_{15}$H$_{18}$O (M$^{+\cdot}$): 214.1358; found 214.1362.
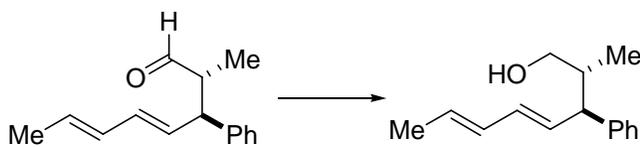
syn- (4E,6E)-2-Methyl-3-phenylocta-4,6-dien-1-ol (27ba′): General Procedure **D** (2 mol% catalyst loading, CH$_2$Cl$_2$) was followed employing 148 mg of **29b** (0.70 mmol) and the initial reaction time 12 h at ambient temperature. Solvent was removed to afford the *syn*-(4*E*,6*E*)-2-methyl-3-phenylocta-4,6-dien-1-al **27ba** (*syn: anti* = 97: 3). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.74 (d, J = 2.8 Hz, 1H), 7.41-7.23 (m, 5H), 6.17-6.02 (m, 2H), 5.86-5.62 (m, 2H), 3.58 (t, J = 8.9 Hz, 1H), 2.89-2.76 (m, 1H), 1.78 (d, J = 7.5 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.5, 141.2, 131.8, 131.1, 130.8, 129.1, 128.5, 127.8, 126.6, 50.8, 50.3, 17.9, 12.5 ppm. Diisobutylaluminum hydride reduction of **27ba** followed by purification by flash chromatography (20 % EtOAc/hexanes) gave 127 mg (86 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.12-

7.29 (m, 5H), 6.05 (dd, J = 14.6, 10.3 Hz, 1H), 5.97 (ddq, J = 14.4, 10.2, 1.5 Hz 1H), 5.74 (dd, J = 14.1, 9.3 Hz, 1H), 5.58 (dq, J = 14.4, 6.7 Hz), 3.64 (dd, J = 10.6, 4.4 Hz, 1H), 3.47-3.58 (m, 1H), 3.12 (t, J = 9.3 Hz, 1H), 1.97-2.06 (m, 1H), 1.68 (d, J = 6.5 Hz, 3 H), 1.46 (s, 1H), 0.75 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.4, 133.7, 131.2, 130.8, 128.5, 128.4, 127.9, 126.2, 66.6, 52.7, 40.5, 18.0, 15.2 ppm; MS (EI, 70 V) m/z: 216 (M$^{+\cdot}$), 157, 141, 129, 117, 105, 91, 84, 77, 65. HRMS m/z calcd for C$_{15}$H$_{20}$O (M$^{+\cdot}$): 216.1514; found 216.1511.
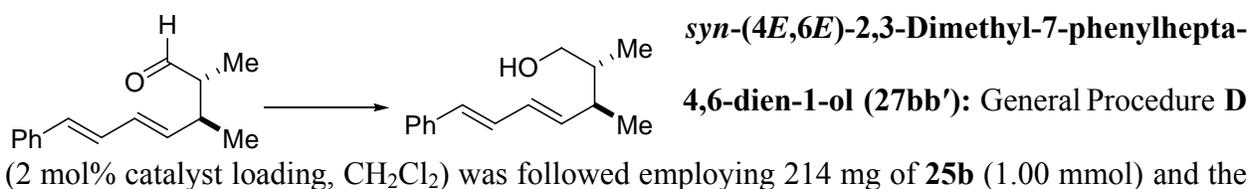
syn-(4E,6E)-2,3-Dimethyl-7-phenylhepta-4,6-dien-1-ol (27bb′): General Procedure **D** (2 mol% catalyst loading, CH$_2$Cl$_2$) was followed employing 214 mg of **25b** (1.00 mmol) and the initial reaction time 3 h (no PPh$_3$, no heating). Solvent was removed to afford the a mixture of *syn-(4E,6E)-2-methyl-3-phenylocta-4,6-dien-1-al* **27ba** and *syn-(4E,6E)-2,3-dimethyl-7-phenylhepta-4,6-dien-1-al* **27bb** (67: 33), Diisobutylaluminum hydride reduction of the mixtuure followed by purification by flash chromatography (20 % EtOAc/hexanes) gave 193 mg (90 %) of a mixture of the title compound **27ba′** and **27bb′** as colorless oil, including 28 mg pure **27bb′**. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.18-7.40 (m, 5H), 6.75 (dd, J = 15.6, 10.3 Hz, 1H), 6.47 (d, J = 15.7 1H), 6.21 (dd, J = 15.2, 10.3 Hz), 5.78 (dd, J = 15.2, 8.2 Hz), 3.62 (dd, J = 10.6, 5.9 Hz, 1H), 3.48 (dd, J = 10.6, 6.4 Hz, 1H), 2.25-2.37 (m, 1H), 1.61-1.72 (m, 1H), 1.32 (s, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 140.0, 137.5, 130.5, 129.6, 129.2, 128.5, 127.2, 126.1, 66.6, 40.9, 38.9, 16.5, 13.7 ppm; MS (EI, 70 V) m/z: 216 (M$^{+\cdot}$), 183, 169, 157, 142, 129, 115, 105, 91, 79, 65. HRMS m/z calcd for C$_{15}$H$_{20}$O (M$^{+\cdot}$): 216.1514; found 216.1510.

3.0 ENANTIOSELECTIVE CLAISEN REARRANGEMENTS ENABLED BY CATALYTIC ASYMMETRIC DI(ALLYL) ETHER SYNTHESES

3.1 ICR REACTION WITH ENANTIOENRICHED SUBSTRATES

The success of ICR reaction suggested an operationally simple one-step strategy for preparing an enantioenriched Claisen adduct from enantioenriched di(allyl) ether, whose chiral centers can be easily introduced from asymmetric nucleophilic addition. Rigorous translation of substrate chirality to the incipient stereogenic centers emerging from bond reorganization is among the defining characteristics of [3,3] sigmatropic rearrangements. Thermal Claisen rearrangements routinely prove *via* chair-like transition states that substituents residing at the carbinol stereocenter (R^{eq}) are oriented in pseudoequatorial positions. Considering that the ICR methodology makes the di(allyl) ether the immediate precursor to the allyl vinyl ether Claisen substrate, this analysis implicates an enantioenriched di(allyl) ether as a direct progenitor of an asymmetric aliphatic Claisen rearrangement. The enantioenriched (*S*)-(*E*)-1-phenyl-penten-3-ol (**30a**) was prepared by the an amino alcohol (*N*-methyl-α,α-diphenylprolinol, **33**)-catalyzed addition of diethylzinc to cinnamaldehyde.[67] Following the *O*-allylation, subjecting the resulting (*S*)-di(allyl) ether **31a** (84% ee) to the optimized ICR conditions delivered an enantioenriched

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[67] The method for preparing the amino alcohol ligand and the procedure for diethyl zinc addition to aldehyde: Soai, K.; Okawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987,** *109*, 7111-7115. The enantioselectivity in the diethyl zinc addition was not optimized.

pentenal (2*S*, 3*R*)-**32a** with good chairality transfer (84 % ee) and good diastereoselection (*syn:*

anti = 95: 5, Scheme 25).
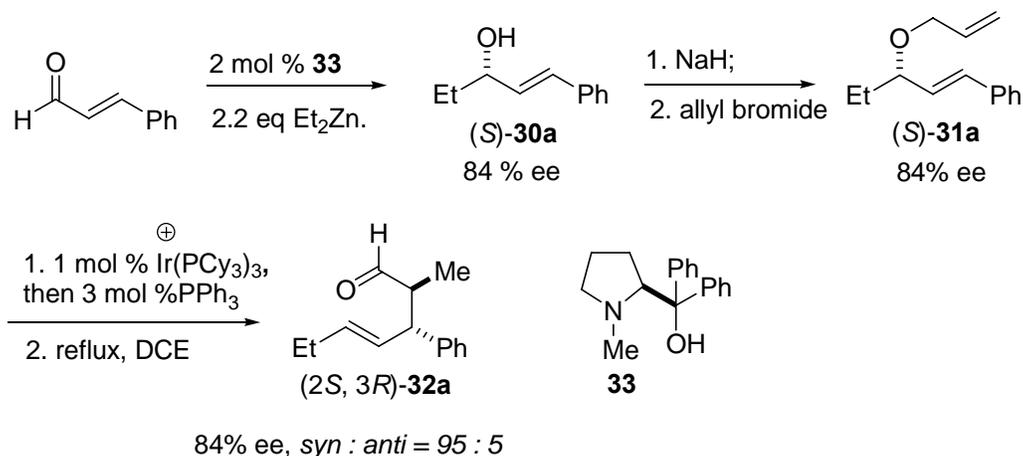
Scheme 25. ICR reaction of enantioenriched di(allyl) ether

3.2   ONE-POT REACTION FROM ALDEHYDE TO ENANTIOENRICHED

DI(ALLYL) ETHER

3.2.1 Reaction development

Reaction design merging a catalytic asymmetric organometallic-aldehyde addition with an *in situ* *O*-allylation of the reaction intermediate metal alkoxide is attractive for preparing the enantioenriched di(allyl) ether in a single step. Combining this reaction sequence with a subsequent ICR reaction of enantioenriched di(allyl) ethers would provide the enantioenriched Claisen adducts in two steps from the easily obtained precursor (Figure 24).[68]

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[68] After our result has been published in *J. Am. Chem. Soc.* **2006**, *128*, 4232-4233, Trost reported a three-step strategy using Pd(0)-catalyzed asymmetric allylic alkylation-ICR reaction, see: Trost, B. M.; Zhang, T. *Org. Lett.* **2006**, *8*, 6007-6010.

asymmetric addition $R^{eq}M$

in situ allylation

Claisen rearrangement

Ir(PCy₃)₃BPh₄ isomerization

first step

second step
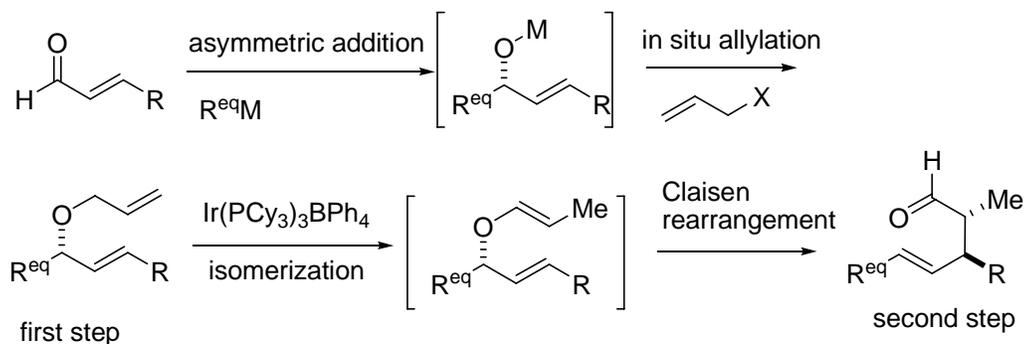
Figure 24. Cascade addition/allylation reactions following ICR reaction

With the goal of using a catalytic asymmetric transformation to establish substrate enantioenrichment, an amino alcohol-catalyzed diethylzinc-enal addition was selected to prepare the requisite enantioenriched di(allyl) ether ICR substrates for extensive data with readlly available reagent.[69] Nugent's MIB ligand[70] had previously been demonstrated to be a satisfactory catalyst for the diethylzinc-enal addition.[71] However, little information existed regarding the potential for affecting the direct *O*-alkylation of the zinc alkoxide reaction intermediates. The covalent character of the Zn-O bonds and the highly aggregated nature of zinc alkoxides were expected to make direct *O*-alkylation difficult. For evaluating these reactions, cinnamaldehyde reacted with Et₂Zn (1.0 equivalent) with 2 mol% (-)-MIB catalyst to afford the proposed intermediate enantioenriched zinc alkoxide **S-30a′** in 93% ee,[72] whose direct *O*-allylation with allyl bromide failed to afford any desired di(allyl) ether. A solution merging the

[69] Review of dialkyl zinc addition to aldehyde, see: (a) Soai, K.; Shibata, T.; In *Comprensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, **1999**; pp 911-922. (b) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757-824. recent paper (c) Kang, S. W.; Ko, D. H.; Kim, K. H.; Ha, D. C.; *Org. Lett.* **2003**, *5*, 4517-4519.

[70] (a) Nugent, W. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1369. (b) Chen, Y. K.; Jeon, S. J.; Walsh, P. J.; Nugent, W. A.; Kendall, C.; Wipf, P.; *Org. Synthese* **2005**, *82*, 87. (c) (-)-MIB catalyzed diphenylzinc addition to aldehyde, including α,β-unsaturated aldehyde, see: Kim, J. G.; Walsh, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 4175-4178.

[71] Lurain, A. E.; Maestri, A.; Kelly, A. R.; Carroll, P. J.; Walsh, P. J.; *J. Am. Chem. Soc.* **2004**, *126*, 13608.

[72] The enantiomer excess is determined by HPLC separation of (*S*)-(*E*)-1-phenyl-penten-3-ol afforded after workup with water.

addition and allylation was suggested by Lee's report that bis(alkoxy)zinc species undergo Pd(0)-catalyzed *O*-allylation (eq 12).[73]

$$PhCH_2OH \xrightarrow[\substack{2) \ 5 \ mol\% \ Pd(PPh_3)_4 \\ allyl \ acetate}]{1) \ 0.5 \ eq \ Et_2Zn} \quad \diagup\!\!\!\diagup\!\!\!\diagdown OCH_2Ph \quad (12)$$
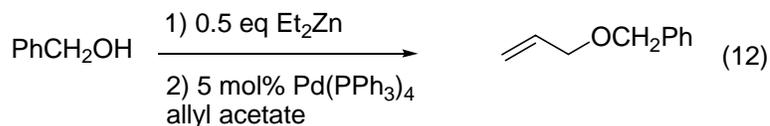
But subjecting the mixed ethylzinc alkoxide **30a′** to the Pd(0)-catalyzed allylation under the same condition afforded the alcohol **30a** as the major product, with a mixture of ethers as minor (< 10 % yield) products. From the NMR spectra, the mixture includes the desired di(allyl) ether (**31a**) and by-product triene ether (**34**). The HPLC isolation of enantiomers indicated that the di(allyl) ether **31a** was enantioenriched pure (93 % ee) but the triene ether **34** was racemic. The combined yield was improved to 40 % when 0.65 equivalent instead of 1.0 equivalent diethylzinc was used in this reaction (Scheme 26).
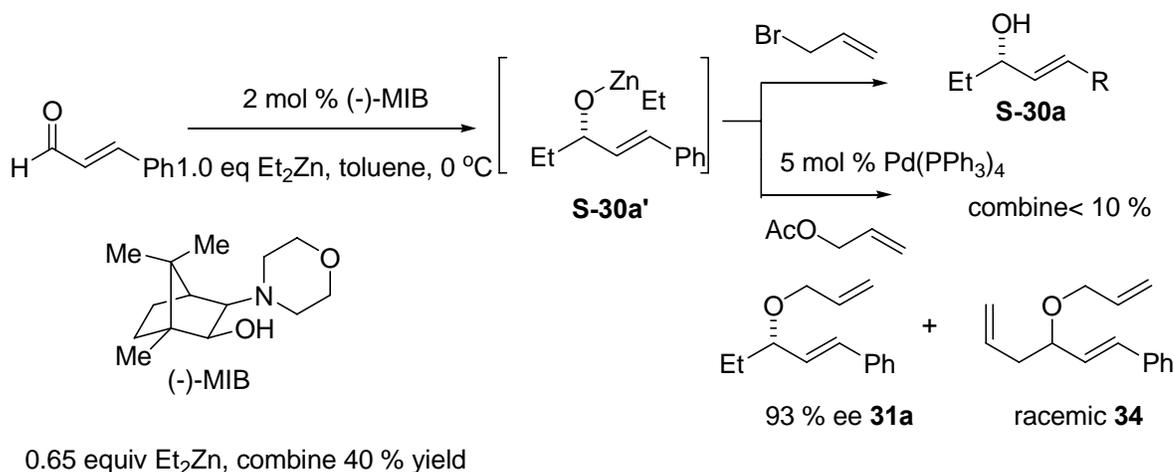
Scheme 26. Initial investigation for cascade addition/allylation process

It has been reported that the transmetalation of diethyl zinc or ethyl zinc alkoxide with π-allylpalladium complex afforded allyl zinc intermediates and EtPdOAc, which afforded Pd(0) catalyst and ethyl acetate after reductive elimination. The nucleophlic allylic zinc reagents

[73] Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369-4372.

caused the allylation of aldehydes, ketones and even esters in the absence of any catalyst (Figure 25).[74]
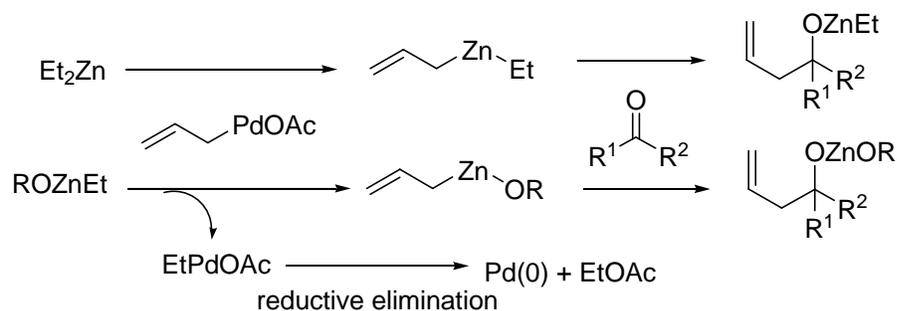
Figure 25. The Pd-Zn transmetalation and allylation

Based on the above discussion, it is believed that the addition of unreacted cinnemaldehyde with formed allyl zinc reagent (**35**) afforded the asymmetric bis(alkoxy)zinc species (**36**). After the Pd(0)-catalyzed *O*-allylation, the enantioenriched di(allyl) ether **31a** and the triene ether **34** were afforded (Figure 26). For blocking this Pd-Zn transmetalation process, the more basic ethyl ligand should be replaced by the less reactive oxygen ligand.
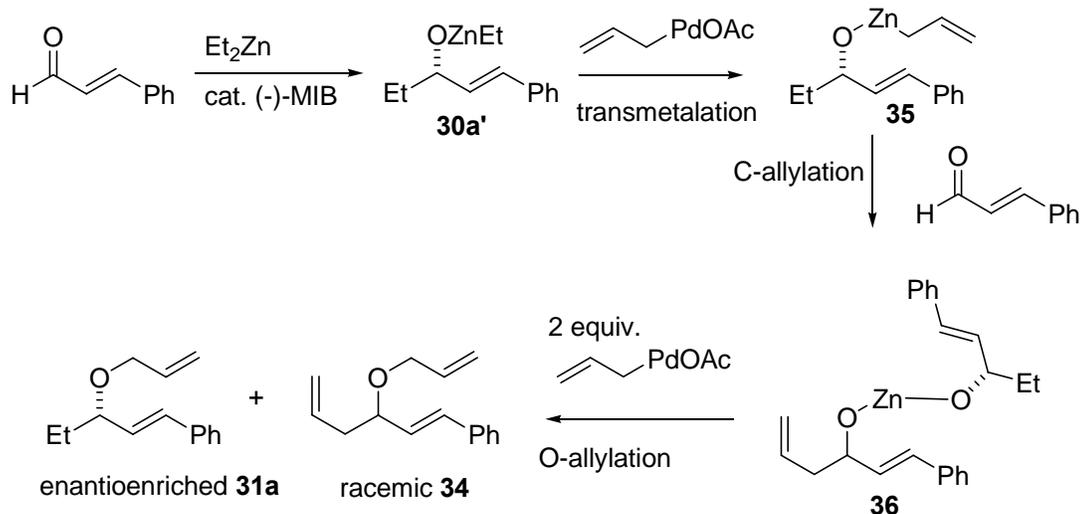
Figure 26. Mechanism of the formation of by-product 34

[74] Yasui, K.; Yajima, T.; Taniseki, Y.; Fugami, K.; Tanaka, A.; Tamaru, Y. *Tetrahedron Lett.* **1993**, *34*, 7619.

For removing this ethyl ligand, an active proton was required to react with ethylzinc alkoxide to release the ethane. The addition of one equivalent alcohol generated an asymmetric bis(alkoxy)zinc species, which consumed an additional equivalent electrophiles in the Pd(0)-catalyzed allylation step (Scheme 27) to form a mixture of two allyl ethers.
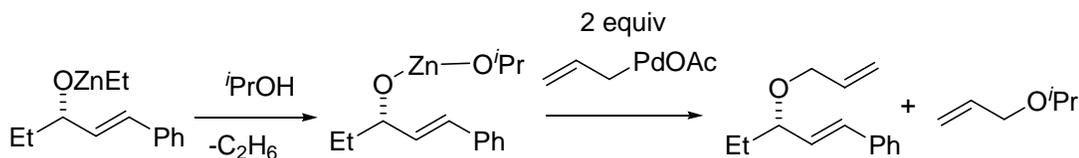
Scheme 27. Alcohols as additive in one pot reaction

Acetic acid was a good choice for this specific aim because the formed zinc acetate is less basic than the zinc alkoxide to ensure no side reactions. Treating the ethylzinc alkoxide **S-30a′** with 1.0 equivalent acetic acid caused the more basic alkyl ligand to be selectively protonated to afford the alkoxyzinc carboxylate **S-30a″**, which subsequently reacted with the π-allylpalladium complex[75] to deliver the desired di(allyl) ether **S-31a** in 79 % yield (93 % ee). This Pd(0)-catalyzed allylation procedure was slow at ambient temperature, the completion of the C-O coupling reaction required 5 days as monitored by TLC. But the reaction was much accelerated at warm conditions, the reaction was completed in 6 h at 55 °C in THF solvent. Enantioenriched di(allyl) ether in hand, it was subjected to the standard ICR condition to afford the enantioenriched 2,3-*syn* disubstituted heptenal Claisen rearrangement product (**(2R,3S)-32a**) with enantiomeric purity identical to that of the di(allyl) ether starting material (93 % ee, Scheme 28). The successful execution of this reaction affirmed our original reaction design as an efficient, two-step approach to the enantioselective aliphatic Claisen rearrangement.

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[75] The *in situ* Pd(0) catalyst was produced from 5 mol % Pd(OAc)$_2$ and 25 mol % PPh$_3$ instead of the preformed Pd(PPh$_3$)$_4$ catalyst in Lee's precedent. Then adding 1.5 equivalent of allyl acetate provided a convenient condition for this C-O coupling reaction.
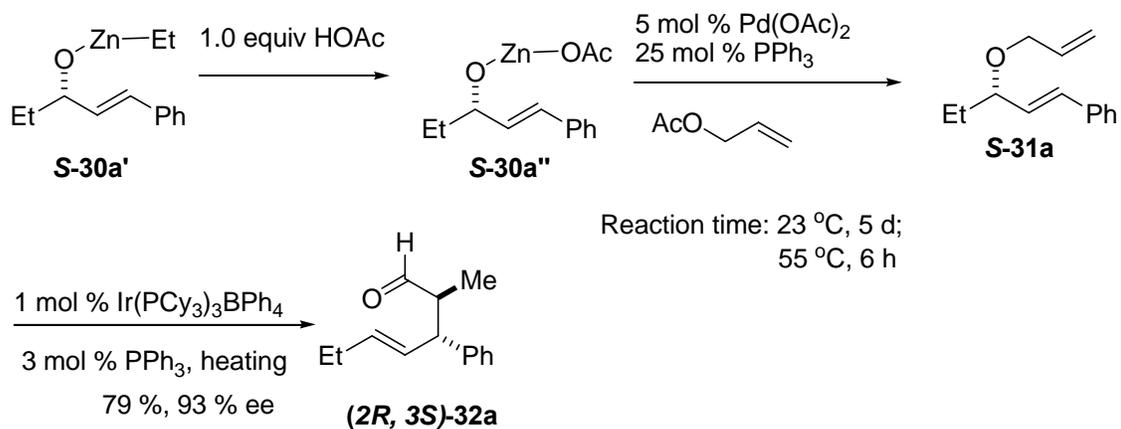
Scheme 28. Synthesis and ICR of enantioenriched di(allyl) ethers

3.2.2 One-pot addition/allylation followed by ICR for the preparation of enantioenriched Claisen rearrangement products

Merging this one-step enantioselective di(allyl) ether synthesis with a subsequent ICR reaction provided access to a variety of enantioenriched Claisen adducts from readily obtained diethylzinc and conjugated enal reaction partners (Table 5). The merged addition-allylation sequence afforded enantioenriched di(allyl) ether ICR substrates incorporating C3 aryl (entry **a, b**), alkenyl (entry **c**), aliphatic alkyl (entry **d**), or oxygen-substituted alkyl substituents (entry **e**) in good yields (73-87 %) and high enantioselectivies (88-98 % ee). Each of these di(allyl) ether substrates participated in the ICR reaction with faithful translation of chirality, delivering the pentenal derivatives with high absolute and relative stereocontrol. The ICR reaction of di(allyl) ether possessing trisubstituted allyl ether moiety (entry **f**) proceeds with a similarly high stereoselectivity albeit with some erosion of olefin stereochemistry due to high Claisen rearrangement temperatures.

Table 5. Synthesis and ICR of enantioenriched di(allyl) ethers 31a-f

31a-e → **32a-e**
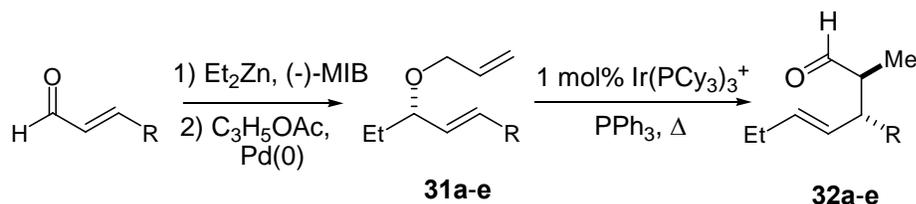
entry	% yield **31** (% ee)[a]	% yield **32** (*syn:anti*)[b]	% ee **32**[c]
a	**31a** (R = Ph)75 (93)	**32a** (R = Ph)82 (95:5)	92
b	**31b** (R = 2-furyl)79 (96)	**32b** (R = 2-furyl)75 (95:5)	96
c	**31c** (R = *E*-CHCHPh)87 (93)	**32c** (R = *E*-CHCHPh)77 (95:5)	93
d	**31d** (R = $^nC_5H_{11}$)80 (88)	**32d** (R = $^nC_5H_{11}$)70 (97:3)	87
e	**31e** (R = CH$_2$OBn)73 (93)	**32e** (R = CH$_2$OBn)60 (96:4)	92
f[e]	**31f** 84 (98)	**32f** 81 (92:8)[d]	97

a) Enantiomeric excess determined for allylic alcohol obtained by protonation of the zinc alkoxide prior to *O*-allylation. b) Diastereomer ratios determined by ^{1}H NMR of crude product mixtures. c) Enantiomer ratios determined by chiral HPLC or GC. d) The Claisen adduct **32f** was obtained as an 83:17 *E:Z* mixture of olefin isomers. Enantiomer and diastereomer ratios are reported for the *E* isomer (eq 13).

31f → **32f** (*E/Z* = 83: 17)   (13)
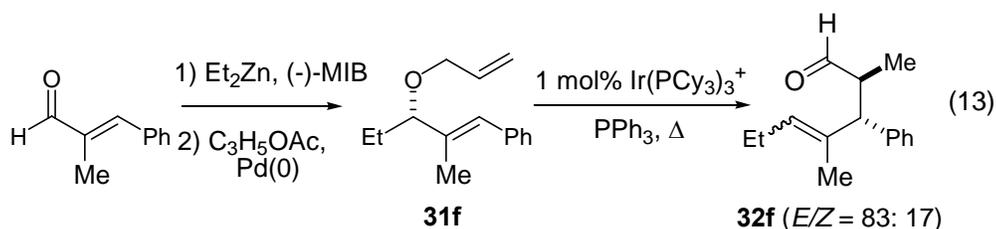
A benzyloxy-substituted di(allyl) ether (**31e**) offered the potential for a competing allyl ether isomerization pathway. The isomerization process was required to be quenched in a short time (10 min) to ensure that not much side isomerization product formed. The desired product (**32e**) was obtained in a modest yield (eq 14). A longer reaction time increased the yield of by-product homoallyl-vinyl ether (**31e′**)

Equation (14) scheme:
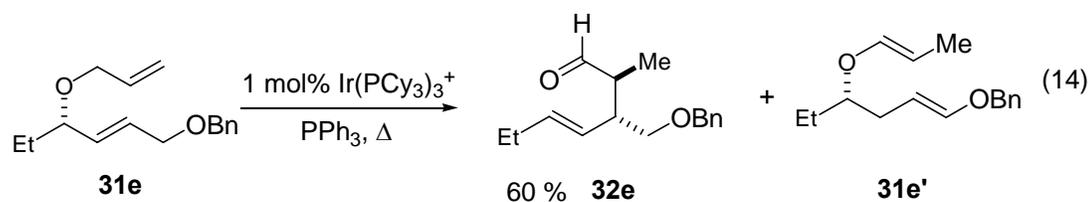
1 mol% Ir(PCy$_3$)$_3$$^+$, PPh$_3$, Δ

31e → 60 % **32e** + **31e'** (14)

The asymmetric di(allyl) ether synthesis was not limited to procedures employing only unsubstituted allyl acetate as the incipient electrophile. Some substituted allyl acetates worked as well. Compound (*E*)-3-(trimethylsilyl)allyl acetate provided the derived allyl Pd(0) complexes with a strong bias for regioselective nucleophilic addition because of the large size of the trimethylsilyl group. Because of this size, the isomerization of this substituted allyl ether was more difficult than that of other entries. Upon treatment of 2 mol% catalyst **18** and quenching in 6 h at 50 °C, the thermolysis afforded a 50% yield Claisen product **38** plus recovered staring materials (Scheme 29).

Scheme 29 content:

1) Et$_2$Zn, (-)-MIB 2) Pd(0)

TMS⁀⁀OAc

37, 77 %, 93 % ee

2 mol% Ir(PCy$_3$)$_3$$^+$, 50 °C, 6 h

PPh$_3$ heating

38, 50 %, 93 % ee, *syn : anti* = 95: 5
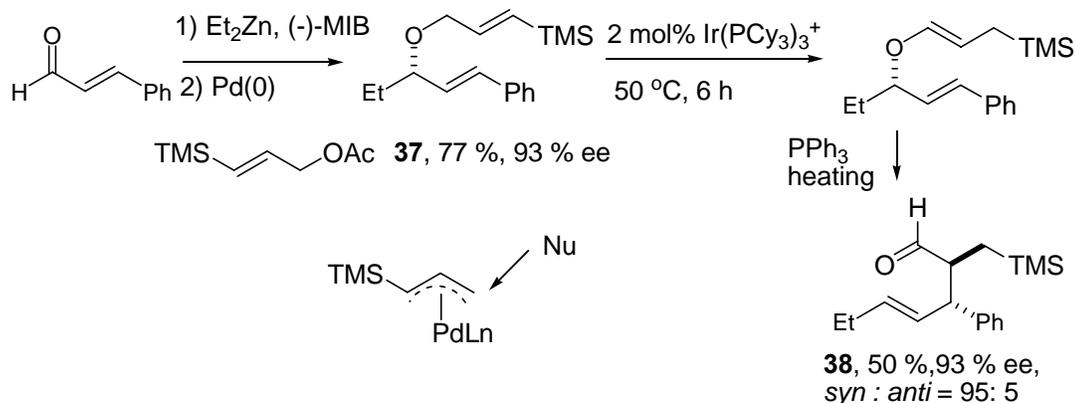
Scheme 29. Preparation and ICR of TMS-substituted di(allyl) ether

But (*E*)-but-2-enyl acetate provided a very poorly regioselective allylation (the branched product **39** : the non-branched product **40** = 2 : 1. The **40** was a mixture of *syn-* and *anti-* diastereomers and the **39** was a mixture of *E-* and *Z-* isomers). Upon treatment with the ICR conditions, the di(allyl) ether **39** afforded a very low yield of enal (**41**). No ICR was observed in the branched di(allyl) ether **40** (Scheme 30).
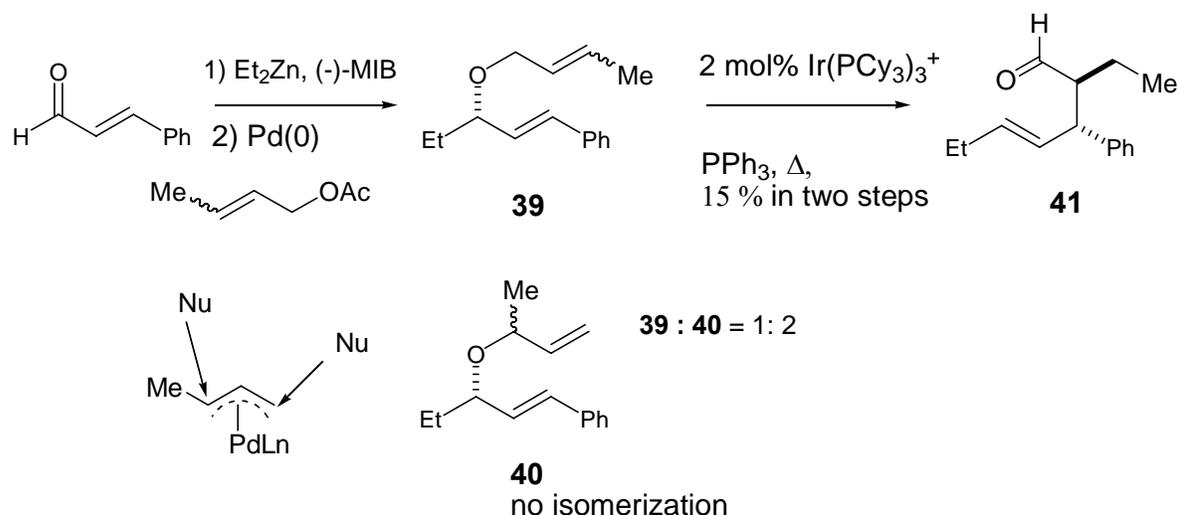
Scheme 30. Poor selectivity afforded in the reaction with crotyl acetate

3.2.3 One-step reaction from alkenyl zinc addition

Enantioenriched di(allyl) ether ICR substrates also were prepared from alkenyl zinc reagents[76] addition to aldehyde following the Pd(0)-catalyzed *O*-allylation. Alkenyl zinc reagents were readily obtained from hydroboration[77] or hydrozirconation[78] of alkynes followed by the transmetalation with a zinc species. The hydroboration was examined first for its cheap starting material. Walsh's modified procedure[79] was followed for the hydroboration. It was worthy of note that the solvents and borane source were important for the *in situ* Pd(0)-catalyzed allylation. The dimethylsulfide in the reagent $BH_3 \cdot Me_2S$ deactivated the Pd(0) catalyst to cause the

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[76] The addition of the divinyl zinc reagent, see: (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645-5648. The addition of the diisopropenyl zinc reagent, see: (b) Soai, K. Inorganica Chimica Acta. **1999**, *296*, 33. The addition of the vinyl zinc halide reagent, see: (c) Oppolzer, W.; Radinov, R. N. *Tetrahedron. Lett.* **1991**, *32*, 5777-5780.
[77] Trivinylborane reagent, see: (a) Srebnik, M. *Tetrahedron. Lett.* **1991**, *32*, 2449-2452. Alkyl vinyl zinc, see: (b) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta.* **1992**, *75*, 170-173. (c) Oppolzer, W.; Radinov, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 1593-1594.
[78] Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, 63, 6454-6455.
[79] For (-)-MIB-catalyzed addition of *in situ*-generated vinyl zinc reagents to benzaldehyde, see: (a) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem.. Soc.* **2002**, *124*, 12225-12231. (b) Lurain, A. E.; Walsh, P. J. *J. Am. Chem.. Soc.* **2003**, *125*, 10677-10683. For the paracyclophanes-catalyzed addition see: (d) Dahmen, S.; Brase, S. *Org. Lett.* **2001**, *3*, 4119-4122.

allylation to be impossible. The THF as ligand and solvent in the reagent $BH_3 \cdot THF$ was not a good solvent for the organozinc asymmetric addition to aldehydes. Considering these factors, the reagent $BH_3 \cdot THF$ was used first, then the solvent was changed from THF to pentane or toluene before transmetalation. Indeed this modified procedure worked, treatment of 2 equivalents of cyclohexene with $BH_3 \cdot THF$ afforded dicyclohexylborane in THF. Then 1-heptyne was added to prepare dicyclohexyl vinyl borane. After removal of the THF in vacuum and recharging pentane or toluene, diethylzinc (solution in hexanes) was added to afford ethyl vinylzinc reagent. The vinyl group was transfered to aldehydes in the presence of amino alcohol catalyst ((-)-MIB) to afford the enantioenriched ethylzinc alkoxide, which subsequently reacted with acetic acid. Finally species reacted with the π-allylpalladium complex to afford the enantioenriched di(allyl) ethers (**42a**) in 62 % yield (87 % ee) (Figure 27). Subjecting the di(allyl) ether **42a** to the ICR condition provided the pentenal with optical purity matching that of the di(allyl) ether precursor (**43a**, 86 % ee, 80 % yield). A sterically hindered terminal alkyne 3,3-dimethyl-1-butyne was subjected to the same condition to afford **42b**, which subsequently was treated under ICR conditions to afford the enantioenriched ICR adduct (**43b**, eq 15).
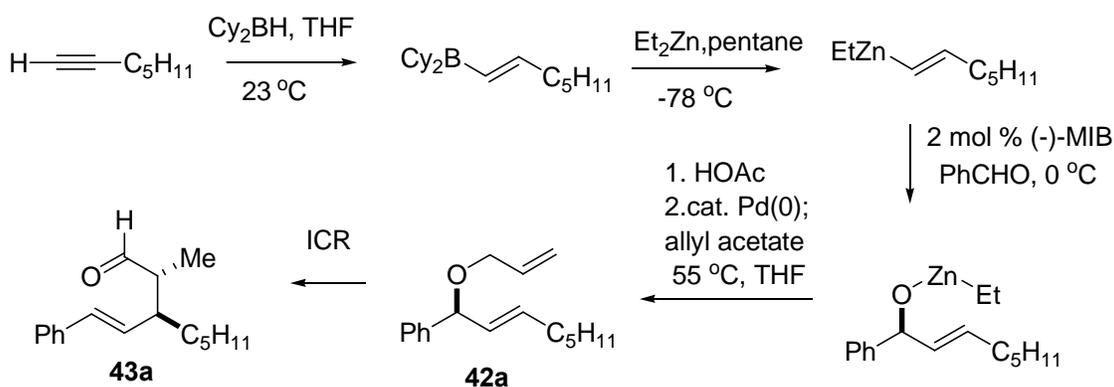
Figure 27. One step reaction from alkenyl zinc reagent for preparing enantioenriched di(allyl) ether

$$H\text{—}\!\!\equiv\!\!\text{—}\!\!\diagdown\!\!\diagup \quad \xrightarrow[\text{reaction}]{\text{one step}} \quad \text{42b} \quad \xrightarrow{\text{ICR}} \quad \text{43b} \quad (15)$$

63 %, 92 % ee   **42b**   80 %   **43b**
syn:anti = 92: 8
93 % ee
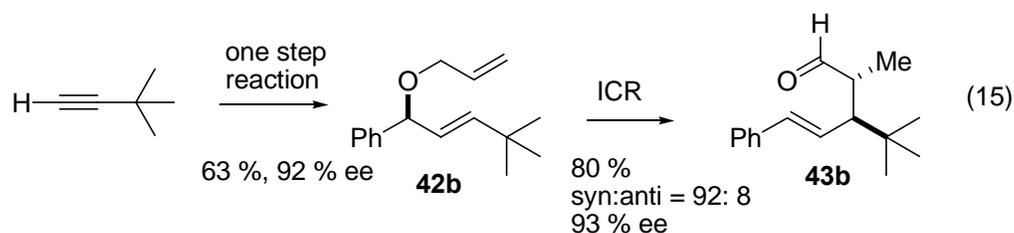
In conclusion, an asymmetric di(allyl) ether synthesis-ICR reaction sequence provided a convenient access to enantioselective aliphatic Claisen rearrangement products from easily obtained starting materials. This methodology offered an operationally simple, two step procedure for realizing highly enantio- and diastereoselective [3,3] sigmatropic rearrangements of aliphatic allyl vinyl ethers. The potential of this reaction technology to simplify the execution of the enantioselective Claisen rearrangements should allow these reactions to be readily integrated into asymmetric synthesis activities.

3.3 SYNTHESIS OF (+)-DI-*O*-METHYL CALOPIN

To exploite this two step protocol consist of the asymmetric di(allyl) ether synthesis and ICR reaction in target-based synthesis, we undertook a synthesis of a lactone (+)-7,8-*di-O*-methylcalopin (**44**). The calopins constitute a new class of mushroom metabolites, which are in part responsible for the bitter taste of *Boletus calopus* (German: Schönfussröhrling) and related mushrooms.[80] Common to all compounds are a δ-lactone ring with three contiguous stereogenic centres. Two syntheses have been reported: Steglish used a highly stereoselective ene reaction;[81] Toste used a Re-oxo complex-catalyzed coupling of propargyl alcohols with enantioenriched

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[80] Hellwig, V.; Dasenbrock, J.; Gräf, C.; Kahner, L.; Schumann, S.; Steglich, W. *Eur. J. Org. Chem.* **2002**, *17*, 2895–2904.
[81] (a) Ebel, E.; Knör, S.; Steglich, W. *Tetrahedron* **2002**, *59*, 123-129. (b) Ebel, E.; Knör, S.; Steglich, W. *Eur. J. Org. Chem.* **2002**, *17*, 2905-2912.

crotylsilanes.[82] Two of its three stereocentres were easily set by the addition/allylation ICR protocols and the third one (tertiary alcohol) is obtained through stereoselective nucleophilic additions (Figure 28).
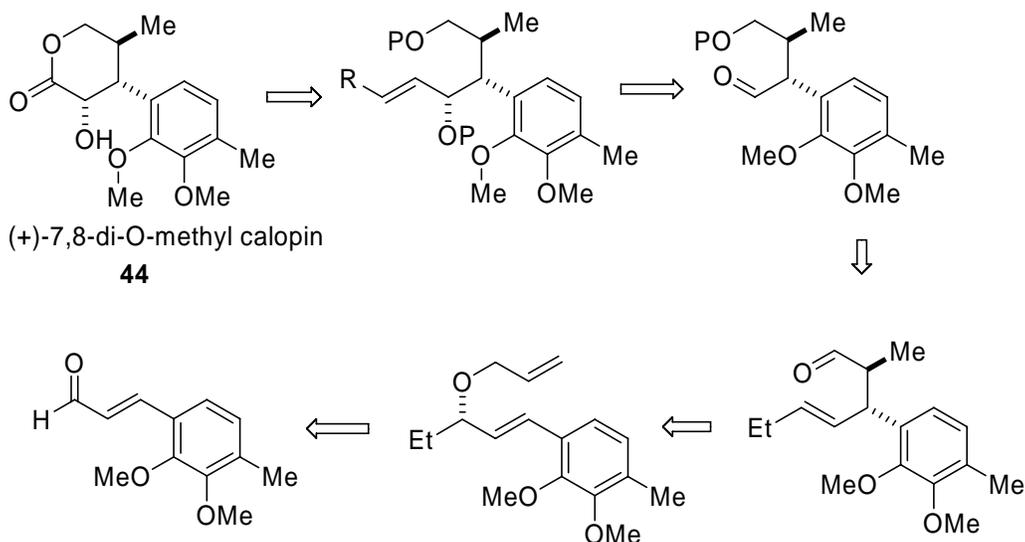
Figure 28. Retrosynthesis of (+)-7,8-*di-O*-methylcalopin

For realizing our addition-allylation-ICR protocol, the α,β-unsaturated aldehyde was required to be prepared first. There were some methodologies to prepare enals from aldehydes. Compound 2,3-dimethoxy-4-methylbenzaldehyde (**45**), which was obtained from metalation and methylation of 2,3-dimethoxybenzaldehyde,[83] was treated first with Wittig reagent Ph₃PCHCHO at reflux in benzene. But the yield of enal **46** was low (50 %) and some dienal was produced as a by-product (Scheme 31). The aldehyde **45** was treated with the Wittig reagent Ph₃PCHCOOMe to afford unsaturated ester **47** in high yield. Then the ester **47** was reduced to allyl alcohol **48**, which was oxidized to afford a 68 % yield of enal **46** in three steps.

[82] Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760-15761.
[83] Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078-1083.
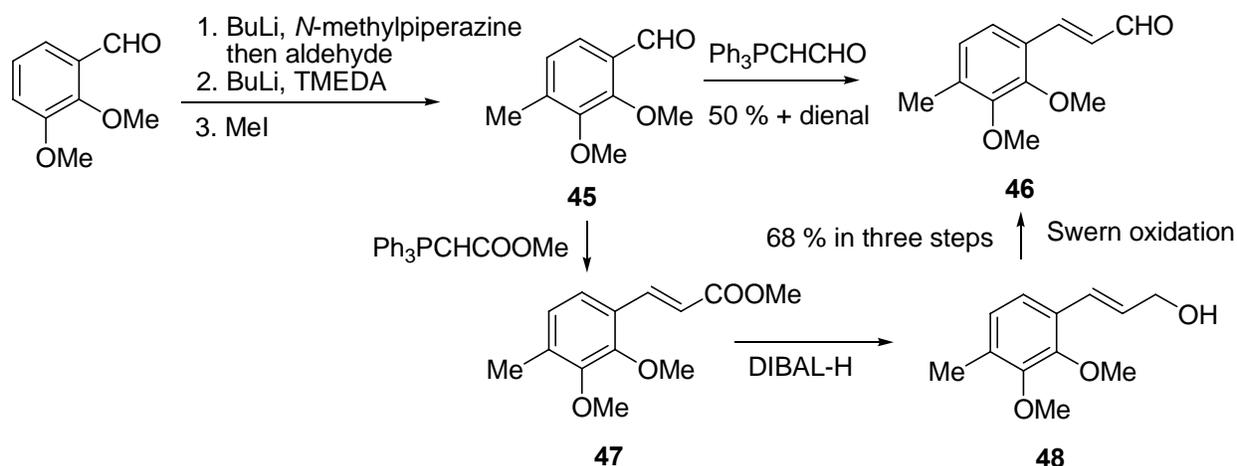
Scheme 31. Preparation of unsaturated aldehyde with Wittig olefination

This three steps strategy was not ideal for a concise synthesis. A superior method consisted of treating aldehyde **45** with Meyers's lithium (*Z*)-*tert*-butyl(2-(diethoxyphosphoryl)vinyl)amide (**49**),[84] which was prepared *in situ* by lithium *tert*-butyl(vinyl)amide with (EtO)$_2$P(O)Cl, to afford the unsaturated imine after elimination. The enal **46** was formed only after acidic work up so that no dienal was observed. In this reaction, 65 % of unsaturated aldehyde **46** was formed in a single step (Scheme 32).
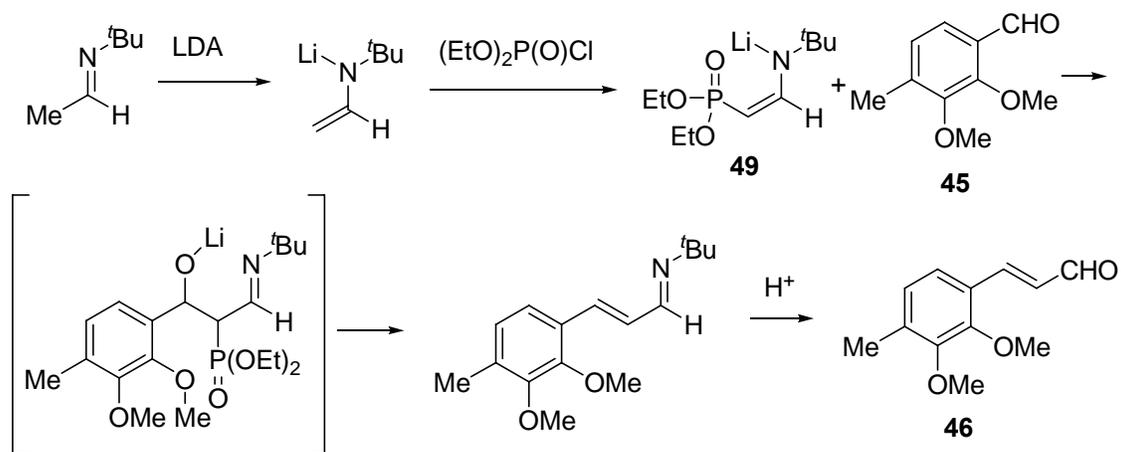
Scheme 32. One step preparation from aldehyde to enal

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[84] Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788.

Then the one-pot diethylzinc-enal addition/Pd(0)-catalyzed *O*-allylation reaction afforded the enantioenriched di(allyl) ether **50** with good yield and enantiomer excess (90 %, 90 % ee). The enantioenriched di(allyl) ether **50** was treated with 1.0 mol% Ir(PCy$_3$)$_3$BPh$_4$ and thermolysis at 80 °C to afford *syn*-2,3-disubstituted pentenal (**51**, *syn : anti* = 94 : 6 according to the crude proton NMR spectrum), which was reduced by DIBAL-H without further purification to alcohol (**52**) and protected by the benzyl group to yield **53**. 80 % yield was afforded in three steps. Then OsO$_4$-catalyzed dihydroxylation followed by NaIO$_4$ cleavage transformed the olefin to the desired aldehyde (**54**, *syn: anti*= 93: 7) (Scheme 33). [85]
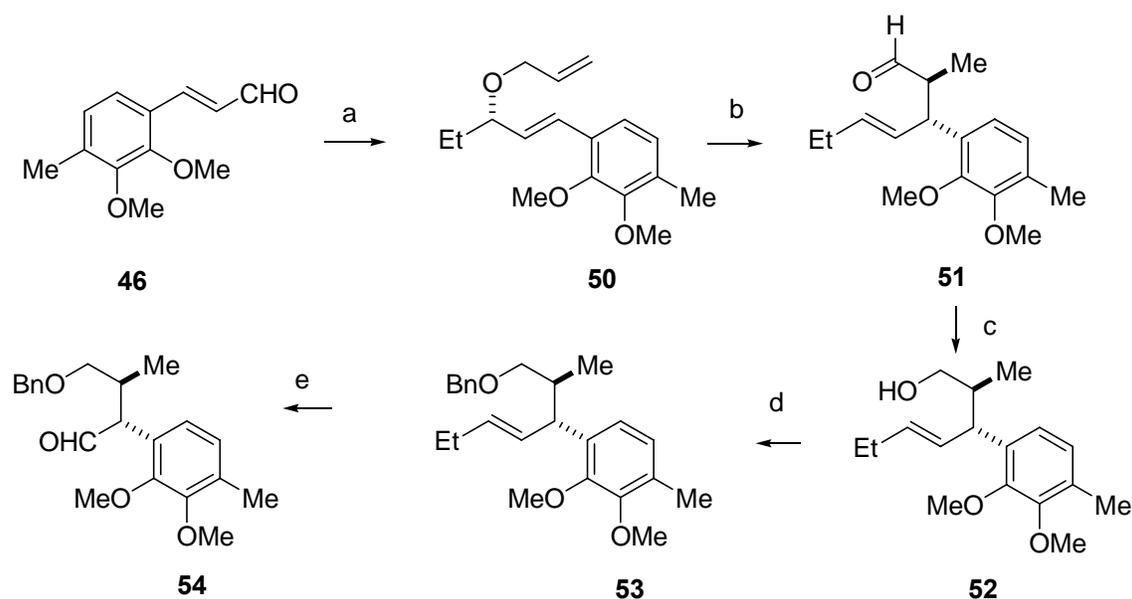
Reagent and conditions: (a) 1. 2 mol% (-)-MIB, Et$_2$Zn, toluene, 0 °C, then 1.0 equiv. HOAc; 2. 5 mol% Pd(OAc)$_2$, 25 mol% PPh$_3$, 1.5 equiv allyl acetate, THF, 60 °C, 90 %, 90 % ee; (b) 1 mol% Ir(PCy$_3$)$_3$BPh$_4$,DCE/acetone 50, ambient temperature, then 3 mol% PPh$_3$, 80 °C, 12 h, *syn : anti* = 94 : 6; (c) DIBAL-H, -78 °C; (d) NaH, BnBr, THF, 60 °C, 80 % in three steps; (e) 1. 5 mol% OsO$_4$, *N*-methyl-morpholine oxide, 2. NaIO$_4$, 78 %, *syn : anti* = 93: 7.

Scheme 33. One pot reaction followed by ICR

For the next step, we investigated a Felkin favored nucleophilic addition to aldehyde **54** to obtain desired diastereomer of the 3,4-*anti* secondary alcohol **55** (Figure 29). The vinyl

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[85] Ozonolysis afford aldehyde with worse diastereomer because of epimerization.

Grignard reagent afforded near 1 : 1 ratio of two diastereomers. The alkenyl zinc reagent, [86] which was prepared from the terminal alkyne through hydrozirconination (Cp$_2$ZrHCl) and transmetalation (Et$_2$Zn), afforded a much better diastereomer ratio and the desired allyl alcohol **55** was isolated with 67 % yield.
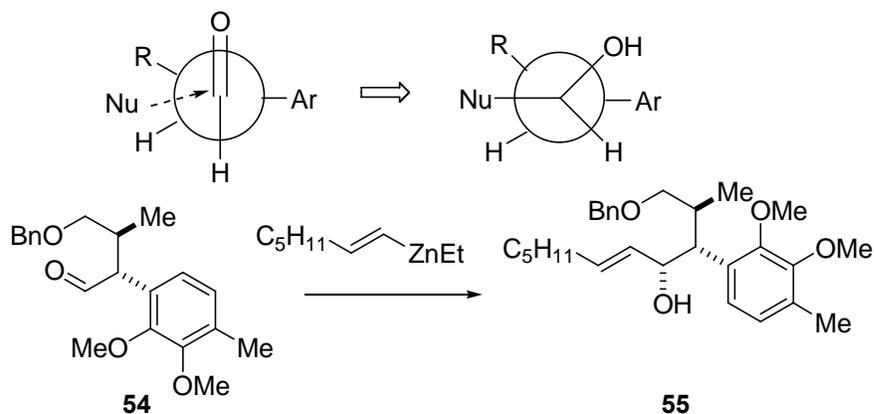
Figure 29. Felkin favored nucleophilic addition

The alcohol **55** was protected with a TBS group to provide **56** and the subsequent ozonolysis afforded the aldehyde **57**. Benzyl group deprotection (10 % Pd/C, 1 atm H$_2$) followed by the intramolecular cyclization afforded a δ-lactol (**58**) as a mixture of diastereomers, which was oxidized with 5 mol% tripropylamino perruthenate (TPAP) and excess NMO to afford a δ-lactone (**59**). TBAF caused the decomposition of the substrate in the deprotection of the TBS ether. Finally, the much milder reagent tris(dimethylamino)sulfonium difluorotrimethylsilicate (Me$_2$N)$_3$S F$_2$SiMe$_3$ (TASF) [87] was used to afford a clean product **44** in DMF at ambient temperature. The product has same ^{1}H NMR, ^{13}C NMR and [α]$_D$ data as those in reference (Scheme 34). [88]

[86] (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197.
[87] Application of TASF, see: Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436-6437.
[88] Ref 82.
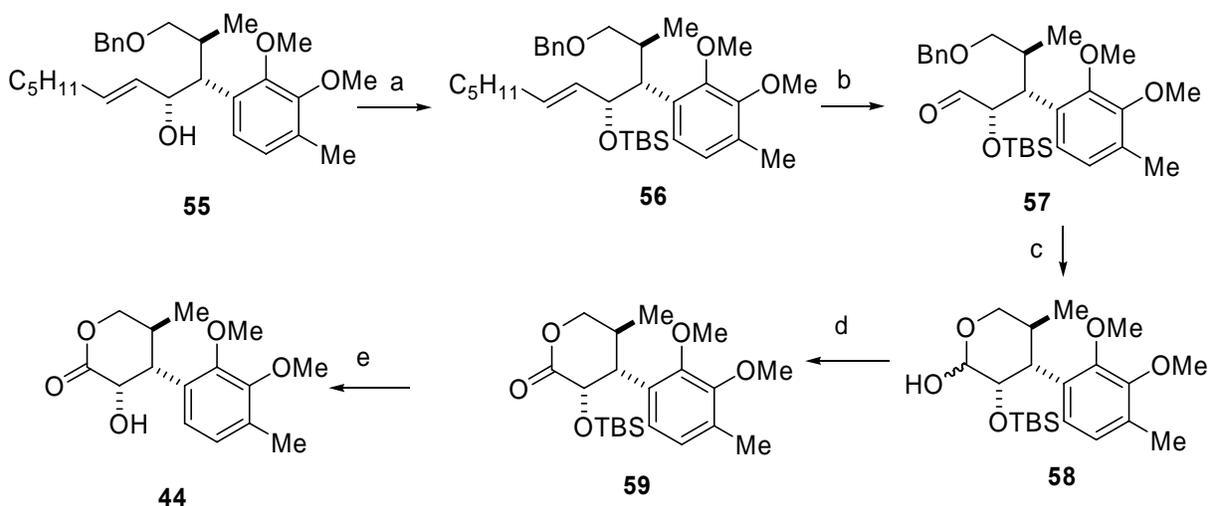
Reagents and conditions: (a) TBSCl, imidazole, DMF; (b) O_3, CH_2Cl_2, -78 °C, then Me_2S, -78-23 °C, 72 % in two steps; (c) 5 % Pd-C, H_2, EtOAc; (d) 5 mol% TPAP, *N*-methyl-morpholine oxide, CH_2Cl_2; (e) $(Me_2N)_3S$ F_2SiMe_3(TASF), DMF, 81 % in three steps.

Scheme 34. Synthesis route-finish the synthesis

The asymmetric Claisen reaction is still not a very popular process. This chapter describes clear solutions to this problem using an asymmetric alkyl zinc reaction. Claisen rearrangement proceeds quite smoothly in the presence of the Ir(I) complex as isomerization catalyst. The transformation from simple starting materials to complex, important functionality is a main goal of synthetic chemistry. We have described a method in which this is accomplished in a very efficient manner. All materials taken alone are very simple, standard reagents, but are creatively combined to generate important structures. The utility of this type of transformation is shown by the synthesis of (+)-calopin dimethyl ether.

3.4   EXPERIMENTAL SECTION

3.4.1 Experiment of section 3.2

3.4.1.1 One-pot reaction following ICR for preparation of enantioenriched Claisen adducts

General one-pot procedure E for preparing of enantioenriched di(allyl)ethers with diethyl zinc addition and Pd(0)-catalyzed allylation: To a 0 ^{o}C solution of 1,7,7-trimethyl-3-morpholinobicyclo [2.2.1]heptan-2-ol ((-)-MIB) (2 mol%, 0.02 mmol) in 2 ml of pentane or toluene was added Et$_2$Zn (1.0 M in hexanes, 1.05 equiv., 1.05 mmol) *via* syringe. A solution of aldehydes (1.0 mmol) in 1 ml pentane or toluene was added slowly (0.33 M final concentration in aldehydes) and the reaction mixture was stirred at 0 ^{o}C until the reaction was complete as monitored by TLC (about 6 h). A solution of acetic acid (1.05 equiv.) in 2 ml THF was added *via* syringe dropwise and the solution was stirred 10 min. A solution of palladium acetate (5 mol%), PPh$_3$ (25 mol%) and allyl acetate (1.5 equiv.) in anhydrous 10 ml THF was added and the reaction was heated at 60 ^{o}C for 12 h. The reaction mixture was cooled to ambient temperature and passed a short silica gel column to remove the salt, the solvent was removed *in vacuo* and the residue was purified as indicated. Enantioselectivity for the Et$_2$Zn addition was determined for the allylic alcohol obtained by quenching the Et$_2$Zn addition reaction with saturated NH$_4$Cl solution and extracting the resulting mixture with Et$_2$O (3x). The combined organic extracts were dried (MgSO$_4$), concentrated and purified allylic alcohol was obtained using indicated method.
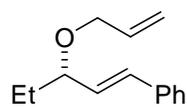
1-((*S,E*)-3-(allyloxy)pent-1-enyl)benzene (31a): General procedure **E** was followed employing cinnamaldehyde (132 mg, 1.0 mmol), 4.8 mg (-)-MIB (0.02 mmol), 1.05 ml Et$_2$Zn (1.0 M in hexanes, 1.05 mmol), 0.069 ml HOAc (1.05 mmol), 11.2 mg

Pd(OAc)$_2$ (0.05 mmol), 65.5 mg PPh$_3$ (0.25 mmol) and 0.163 ml allyl acetate (1.5 mmol). The crude product was purified by flash chromatograph on silical gel (2 % EtOAc in hexanes) to yield 151 mg (75 %) of the title compound as light yellow oil. Separating the allylic alcohol (**30a**) enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 1.0 ml/min, 10 % *i*-PrOH, 90 % hexanes, T$_r$ 13.4 (R) and 16.3 (S) provided the enantiomer ratio: 3R: 3S = 3.6: 96.4 (93 % ee).
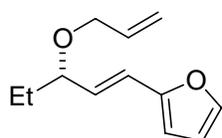
2-((*S*,*E*)-3-(Allyloxy)pent-1-enyl)furan (31b) : General procedure **E** was applied to *trans*-3-(2-furyl)-acrolein (122 mg, 1.0 mmol). The crude product was purified by column chromatography on silical gel (2 % EtOAc in hexanes) to yield 152 mg (79 %) of the title compound as light yellow oil. [α]$_D$ = -76.1 (c 3.44, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.36 (d, J = 1.8 Hz, 1H), 6.38 (dd, J = 3.3, 1.8 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H), 6.25 (d, J = 3.2 Hz, 1H), 6.04 (dd, J = 15.9, 7.7 Hz, 1H), 5.95 (dddd, J = 17.2, 10.4, 6.0, 5.1 Hz, 1H), 5.30 (dq, J = 17.2, 1.7 Hz, 1H), 5.18 (dq, J = 10.4, 1.5 Hz, 1H), 4.10 (ddt, J = 12.8, 5.1, 1.5 Hz, 1H), 3.89 (ddt, J = 12.8, 6.0, 1.4 Hz, 1H), 3.78 (q, J = 6.8 Hz, 1H), 1.55-1.78 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 152.31, 144.81, 135.14, 129.14, 120.20, 116.46, 111.17, 107.68, 81.01, 69.22, 28.58, 9.72 ppm; IR (liquid film): 2965, 2933, 2875, 1647, 1489, 1462, 1152, 1073, 1013, 964, 927, 734 cm^{-1}; MS (EI, 70 V): *m/z* 192 (M$^{+\cdot}$), 163, 151, 135, 121, 109, 91, 81, 65, 57; HRMS *m/z* calcd for C$_{12}$H$_{16}$O$_2$ (M$^{+\cdot}$): 192.1150. found 192.1153. The allylic alcohol (*S*,*E*)-1-(furan-2-yl)pent-1-en-3-ol (**30b**) was purified by flash chromatography on silica gel (16 % ethyl acetate in hexanes). [α]$_D$ = -6.4 (c 1.74, CHCl$_3$). Separation of the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.5

ml/min, 5 % *i*-PrOH, 95 % hexanes, T_r 18.69 (*R*) and 20.52 (*S*) provided the enantiomer ratio: 3*R*: 3*S* = 2.0: 96.6 (96 % ee).
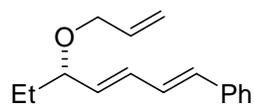
1-((*S,1E,3E*)-5-(Allyloxy)hepta-1,3-dienyl)benzene **(31c):** General procedure **E** was applied to (2*E*,4*E*)-5-phenylpenta-2,4-dienal[89] (1.4 mmol, 222 mg). The crude product was purified by column chromatography on silical gel (2 % EtOAc in hexanes) to yield 278 mg (87 %) of the title compound as a light yellow oil. $[\alpha]_D$ = -77.7 (c 2.33, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.22-7.45 (m, 5H), 6.82 (dd, J = 15.7, 10.5 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.36 (dd, J = 15.3, 10.4 Hz, 1H), 5.96 (dddd, J = 17.2, 10.3, 6.0, 5.2 Hz, 1H), 5.70 (dd, J = 15.3, 8.0 Hz, 1H), 5.31 (dq, J = 17.2, 1.7 Hz, 1H), 5.19 (dq, J = 10.3, 1.5 Hz, 1H), 4.10 (ddt, J = 12.8, 5.2, 1.5 Hz, 1H), 3.89 (ddt, J = 12.8, 6.0, 1.4 Hz, 1H), 3.75 (q, J = 6.9 Hz, 1H), 1.55-1.78 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 137.1, 135.2, 134.7, 132.6, 132.4, 128.6, 128.3, 127.5, 126.3, 116.5, 81.2, 69.2, 28.6, 9.8 ppm. MS (EI, 70 V): *m/z* 228 (M$^{+\cdot}$), 199, 187, 171, 157, 129, 115; HRMS *m/z* calcd for C$_{16}$H$_{20}$O (M$^{+\cdot}$): 228.1514; found 228.1532. The allylic alcohol (*S,4E,6E*)-7-phenylhepta-4,6-dien-3-ol (**30c**) was purified by flash chromatography on silica gel (16 % ethyl acetate in hexanes). $[\alpha]_D$ = +2.1 (c 2.12, CHCl$_3$). Separating the enantiomers by chiral HPLC Daicel Chiracel™ OD-H column, flow rate 1.0 ml/min, 10 % *i*-PrOH, 90 % hexanes, T_r 7.49 (*R*) and 9.57 (*S*) provided the enantiomer ratio: 3*R*: 3*S* = 3.5: 96.5 (93 % ee).
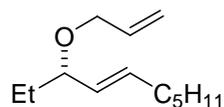
(*S,E*)-3-(Allyloxy)dec-4-ene (31d): General procedure **E** was applied to (*E*)-

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[89] Kim, D. D.; Lee, S. J.; Beak, P. *J. Org. Chem.* **2005**, *70*, 5376-5386.

oct-2-enal (1.0 mmol, 126 mg). The crude product was purified by column chromatography on silical gel (2 % EtOAc in hexanes) to yield 157 mg (80 %) of the title compound as light yellow oil. $[\alpha]_D$ = -13.6 (c 3.77, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.85-5.98 (m, 1H), 5.58 (dt, J = 15.4, 6.7 Hz, 1H), 5.22-5.30 (m, 2H), 5.15 (d, J = 10.3 Hz, 1H), 4.03 (ddt, J = 12.8, 5.2, 1.5 Hz, 1H), 3.81 (ddt, J = 12.8, 6.0, 1.3 Hz, 1H), 3.56 (q, J = 7.1 Hz, 1H), 2.05 (q, J = 7.0 Hz, 2H), 1.48-1.71 (m, 2H), 1.26-1.50 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 135.4, 134.3, 130.5, 116.3, 81.8, 68.7, 32.7, 31.3, 28.9, 28.5, 22.5, 14.0, 9.9 ppm; MS (EI, 70 V): m/z 167 (M^{+}·-Et), 125, 97, 67, 55; HRMS m/z calcd for C$_{11}$H$_{19}$O (M^{+}·-Et): 167.1436; found 167.1442. The allylic alcohol (S,E)-dec-4-en-3-ol (**30d**) was purified by flash chromatography on silica gel (16 % ethyl acetate in hexanes). Then (S,E)-dec-4-en-3-ol (**41d**) (15.6 mg, 0.1 mmol), (R)-2-Methoxy-2-phenylacetic acid (18.3 mg, 0.11 mmol), 1,3-dicyclohexylcarbodimide (DCC, 22.7 mg, 0.11 mmol), 4-(dimethylamino)pyridine (DMAP, 1.3 mg, 0.01 mmol) was mixed in CH$_2$Cl$_2$ 1 ml and stirred 12 h at ambient temperature, then remove the solvent and the crude product was purified by flash chromatograph on silical gel (4 % EtOAc in hexanes) to yield (2R)-(S,E)-dec-4-en-3-yl 2-methoxy-2-phenylacetate. Separating the diastereomer by chiral HPLC [Zorbax (4.6 mm X 25 cm) column, flow 0.8 ml/min, 2 % ethyl acetate, 98 % hexanes, T$_r$ 10.01 (**3R**) and 9.17 (**3S**)] provided the diastereomer ratio: 3R: 3S = 5.9: 94.1 (88 % ee).
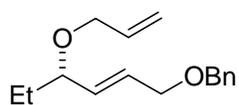
1-((((S,E)-4-(Allyloxy)hex-2-enyloxy)methyl)benzene (31e): General procedure **E** was followed employing (E)-4-(benzyloxy)but-2-enal[90] (176 mg, 1.0 mmol). The crude product was purified by flash chromatograph on silical gel (5 %

[90] Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564-577.

EtOAc in hexanes) to yield 180 mg (73 %) of the title compound as light yellow oil. $[\alpha]_D$ = -26.9 (c 2.87, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20-7.38 (m, 5H), 5.87-6.00 (m, 1H), 5.78 (dt, J = 15.6, 5.6 Hz, 1H), 5.61 (dd, J = 15.6, 7.6 Hz, 1H), 5.29 (d, J = 17.2 Hz, 1H), 5.18 (d, J = 10.4 Hz, 1H), 4.04-4.11 (m, 3H), 3.87 (ddt, J = 12.8, 5.9, 1.3 Hz, 1H), 3.69 (q, J = 6.8 Hz, 1H), 1.50-1.76 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 138.16, 135.11, 133.72, 129.24, 128.32, 127.66, 127.55, 116.46, 80.86, 71.98, 70.05, 69.13, 28.32, 9.75 ppm; MS (EI, 70 V): m/z 217 (M$^{+\cdot}$-Et), 199, 181, 169, 159, 143, 131, 125, 117, 105; HRMS m/z calcd for C$_{14}$H$_{17}$O$_2$ (M$^{+\cdot}$-Et): 217.1229. found 217.1227. The allylic alcohol (*S,E*)-6-(benzyloxy)hex-4-en-3-ol (**30e**) was purified by flash chromatography on silica gel (16 % ethyl acetate in hexanes). Separation of the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.5 ml/min, 5 % *i*-PrOH, 95 % hexanes, T$_r$ 24.70 (*R*) and 26.93 (*S*) provided the enantiomer ratio: 3*R*: 3*S* = 2.7: 71.7 (93 % ee). $[\alpha]_D$ = +5.8 ° (c 3.89, CHCl$_3$).
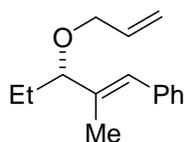
1-((*S,E*)-3-(Allyloxy)-2-methylpent-1-enyl)benzene (31f): General procedure A was applied to (*E*)-2-methyl-3-phenylacrylaldehyde(1.0 mmol, 146 mmol). The crude product was purified by column chromatography on silical gel (2 % EtOAc in hexanes) to yield 181 mg (84 %) of the title compound as light yellow oil. $[\alpha]_D$ = +9.3 (c 5.48, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.24-7.44 (m, 5H), 6.47 (s, 1H), 5.93-6.05 (m, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.22 (d, J = 10.3 Hz, 1H), 4.06 (ddt, J = 12.8, 5.1, 1.4 Hz, 1H), 3.88 (ddt, J = 12.8, 6.1, 1.4 Hz, 1H), 3.75 (t, J = 6.9 Hz, 1H), 1.87 (d, J = 1.3 Hz, 3H), 1.55-1.84 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 137.7, 137.4, 135.2, 128.9, 128.0, 127.9, 126.3, 116.4, 86.9, 68.9, 26.6, 12.3, 10.3 ppm; IR (liquid film): 2963, 1446, 1327, 1074, 918, 698 cm^{-1}; MS (EI, 70 V): m/z 216 (M$^{+\cdot}$), 187, 159, 145, 129, 117, 105, 91, 77; HRMS m/z

calcd for $C_{15}H_{20}O$ ($M^{+.}$): 216.1514; found 216.1507. The allylic alcohol (*S,E*)-2-methyl-1-phenylpent-1-en-3-ol (**30f**) was purified by flash chromatography on silica gel (16 % ethyl acetate in hexanes). Separation of the enantiomers by chiral HPLC Daicel Chiracel[TM] OD-H column, flow rate 0.6 ml/min, 3 % *i*-PrOH, 97 % hexanes, T_r 21.15 (*R*) and 23.40 (*S*) provided the enantiomer ratio:3*R*:3*S* = 0.8: 98.7 (98 % ee). $[\alpha]_D$ = +37.6 (c 1.74, CHCl$_3$).

((1*E*)-3- ((*S,E*)-1-Phenylpent-1-en-3-yloxy)prop-1-enyl)trimethylsilane (37): General procedure **E** was applied to cinnamaldehyde (1.0 mmol, 132 mg) and (*E*)-3-(trimethylsilyl)allyl acetate[91] (1.5 mmol, 258 mg). The crude product was purified by column chromatography on silical gel (2 % EtOAc in hexanes) to yield 211 mg (77 %) of the title compound as a light yellow oil. $[\alpha]_D$ = -71.3 (c 3.57, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$):
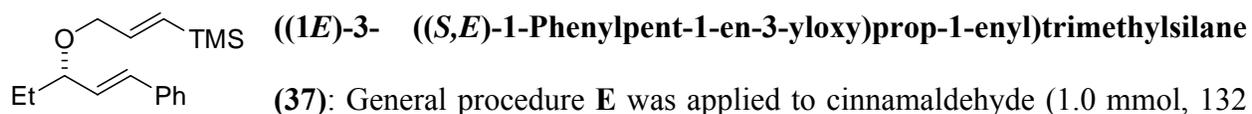
δ 7.19-7.41 (m, 5H), 6.51 (d, J = 15.9 Hz, 1H), 6.11 (dt, J = 18.7, 4.8 Hz, 1H), 6.07 (dd, J = 15.9, 8.0 Hz, 1H), 5.92 (dt, J = 18.7, 1.4 Hz, 1H), 4.12 (ddd, J = 13.2, 4.6, 1.6 Hz, 1H), 3.92 (ddd, J = 13.2, 5.1, 1.4 Hz, 1H), 1.49-1.81 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.08 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 142.9, 136.7, 132.2, 131.4, 130.5, 128.5, 127.6, 126.4, 82.0, 71.3, 28.6, 9.9, -1.4 ppm; MS (EI, 70 V): *m/z* 274 (M$^{+.}$), 259, 245, 216, 202, 171, 161, 145, 129, 115, 103, 91, 75; HRMS *m/z* calcd for $C_{15}H_{20}O$ (M$^{+.}$): 274.1753; found 274.1766.
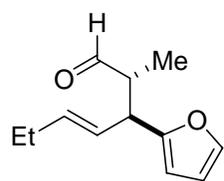
(*E,2R,3S*)-3-(furan-2-yl)-2-methylhept-4-enal (32b): General Procedure **D** was followed employing 2-((*S,E*)-3-(allyloxy)pent-1-enyl)furan (**31b**, 130 mg, 0.68 mmol) and 1 mol% catalyst (3.1 mg Ir-dimer, 5,7 mg PCy$_3$ and 2.3 mg NaBPh$_4$) in dichloroethane for 30 min. The reaction was heated at reflux for 16 h. *(2R,3S):*

[91] Trost, B. B.; Self, C. R. *J. Am. Chem. Soc.* **1983**, *105*, 5942-5944.

(2S,3R) = 95 : 5. Purification by flash chromatograph on Iatrobeads neutral (pH = 7) silica gel (2.5 % ethyl ether in hexanes) to yield 97 mg (75 %) of the title compound as a colorless oil. Separating the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 0.8 ml/min, 0.8% *i*-PrOH, 99.2% hexanes, T_r 8.45 *(2S,3R)* and 10.12 *(2R,3S)* provided the enantiomer ratio: *(2R,3S)*:*(2S, 3R)* = 98:2 (96% ee). $[\alpha]_D$ = +75.6 (c 0.66, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.69 (d, J = 1.9 Hz, 1H), 7.33 (dd, J = 1.9, 0.9 Hz, 1H), 6.29 (dd, J = 3.2, 1.9 Hz, 1H), 6.06 (dt, J = 3.2, 0.8 Hz, 1H), 5.65 (dt, J = 15.3, 5.9 Hz, 1H), 5.54 (ddt, J = 15.3, 8.2, 1.2 Hz, 1H), 3.71 (dd, J = 8.2, 6.6 Hz, 1H), 2.78 (qdd, J = 7.0, 6.6, 1.9 Hz, 1H), 1.00 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.0, 155.0, 141.5, 136.8, 125.9, 110.1, 106.3, 49.7, 43.8, 25.4, 13.5, 11.4 ppm; MS (EI, 70 V): *m/z* 192 (M$^{+\cdot}$), 163, 135, 117; HRMS *m/z* calcd for C$_{12}$H$_{16}$O$_2$ (M$^{+\cdot}$): 192.1150. found 192.1146.
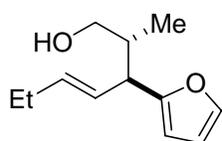
(E,2R,3S)-3-(furan-2-yl)-2-methylhept-4-en-1-ol **(32b′)**: Diisobutyl aluminum hydride (1.0 ml, 1.0 M in hexanes, 1.0 mmol) reduction of aldehyde **32b** (97 mg, 0.5 mmol) followed by purification by flash chromatography (16 % EtOAc/hexanes) gave 79 mg (81 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.33 (dd, J = 1.8, 0.84 Hz, 1H), 6.30 (dd, J = 3.2, 1.8 Hz, 1H), 6.02 (dd, J = 3.2, 0.6 Hz, 1H), 5.53-5.66 (m, 2H), 3.59 (dd, J = 11.0, 5.8 Hz, 1H), 3.50 (dd, J = 11.0, 5.9 Hz, 1H), 3.37-3.42 (m, 1H), 1.98-2.14 (m, 3H), 1.56 (brs, 1H), 1.00 (t, J = 7.4 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 156.82, 140.89, 134.24, 127.80, 109.95, 105.50, 66.16, 45.24, 39.77, 25.46, 14.43, 13.62 ppm; IR (liquid film): 3358, 2963, 2932, 2875, 1590, 1461, 1932, 1010, 971, 728 cm^{-1}; MS (EI, 70 V): *m/z* 194 (M$^{+\cdot}$), 135, 117, 107, 91, 79, 65, 55; HRMS *m/z* calcd for C$_{12}$H$_{18}$O$_2$ (M$^{+\cdot}$): 194.1307. found 194.1309.

(2R,3R,4E)-2-Methyl-3-styrylhept-4-enal (32c): General Procedure **D** was followed employing 1-((S,1E,3E)-5-(allyloxy)hepta-1,3-dienyl)benzene (**31c**, 228 mg, 1.0 mmol) and 1 mol% catalyst (4.5 mg Ir-dimer, 8.4 mg PCy$_3$ and 3.4 mg NaBPh$_4$) in dichloroethane for 10 min. The reaction was heated at reflux for 18 h. *(2R,3R): (2S:3S)* = 95 : 5. Purification by flash chromatograph on Iatrobeads neutral (pH7) silica gel (2.5 % ethyl ether in hexanes) to yields 176 mg (77 %) of the title compound as colorless oil. Separation of the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.8 ml/min, 1.0 % *i*-PrOH, 99.0 % hexanes, T$_r$ 14.03 *(2S, 3S)* and 20.67 *(2R, 3R)* provided the enantiomer ratio: *(2S,3S): (2R,3R)* = 3.7 : 96.3 (93% ee). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.69 (d, J = 2.3 Hz, 1H), 6.44 (d, J = 15.9 Hz, 1H), 6.12 (dd, J = 15.8, 8.1 Hz, 1H), 5.60 (dt, J = 15.4, 6.1 Hz, 1H), 5.45 (dd, J = 15.4, 7.5 Hz, 1H), 3.22 (q, J = 7.5 Hz, 1H), 2.50 (ddqd, J = 8.1, 7.5, 7.0, 2.3 Hz, 1H), 1.11 (d, J = 7.0 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.7, 137.1, 134.7, 129.5, 128.5, 128.2, 127.3, 126.2, 50.4, 47.4, 25.6, 13.7, 11.4 ppm; IR (liquid film): 2962, 1726, 1450, 969, 748, 694 cm^{-1}; MS (EI, 70 V): *m/z* 228 (M$^{+\cdot}$), 213, 199, 171, 143, 129, 115; HRMS *m/z* calcd for C$_{16}$H$_{20}$O (M$^{+\cdot}$): 228.1514. found 228.1509.
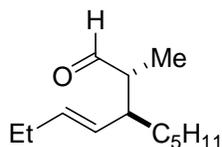
(2R,3S)-3-((E)-But-1-enyl)-2-methyloctanal (32d): General Procedure **D** was followed employing (S,E)-3-(allyloxy)dec-4-ene (**31d**, 392 mg, 2.0 mmol) and 1 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloroethane for 10 min. The reaction was heated at reflux for 18 h. *(2R,3R): (2S:3S)* = 97 : 3. Purification by flash chromatograph on Iatrobeads neutral (pH = 7) silica gel

(2.5 % ethyl ether in hexanes) yields 274 mg (70 %) of the title compound as colorless oil.

Separating the enantiomers by chiral GC (Chiracel G-TA column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 50 °C for 2.00 min, ramp @ 2.00 °C/min to 160 °C, hold for 20.00 min, T_r 7.17 (2*S*,3*R*) and 9.22 (2*R*,3*S*) provided the enantiomer ratio: (2*R*,3*S*):(2*S*, 3*R*) = 93.5:6.5 (87 % ee). $[\alpha]_D$ = +10.6 (c 0.71, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.64 (d, J = 2.2 Hz, 1H), 5.50 (dt, J = 15.3, 6.4 Hz, 1H), 5.21 (ddt, J = 15.3, 8.9, 1.4 Hz, 1H), 2.21-2.38 (m, 2H), 1.97-2.07 (m, 2H), 1.11-1.40 (m, 9H), 1.04 (d, J = 5.9 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.7, 134.4, 129.8, 50.7, 44.3, 31.7, 31.6, 26.8, 25.9, 22.5, 14.0, 13.9, 11.0 ppm; IR (liquid film): 2930, 1727, 1460, 1378, 970, 723 cm^{-1}; MS (EI, 70 V): *m/z* 196 (M$^{+\cdot}$), 167, 153, 139, 125, 97, 83, 73; HRMS *m/z* calcd for C$_{13}$H$_{24}$O (M$^{+\cdot}$): 196.1827; found 196.1825.
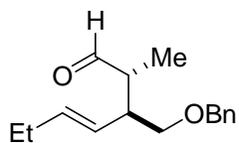
(E,2R,3S)-3-((Benzyloxy)methyl)-2-methylhept-4-enal (32e): General Procedure **D** was followed employing 1-(((*S*,*E*)-4-(allyloxy)hex-2-enyloxy)methyl)benzene (**31e**, 123 mg, 0.5 mmol) and 1 mol% catalyst (2.3 mg Ir-dimer, 4.2 mg PCy$_3$ and 1.7 mg NaBPh$_4$) in dichloroethane for 10 mi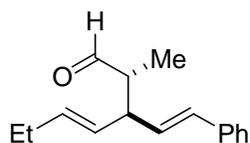n. The reaction was heated at reflux for 18 h. *(2R,3S) : (2S:3S) = 96 : 4*. Purification by flash chromatograph on Iatrobeads neutral (pH = 7) silica gel (2.5 % ethyl ether in hexanes) yields 74 mg (60 %) of the title compound as colorless oil. Separation of the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.8 ml/min, 0.8 % *i*-PrOH, 99.2 % hexanes, T_r 20.27 (2*S*, 3*R*) and 24.71 (2*R*, 3*S*) provided the enantiomer ratio: (2*S*,3*R*): (2*R*,3*S*)= 4.1: 95.9 (92 % ee). $[\alpha]_D$ = +53.6 (c 1.51, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.70 (d, J = 1.2 Hz, 1H), 7.27-7.61 (m, 5H), 5.60 (dt, J = 15.4, 6.3 Hz, 1H), 5.35 (dd, J = 15.4, 8.3 Hz, 1H), 4.48 (s, 2H), 3.50 (dd, J = 9.3, 5.8 Hz,

1H), 3.45 (dd, J = 9.3, 7.9 Hz, 1H), 2.79-2.87 (m, 1H), 2.48-2.56 (m, 1H), 2.03 (qd, J = 7.4, 6.3

Hz, 2H), 1.06 (d, J = 6.9 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ

204.7, 138.2, 135.3, 128.4, 127.6 (3C, overlap), 126.6, 73.2, 70.7, 47.9, 44.2, 25.7, 13.7, 9.9

ppm; MS (EI, 70 V): *m/z* 246 (M$^{+\cdot}$), 188, 158, 125, 105, 91, 81, 65; HRMS *m/z* calcd for

C$_{16}$H$_{22}$O$_2$ (M$^{+\cdot}$): 246.1620 found 246.1622.
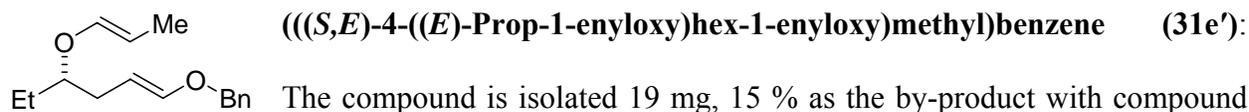
(((S,E)-4-((E)-Prop-1-enyloxy)hex-1-enyloxy)methyl)benzene (31e′): The compound is isolated 19 mg, 15 % as the by-product with compound **32e**. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.30-7.65 (m, 5H), 6.37 (d, J = 12.6 Hz, 1H), 6.08 (dq, J = 12.3, 1.5 Hz, 1H), 4.81-4.94 (m, 2H), 4.67 (s, 2H), 3.45-3.53 (m, 1H), 2.13-2.19 (m, 2H), 1.55 (dd, J = 6.7, 1.4 Hz, 3H), 1.49-1.65 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 147.51, 146.03, 137.12, 128.45, 127.84, 127.53, 100.41, 100.16, 81.95, 71.02, 31.99, 26.10, 12.51, 9.53 ppm.
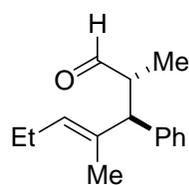
(E,2R,3R)-2,4-Dimethyl-3-phenylhept-4-enal (32f): General Procedure **D** was followed employing 1-((S,E)-3-(allyloxy)-2-methylpent-1-enyl)benzene (**31f**, 432 mg, 2.0 mmol) and 1 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloromethane for 10 min. After the initial reaction time, triphenylphosphine (15.2 mg, 3 mol%) was added, the solvent was evaporated, and the residue was dissolved in 5 ml dry toluene. The resulting solution was heated at reflux for 18 h; *(2R$_E$, 3R$_E$): (2S$_E$, 3S$_E$): Z$_{C4-5}$* = 76.4: 6.6: 17.0. Purification by flash chromatograph on Iatrobeads neutral (pH7) silica gel (2.5 % ethyl ether in hexanes) yields 350 mg (81 %) as colorless oil. Separating the enantiomers by chiral HPLC (Daicel Chiracel^{TM} OD-H column, flow rate 0.8

ml/min, 0.8% *i*-PrOH, 99.2% hexanes, T_r 7.90 (*2S,3S*) and 11.4 (*2R,3R*) provided the enantiomer

ratio: (*2R,3R*):(*2S, 3S*) = 98.5:1.5 (97% ee). $[\alpha]_D$ = -36.5 (c 6.23, CHCl$_3$). ^{1}H NMR (300 MHz,

CDCl$_3$): δ 9.58 (d, J = 3.9 Hz, 1H), 7.18-7.34 (m, 5H), 5.43 (t, J = 7.0 Hz, 1H), 3.34 (d, J = 11.4

Hz, 1H), 2.90-3.01 (m, 1H), 2.05-2.18 (m, 2H), 1.59 (s, 3H), 1.04 (t, J = 7.4 Hz, 2H), 0.98 (d, J =

6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.3, 140.6, 135.1, 129.5, 128.6, 128.4, 128.3,

128.1, 126.6, 56.1, 47.7, 21.1, 15.0, 14.0, 13.4 ppm; MS (EI, 70 V): *m/z* 216 (M$^{+\cdot}$), 201, 187,

173, 159, 143, 131, 117, 105, 91; HRMS *m/z* calcd for C$_{15}$H$_{20}$O (M$^{+\cdot}$): 216.1514 found 216.1502.
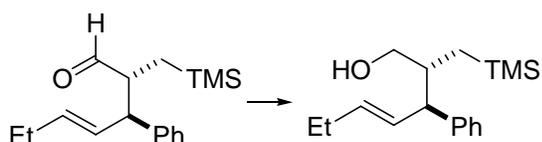
(*E,2R,3S*)-2- ((Trimethylsilyl)methyl)-3-phenylhe pt-4-en-1-ol (38′): General Procedure **D** was followed employing ((1*E*)-3-((*S,E*)-1-phenylpent-1-en-3-yloxy)prop-1-enyl)trimethylsilane (**48**, 137 mg, 0.5 mmol) and 1 mol% catalyst (2.3 mg Ir-dimer, 4.2 mg PCy$_3$ and 1.7 mg NaBPh$_4$) in dichloroethane for 20 h. The reaction was heated at

reflux for 12 h to afford (*E,2R,3S*)-2- ((trimethylsilyl)methyl)-3-phenylhe pt-4-en-1-al (**38**);

(*2R,3S*): (*2R,3R*) = 95 : 5. Due to the sensitivity of aldehydes **38** toward epimerization,

Diisobutylaluminum hydride (1.0 ml, 1.0 M in hexanes, 1.0 mmol) reduction of **38** followed by

purification by flash chromatography (16 % EtOAc/hexanes) gave 70 mg (50 %) of the title

compound as a colorless oil. Separating the enantiomers by chiral HPLC (Daicel Chiracel^{TM} OD-

H column, flow rate 0.5 ml/min, 5.0% *i*-PrOH, 95.0% hexanes, T_r 7.08 (*2S,3R*) and 8.68 (*2R,3S*)

provided the enantiomer ratio: (*2R,3S*):(*2S, 3R*) = 95.5:4.5 (91% ee). $[\alpha]_D$ = +39.1 (c 2.20,

CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.19-7.34 (m, 5H), 5.71 (dd, J = 15.3, 8.6 Hz, 1H), 5.62

(dt, J = 15.3, 5.7 Hz, 1H), 3.73 (dd, J = 11.1, 3.7 Hz, 1H), 3.55 (dd, J = 11.1, 5.6 Hz, 1H), 3.29 (t,

J = 8.4 Hz, 1H), 2.03-2.08 (m, 3H), 1.60 (brs, 1H), 0.43-0.52 (m, 2H), -0.03 (s, 9H) ppm; ^{13}C

NMR (75 MHz, CDCl$_3$): δ 144.0, 133.1, 131.7, 128.4, 128.2, 126.1, 65.5, 54.3, 42.3, 25.5, 16.1, 13.7, -0.8 ppm; MS (EI, 70 V): m/z 243 (M$^{+\cdot}$-H$_2$O-Me), 218, 145, 131, 117, 91, 75, 73.
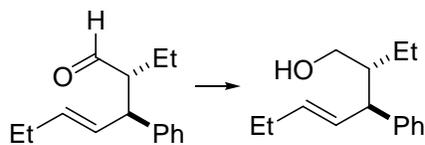
(2R,3S,E)-2-Ethyl-3-phenylhept-4-en-1-ol **(41′):** General procedure **E** was applied to cinnamaldehyde (2.0 mmol, 264 mg) and crotyl acetate (3.0 mmol, 346 mg). The crude product was purified by column chromatography on silical gel (2 % EtOAc in hexanes) to yield 260 mg (60 %) of a mixture of di(allyl) ether (**39** and **40,** ratio 1: 2**).** Then general procedure **D** was followed employing a mixture of (**39** and **40**, 216 mg, 1.0 mmol) and 1 mol% catalyst (4.5 mg Ir-dimer, 8.4 mg PCy$_3$ and 3.4 mg NaBPh$_4$) in dichloroethane for 1.5 h. The reaction was heated at reflux for 12 h to afford (2R,3S,E)-2-Ethyl-3-phenylhept-4-en-1-al (**41**); (2R, 3S): (2R, 3R) = 95: 5. Due to the poor separation of desired product from by-products, the DIBAL-H (1.0 M in hexanes, 2.0 ml, 2.0 mmol) reduction of aldehyde **41** at −78 °C and crude product was purified by flash chromatograph on silical gel (16 % EtOAc in hexanes) to yield 43 mg (20 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.18 (m, 5H), 5.55-5.72 (m, 2H), 3.65-3.80 (m, 2H), 3.24 (t, J = 8.9 Hz, 1H), 1.98-2.07 (m, 2H), 1.69-1.83 (m, 1H), 1.19-1.39 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.84 (t, J = 7.4 Hz, 3H) ppm.

3.4.1.2 One pot reaction from alkenyl zinc addition

General Procedure F: Preparation of di(allyl) ethers from terminal alkynes: Cyclohexene (2.0 equiv.) was added to a solution of BH$_3$.THF (1.0 M in THF, 1.0 equiv.) at 0 °C and stirred 3 h. Then the alkyne (1.0 equiv.) was added to a suspension of dicyclohexylborane at 0 °C and stirred 15 min. The resulting suspension was warmed directly to ambient temperature, stirred for

1 h and THF was removed *in vacuo*. Then pentane was added (1.0 M solution) and cooled to -78 °C. Diethylzinc (1.0 M in hexanes, 1.05 equiv.) and catalyst (-)-MIB (2 mol%) was added at -78 °C and stirred 30 min and warmed to 0 °C. Then benzaldehyde (0.9 equiv.) in pentane (1.0 M solution) was added over 10 min and stirred 3 h. Then acetic acid (1.05 equiv.) in THF (1.0 M solution) was added and continually stirred for 10 min then added *via* syringe to a solution of palladium acetate (5 mol%), PPh$_3$ (25 mol%), allyl acetate (1.5 equiv.) in 10 ml anhydrous THF, The reaction was stirred for 12 h at 60 °C oil bath whereupon the solvent was removed *in vacuo* and the residue purified as indicated. To get enantiomer excess value, same reaction condition without Pd-catalyzed allylation was applied, and saturated NH$_4$Cl solution was added to quench the reaction after alkenylzinc addition. The solution was extracted with Et$_2$O (3x) and the combined organic extracts were dried (MgSO$_4$). The solvent was removed *in vacuo* and the residue purified as indicated.
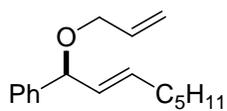
1-((*S*,*E*)-1-(Allyloxy)oct-2-enyl)benzene (42a): General procedure **F** was applied to 1-heptyne (2.0 mmol, 192 mg) and benzaldehyde (1.8 mmol, 191 mg). The crude product was purified by column chromatography on silical gel (2 % EtOAc in hexanes) to yield 302 mg (62 %) of the title compound as light yellow oil. [α]$_D$ = +25.3 (c 2.74, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.24-7.44 (m, 5H), 5.87-6.01 (m, 1H), 5.69 (dt, J = 15.3, 6.4 Hz, 1H), 5.56 (dd, J = 15.3, 7.1 Hz, 1H), 5.27 (d, J = 17.2 Hz, 1H), 5.16 (d, J = 10.4 Hz, 1H), 4.76 (d, J = 7.0 Hz, 1H), 4.00 (dd, J = 12.8, 5.5 Hz, 1H), 3.93 (dd, J = 12.8, 5.5 Hz, 1H), 2.04 (q, J = 7.0 Hz, 2H), 1.27-1.43 (m, 6H), 0.87 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.8, 134.9, 133.7, 130.6, 128.3, 127.3, 126.7, 116.6, 81.8, 68.9, 32.2, 31.3, 28.7, 22.4, 14.0 ppm; IR (liquid film): 3064, 2927, 2856, 1452, 1070, 971, 920, 748, 699 cm^{-1}; MS (EI, 70 V):

m/z 244 (M$^+$), 203, 186, 173, 161, 143, 129, 117, 105, 99, 91, 84; HRMS *m/z* calcd for C$_{17}$H$_{24}$O (M$^+$): 244.1827; found 244.1816. The allylic alcohol (*S,E*)-1-phenyloct-2-en-1-ol (**42a′**) was purified by flash chromatography on silica gel (16 % ethyl acetate in hexanes). Separation of the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.5 ml/min, 5.0 % *i*-PrOH, 95.0 % hexanes, T$_r$ 14.53 (*R*) and 18.27 (*S*) provided the enantiomer ratio: 1*R*: 1*S* = 5.7: 78.8 (87 % ee), [α]$_D$ = +26.4 (c 2.26, CHCl$_3$).
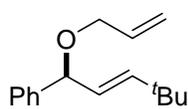
1-((*S,E*)-1-(Allyloxy)-4,4-dimethylpent-2-enyl)benzene (**42b**): General procedure **F** was applied to 3,3-dimethylbut-1-yne (2.0 mmol, 164 mg) and benzaldehyde (1.8 mmol, 191 mg). The crude product was purified by column chromatography on silical gel (2 % EtOAc in hexanes) to yield 290 mg (63 %) of the title compound as light yellow oil. [α]$_D$ = +38.6 (c 2.07, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40-7.62 (m, 5H), 6.10 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.87 (dd, J = 15.6, 0.9 Hz, 1H), 5.62 (dd, J = 15.6, 7.4 Hz, 1H), 5.43 (dq, J = 17.2, 1.7 Hz, 1H), 5.33 (dq, J = 10.4, 1.4 Hz, 1H), 4.91 (d, J = 7.4 Hz, 1H), 4.15 (ddt, J = 12.9, 5.5, 1.3 Hz, 1H), 4.08 (ddt, J = 12.9, 5.6, 1.3 Hz, 1H), 1.17 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.62, 141.94, 135.03, 128.30, 127.30, 126.76, 125.40, 116.76, 82.01, 68.90, 33.00, 29.44 ppm; MS (EI, 70 V): *m/z* 230 (M$^+$), 188, 173, 157, 147, 131, 115, 105; HRMS *m/z* calcd for C$_{16}$H$_{22}$O (M$^+$): 230.1671. found 230.1671. The allylic alcohol (*S,E*)-4,4-dimethyl-1-phenylpent-2-en-1-ol (**53b′**) was purified by flash chromatography on silica gel (16 % ethyl acetate in hexanes). Separation the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.8 ml/min, 5.0 % *i*-PrOH, 95.0 % hexanes, T$_r$ 9.3 (*R*) and 11.8 (*S*) provided the enantiomer ratio: 1*R*: 1*S* = 4.0: 96.0 (92 % ee).
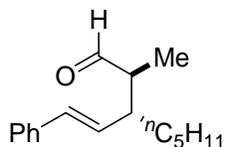
(**E,2S,3R**)-2-Methyl-3-styryloctanal (**43a**): General Procedure **D** was followed employing 1-((**S,E**)-1-(allyloxy)oct-2-enyl)benzene (**42a**, 244 mg, 1.0 mmol) and 1 mol% catalyst (4.5 mg Ir-dimer, 8.4 mg PCy$_3$ and 3.4 mg NaBPh$_4$) in dichloromethane for 10 min. The reaction was heated at reflux for 16 h. *(2S,3R):* *(2R:3R)* = 95 : 5. Purification by flash chromatograph on Iatrobeads neutral (pH7) silica gel (2.5 % ethyl ether in hexanes) yields 195 mg (80 %) of the title compound as colorless oil. Separation of the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 1.0 ml/min, 0.8 % *i*-PrOH, 99.2 % hexanes, T$_r$ 10.05 *(2R,3S)* and 15.14 *(2S,3R)* provided the enantiomer ratio: *(2R, 3S): (2S, 3R)*= 7.0 : 88.7 (86% ee). [α] $_D$ = -27.6 (c 2.54, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.73 (d, J = 1.9 Hz, 1H), 7.23-7.50 (m, 5H), 6.44 (d, J = 15.8, 1H), 6.06 (dd, J = 15.8, 9.0 Hz, 1H), 2.43-2.60 (m, 2H), 1.25-1.49 (m, 6H), 1.14 (d, J = 6.8 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 204.8, 137.1, 131.8, 131.2, 128.5, 127.2, 126.1, 50.7, 44.7, 31.7, 31.6, 27.0, 22.4, 14.0, 11.0 ppm; MS (EI, 70 V): *m/z* 244 (M$^{+\cdot}$), 187, 173, 145, 129, 115, 104, 91; HRMS *m/z* calcd for C$_{17}$H$_{24}$O (M$^{+\cdot}$): 244.1827; found 244.1826.
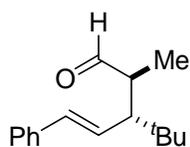
(**E,2S,3R**)-3-*tert*-Butyl-2-methyl-5-phenylpent-4-enal (**43b**): General Procedure **D** was followed employing 1-((**R,E**)-1-(allyloxy)-4,4-dimethylpent-2-enyl)benzene (**42b**, 125 mg, 0.5 mmol) and 1 mol% catalyst (2.3 mg Ir-dimer, 4.2 mg PCy$_3$ and 1.7 mg NaBPh$_4$) in dichloroethane for 10 min. The reaction was heated at reflux for 24 h. *(2S,3R): (2R:3R)* = 92: 8. Purification by flash chromatograph on Iatrobeads neutral (pH7) silica gel (2.5 % ethyl ether in hexanes) yields 100 mg (80 %) of the title compound as colorless oil.stirred 30 min at dichloroethane. Separation of the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.8 ml/min, 0.8 % *i*-PrOH, 99.2 %

hexanes, T_r 12.7 *(2R,3S)* and *(2S,3R)* provided the enantiomer ratio: *(2R,3S): (2S,3R)*= 3.6 : 96.4 (93 % ee). $[\alpha]_D$ = +19.1 (c 1.02, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.87 (d, J = 3.9 Hz, 1H), 7.30-7.48 (m, 5H), 6.53 (d, J = 15.6 Hz, 1H), 6.33 (dd, J = 15.6, 10.7 Hz, 1H), 2.90 (qdd, J = 7.0, 3.9, 2.6 Hz, 1H), 2.15 (dd, J = 10.7, 2.6 Hz, 1H), 1.22 (d, J = 7.0 Hz, 3H), 1.09 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.4, 137.2, 133.8, 128.6, 127.4, 127.2, 126.3, 59.2, 47.2, 34.2, 28.6, 15.6 ppm; MS (EI, 70 V): *m/z* 215 (M$^+$-Me), 188, 173, 147, 105, 77; HRMS *m/z* calcd for C$_{15}$H$_{19}$O(M$^+$-Me): 215.1436; found 215.1439.

3.4.2 Experiment of section 3.3
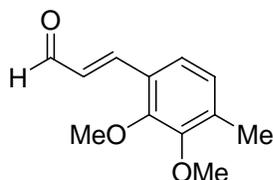
(E)-3-(2,3-Dimethoxy-4-methylphenyl)acrylaldehyde[92] (46): Solution of *n*-butyl lithium (1.6 M in hexanes, 20 ml, 32 mmol) was added to a solution of diisopropylamine (4.5 ml, 32 mmol) in 100 ml dry THF at -78 ^{o}C. The solution was stirred for 10 min then acetaldehyde *N-tert*-butylamine (2.1 ml, 16 mmol) was added and the solution stirred for 30 min. Diethyl chlorophosphate (2.3 ml, 16 mmol) was added and the solution stirred at -78 ^{o}C for 2 h, then allowed to warm to -10 ^{o}C over 3 h and recooled to -78 ^{o}C. Solution of 2,3-dimethoxy-4-methylbenzaldehyde[93] (1.93 g, 10.7 mmol) in 10 ml THF was added to the resulting yellow solution and the reaction allowed to warm slowly to ambient temperature overnight. Add oxalic acid (2.88 g, 32 mmol) in 100 ml water and 100 ml benzene, stirred 3 h, extracted with ethyl ether (2 X 100 ml), washed with 5 % oxalic acid, saturated NaHCO$_3$ and brine. Solvent was evaporated and the residue oil was purified with column chromatography (15 % ethyl acetate in hexanes) to afford yellow solid 1.44 g, 65 %. ^{1}H

[92] Mann, S.; Carillon, S.; Breyne, O.; Marquet, A. *Chem. Eur. J.* **2002**, *8*, 439.
[93] Comins, D. L.; Brown, J. D. *J. Org. Chem*. **1984**, *49*, 1078-1083.

NMR (300 MHz, CDCl$_3$): δ 9.70 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 16.1 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.72 (dd, J = 16.1, 7.8 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 193.9, 152.2, 151.5, 141.4, 136.4, 128.5, 126.1, 126.0, 122.3, 60.9, 59.8, 16.0 ppm. IR: 2937, 2813, 2738, 1671, 1490, 1409, 1270, 1176, 1075, 1022, 822, 787, 768 cm^{-1}. MS (EI, 70 V): *m/z* 206 (M$^{+\cdot}$), 191, 175, 160, 147, 135, 91; HRMS *m/z* calcd for C$_{12}$H$_{14}$O$_3$ (M$^{+\cdot}$): 206.0943; found 206.0936.
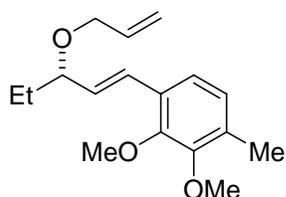
(S,E)-1- (3-(Allyloxy)pent-1-enyl)-2,3-dimethoxy-4-methylbenzene (50): The General Procedure **E** (one-pot addition and allylation) was applied to (*E*)-3-(2,3-dimethoxy-4-methylphenyl)acrylaldehyde (**46**, 1.53 mg, 7.4 mmol). The crude product was purified by column chromatography on silical gel (2 % ethyl acetate in hexanes) to yield 1.86 mg (90 %) of the title compound as light yellow oil. [α]$_D$ = -53.7 (c 10.4, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.17 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 16.1 Hz, 1H), 6.06 (dd, J = 16.1, 8.1 Hz, 1H), 5.90-6.02 (m, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.19 (d, J = 10.4 Hz, 1H), 4.13 (dd, J = 12.8, 5.1 Hz, 1H), 3.92 (dd, J = 12.8, 5.9 Hz, 1H), 3.91 (q, J = 7.0 Hz, 1H), 3.86 (s, 6H), 2.28 (s, 3H), 1.59-1.82 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.6, 150.6, 135.2, 131.7, 130.8, 128.9, 126.5, 125.7, 120.9, 116.4, 81.9, 69.1, 60.6, 60.0, 28.6, 15.7, 9.8 ppm. IR(liquid film) 2963, 2933, 2859, 1460, 1407, 1277, 1074, 1029, 916, 805, 734 cm^{-1}. MS (EI, 70 V): *m/z* 276 (M$^{+\cdot}$), 247, 235, 219, 205, 191, 175, 165; HRMS *m/z* calcd for C$_{17}$H$_{24}$O$_3$ (M$^{+\cdot}$) 276.1725; found 276.1722. The allylic alcohol (*S,E*)-1-(2,3-dimethoxy-4-methylphenyl)pent-1-en-3-ol (**50′**) was purified by column chromatography on silica gel (16 % EtOAc in hexanes). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.12 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 16.1 Hz, 1H), 6.19 (dd, J

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= 16.1, 7.0 Hz, 1H), 4.21 (q, J = 6.5 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H)， 2.25 (s, 3H), 1.61-1.76

(m, 2H), 0.97 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.50, 150.56, 132.77,

131.64, 128.97, 125.73, 124.66, 120.95, 74.65, 60.64, 60.03, 30.13, 15.76, 9.71 ppm; MS (EI, 70

V): m/z 236 (M$^{+\cdot}$), 207, 179, 165, 152; HRMS m/z calcd for C$_{14}$H$_{20}$O$_3$ (M$^{+\cdot}$) 236.1412; found

236.1410. Separating the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow

rate 1.0 ml/min, 5 % i-PrOH, 95 % hexanes, T$_r$ 8.84 (R) and 9.76 (S) provided the enantiomer

ratio: (R) : (S) = 5.2 : 94.8 (90 % ee).
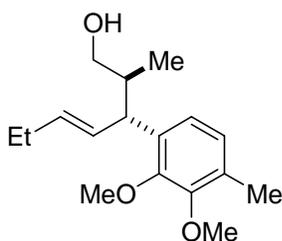
(2S,3R,E)-3- (2,3-Dimethoxy-4-methylphenyl)-2-methylhept-4-en-1-ol (52): General Procedure **D** was followed employing (S,E)-1-(3-(allyloxy)pent-1-enyl)-2,3-dimethoxy-4-methylbenzene (**50**, 1.93 g, 7 mmol) and stirred 30 min at dichloroethane. Then added PPh$_3$ (55 mg,

0.21 mmol) and refluxed in oil bath for 12 h to afford (2S,3R,E)-3-(2,3-Dimethoxy-4-

methylphenyl)-2-methylhept-4-en-1-al (**51**); (2S,3R) : (2R,3R) = 94 : 6. ^{1}H NMR (300 MHz,

CDCl$_3$): δ 9.76 (d, J = 3.3 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 5.60-5.75

(m, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 3.85-3.95 (m, 1H), 2.78-2.84 (m, 1H), 2.33 (s, 3H), 2.02-2.12

(m, 2H), 1.03 (t, J = 6.9 Hz, 3H), 0.98 (d, J = 7.4 Hz, 3H) ppm. Then cooled to -78 ^{o}C and

DIBAL-H (1.0 M in hexanes, 10.5 ml, 10.5 mmol) was added into aldehyde **51** dropwise. After

warm to ambient temperature, saturated saturated sodium tartrate solution salt solution was

added to the reaction to quench the reaction and extracted with ethyl ether. After solvent

Vaporation the oil was purified by flash chromatograph on silical gel (16 % ethyl acetate in

hexanes) to yield 1.55 g (80 %) of the title compound as colorless oil. [α] $_D$ = -9.9 (c 11.9,

CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.89 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 5.70

(dd, J = 15.2, 8.2 Hz, 1H), 5.60 (dt, J = 15.2, 5.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.62-3.77 (m, 2H), 3.37-3.52 (m, 1H), 2.37 (s, 1H), 2.25 (s, 3H), 0.97 (t, J = 7.4 Hz, 3H), 0.73 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.27, 150.70, 134.40, 132.82, 131.38, 129.72, 125.60, 123.23, 66.57, 60.57, 59.82, 43.47, 40.28, 25.46, 15.50, 13.89, 13.60. IR(liquid film): 3444, 2962, 2933, 2874, 2246, 1461, 1408, 1277, 1066, 1027, 910, 805, 734 cm^{-1}; MS (EI, 70 V): m/z 278 (M$^+$), 219, 204, 188, 175; HRMS m/z calcd for C$_{17}$H$_{26}$O$_3$ (M$^+$) 278.1882; found 278.1883.
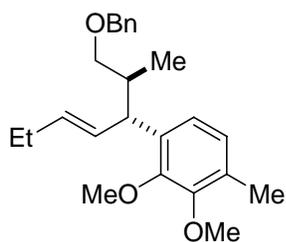
1-((2S,3R,E)-1- (Benzyloxy)-2-methylhept-4-en-3-yl)-2,3-dimethoxy-4-methylbenzene (53): To a suspension of sodium hydride (360 mg, 15 mmol) in 10 ml anhydrous THF added solution of alcohol **52** (1.39 g, 5.0 mmol) in THF, stirred 30 min, then benzyl bromide (1.71 g, 10.0 mmol) was added dropwise and warmed to 60 °C for 12 h, then saturated NH$_4$Cl solution was added to quench the reaction and extracted with ethyl ether (3 X 30 ml). After solvent Vaporation the oil was purified with silica gel (2 % ethyl acetate in hexanes) to afford the title product 1.66 g (90 %) as colorless oil. [α] $_D$ = +16.6 (c 14.3, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.33-7.43 (m, 5H), 6.93 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 5.61 (dd, J = 15.9, 8.2 Hz, 1H), 5.53 (dt, J = 15.9, 5.7 Hz, 1H), 4.60 (d, J = 12.1 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.69 (dd, J = 9.5, 3.6 Hz, 1H), 3.58 (dd, J = 9.5, 8.5 Hz, 1H), 3.39 (dd, J = 8.8, 7.4 Hz, 1H), 2.30 (s, 3H), 2.10-2.20 (m, 1H), 1.99-2.08 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 151.42, 150.90, 138.90, 135.98, 132.63, 131.60, 129.50, 128.20, 127.44, 127.28, 125.54, 122.70, 74.18, 72.98, 60.34, 59.79, 45.34, 37.84, 25.49, 16.20, 15.61, 13.71 ppm; IR(liquid film): 3029, 2961, 2931, 1461,

1408, 1278, 1070, 1028, 969, 910, 734, 698 cm^{-1}. MS (EI, 70 V): *m/z* 368 (M$^{+\cdot}$), 287, 277, 262, 247, 219, 188, 175, 91; HRMS *m/z* calcd for C$_{24}$H$_{32}$O$_3$ (M$^{+\cdot}$): 368.2351; found 368.2348.
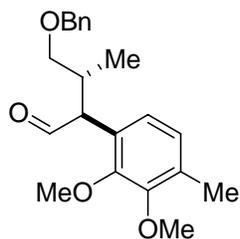
(2S,3R)-4- (Benzyloxy)-2-(2,3-dimethoxy-4-methylphenyl)-3-methylbutanal (54): To a suspention of olefin **53** (368 mg, 1.0 mmol) in ^{t}BuOH-H$_2$O (1 : 1) 5 ml added OsO$_4$ (2.5 % wt. in ^{t}BuOH, 0.655 ml, 0.05 mmol) and *N*-methyl-morpholine oxide (176 mg, 1.5 mmol) and stirred 12 h at 23 ^{o}C, then added Na$_2$SO$_3$ (1.5 g, 12 mmol) and stirred 1 h, extracted with ether, dried and removed solvent to afford the crude diol compound as a mixture of diastereomers. To a solution of the diol residue in 5 ml MeCN-H$_2$O (1 : 1) added NaIO$_4$ (214 mg, 1.0 mmol) and stirred 6 h, extracted with ethyl ether, dried and removed solvent. The residue oil was purified by column chromatography on silical gel (5 % ethyl acetate in hexanes) to yield 267 mg (78 %) of the title compound as a light yellow oil, (2S,3R): (2R,3R) = 93: 7. [α]$_D$ = -67 (c 6.8, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.71 (d, J = 2.8 Hz, 1H), 7.21-7.40 (m, 5H), 6.90 (d, J = 7.9 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H0, 3.77-3.81 (m, 1H), 3.52 (dd, J = 9.3, 5.0 Hz, 1H), 3.39 (dd, J = 9.3, 7.3 Hz, 1H), 2.66-2.77 (m, 1H), 2.26 (s, 3H), 0.76 (d, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 200.5, 151.7, 151.5, 138.2, 131.8, 128.3, 127.6, 127.5, 127.0, 125.7, 124.6, 74.1, 73.0, 60.5, 59.7, 56.3, 34.1, 15.7, 14.6 ppm; IR (liquid film): 2934, 2718, 1721, 1489, 1409, 1278, 1069, 1025, 916, 814, 737, 699 cm^{-1}. MS (EI, 70 V): *m/z* 342 (M$^{+\cdot}$), 312, 314, 204, 191, 173, 163, 148, 133, 103; HRMS *m/z* calcd for C$_{21}$H$_{26}$O$_4$ (M$^{+\cdot}$): 342.1831; found 342.1825; HRMS *m/z* calcd for C$_{20}$H$_{26}$O$_3$ (M$^{+\cdot}$-CO): 314.1882; found 314.1876.
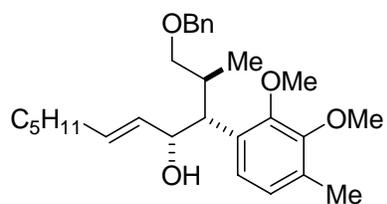
(2S,3R,4R,E)-1-(Benzyloxy)-3-(2,3-dimethoxy-4-methylphenyl)-2-methylundec-5-en-4-ol [94] **(55)**: To a suspention of bis(cyclopentadienyl)zirconium(IV) chloride hydride (Schwartz' reagent, 260 mg, 1.0 mmol) added 1-heptyne (96 mg, 1.0 mmol) and stirred 30 min, cooled to -78 °C and Et₂Zn (1.0 M in hexane, 1.0 ml, 1.0 mmol) was added dropwise over 5 min, then stirred 30 min and warmed to 0 °C, Aldehyde **54** (274 mg, 0.8 mmol) in 2 ml toluene was added over 10 min, stirred 5 h. Saturated NH₄Cl solution was added to quench the reaction and filtrated through silica plug, solvent was evaporated and the residue oil was purified by column chromatography on silica gel (20 % ethyl acetate in hexanes) to yield 236 mg (67 %) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl₃): δ 7.29-7.37 (m, 5H), 6.83 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 5.46 (dt, J = 15.3, 6.6 Hz,1 H), 5.29 (dd, J = 15.3, 7.0 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 4.40 (t, J = 7.2 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.59 (dd, J = 9.4, 5.8 Hz, 1H), 3.45 (dd, J = 9.4, 5.3 Hz, 1H), 3.19-3.25 (m, 1H), 3.07 (s, 1H), 2.25-2.35 (m, 1H), 2.24 (s, 3H), 1.78-1.94 (m, 2H), 1.04-.129 (m, 6H), 0.86 (t, J = 6.9 Hz, 3H), 0.85 (d, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl₃): δ 151.7, 151.3, 138.2, 132.5, 132.3, 131.1, 129.9, 128.3, 127.7, 127.6, 125.1, 124.0, 74.6, 74.1, 73.2, 60.2, 59.8, 35.3, 32.1, 31.1, 28.7, 22.4, 16.3, 15.6, 14.2, 13.9 ppm; IR (liquid film): 3423, 2929, 1491, 1408, 1278, 1070, 1027, 909, 734 cm⁻¹; MS (ESI): *m/z* 463 (M⁺·+Na); HRMS *m/z* calcd for C₂₈H₄₀O₄Na (M⁺·+Na): 463.2824; found 463.2780.
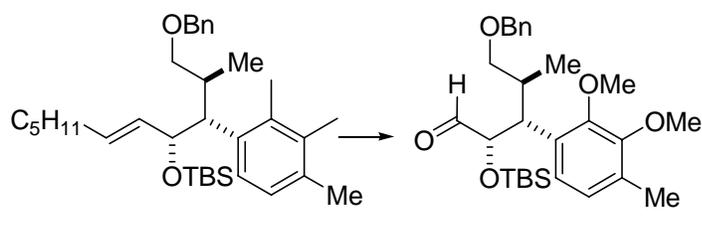
((2S,3R,4S)-5-Benzyloxy)-2- **(tert-butyldimethylsilyloxy)-3-** **(2,3-**

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[94] Wipf, P.; Xu, W. *Tetrahedron. Lett.* **1994**, *35*, 5197.

dimethoxy-4-methylphenyl)-4-methylpentanal (57): To a solution of alcohol **55** (220 mg, 0.5 mmol) in DMF 2 ml added imidazole (66 mg, 1 mmol) and TBSCl (90 mg, 0.6 mmol) and the reaction was stirred 3 h at 80 °C. The reaction was diluted with water and extracted with ethyl ether. After solvent evaporation, the oil was purified by column chromatography on silica gel (2 % ethyl acetate in hexanes) to yield ((*2S,3R,4R,E*)-1-(benzyloxy)-3-(2,3-dimethoxy-4-methylphenyl)-2-methylundec-5-en-4-yloxy)(*tert*-butyl)dimethylsilane (**56**) as colorless oil. Then solved the oil in 20 ml methanol and cooled to -78 °C, the solution was bubbled with ozone until blue colour lasting 10 min. Dimethyl sulfide 0.4 ml was added to the reaction mixture and stirred overnight from -78 °C to ambient temperature. The solvent was evaporated and the oil was purified by column chromatography (5 % ethyl acetate in hexanes) to yield 194 mg (72 %) of the title compound as yellow oil over two steps. $[\alpha]_D$ = -11.7 (c 0.65, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.49 (d, J = 1.2 Hz, 1H), 7.42-7.23 (m, 5H), 6.89 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.39 (d, J = 11.9 Hz, 1H), 4.16 (dd, J = 4.7, 1.2 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.68 (dd, J = 9.0, 4.6 Hz, 1H), 3.42 (dd, J = 9.2, 4.6 Hz, 1H), 3.37 (dd, J = 9.2, 5.5 Hz, 1H), 2.37-2.50 (m, 1H), 2.48 (s, 3H), 0.92 (s, 9H), 0.88 (d, J = 6.9 Hz, 3H), -0.01 (s, 3H), -0.12 (s, 3H) ppm; IR(liquid film): 2930, 2857, 1736, 1462, 1408, 1279, 1254, 1159, 1071, 1027, 838, 778, 698 cm^{-1}; MS (EI, 70 V): 457 (M$^{+\cdot}$-CHO), 429, 349, 337, 321, 207, 165, 105, 91; HRMS *m/z* calcd for C$_{27}$H$_{41}$O$_4$Si (M$^{+\cdot}$-CHO): 457.2774; found 457.2761.
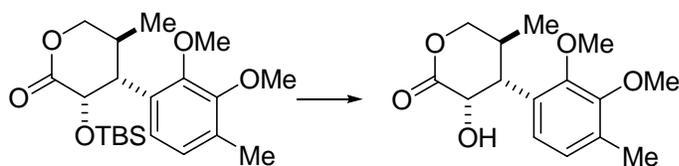
(3S,4R,5S)-4-(2,3-Dimethoxy-4-methylphenyl-3-hydroxy-5-methyl-tetrahydropyran-2-one (44): A solution of the compound **57** (100 mg, 0.2 mmol) in ethyl acetate 10 ml and 5 % Pd/C (10 mg) was

placed under an atmosphere of H_2 and strirred overnight to afford lactol (**58**). After filtration through a Celite plug and washed with ethyl ether, the solvent was evaporated and the resulting oil lactol (**58**) was solved in 10 ml CH_2Cl_2, 4-methylmorpholine *N*-oxide (34 mg, 0.3 mmol) and 4 Å MS (100 mg) was added. Tetrapropylammonium perruthenate (TPAP, 3.5 mg, 0.01 mmol) was added in portion to the reaction mixture. After 2 h, the solution was filtered through a silica plug and washed with CH_2Cl_2. After solvent evaporation, the TBS protected δ-lactone (*3R,4R,5R*)-3-(*tert*-Butyldimethylsilyloxy)-4-(2,3-dimethoxy-4-methylphenyl)-5-methyl-tetrahydropyran-2-one (**59**) 68 mg was obtained, the compound was used directly without further purification. $[\alpha]_D$ = -36.5 (c 0.46, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84 (d, J = 7.9 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 4.49 (dd, J = 11.1, 5.1 Hz, 1H), 4.38 (d, J = 6.2 Hz, 1H), 4.04 (dd, J = 11.1, 9.6 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.26 (dd, J = 9.6, 6.2 Hz, 1H), 2.42-2.55 (m, 1H), 2.25 (s, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.74 (s, 9H), 0.00 (s, 3H), -0.24 (s, 3H) ppm. Then protected lactone (**59**, 38 mg, 0.1 mmol) in DMF 1 ml was added tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF, 55 mg, 0.2 mmol) at 23 °C. After 3 h, the solution was diluted with ethyl ether 10 ml and the resulting mixture was washed with brine, dried over $MgSO_4$, after solvent Vaporation, the oil was purified by column chromatography (50 % ethyl acetate in hexanes) to afford 25 mg (81 % over three steps) the title product as colorless oil. $[\alpha]_D$ = +42 (c 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 4.62 (dd, J = 10.0, 5.1 Hz, 1H), 4.32 (dd, J = 11.5, 5.1 Hz, 1H), 4.12 (t, J = 11.5 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.59 (dd, J = 9.7, 7.9 Hz, 1H), 2.27-2.32 (m, 1H), 2.25 (s, 3H), 1.06. (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.03, 151.47, 150.98, 131.97, 130.14, 125.47, 124.19, 77.20, 70.81, 66.72, 60.21, 59.76, 36.34, 16.40, 15.74 ppm; IR (liquid film): 3467, 2927,

1740, 1463, 1409, 1277, 1071, 1028 cm^{-1}; MS (EI, 70 V): m/z 280 (M$^{+\cdot}$), 251, 205, 165, 91;

HRMS m/z calcd for C$_{15}$H$_{20}$O$_5$ (M$^{+\cdot}$): 280.1311; found 280.1311.

4.0 STEREOSELECTIVE QUATERNARY CARBON CONSTRUCTION ENABLED BY OLEFIN ISOMERIZATION-CLAISEN REARRANGEMENT REACTIONS

Asymmetric construction of quaternary carbon stereocenters continues to pose a special challenge in organic synthesis. In particular, methods accessing quaternary carbons wherein the attendant substituents are not limited by the requirement for specially derivatized or activated reaction components remain especially valuable. The [3,3]-sigmatropic rearrangements are among the well-established methods affording general access to all-carbon stereocenters Ven in architecturally complex settings.[95] Ireland enolate Claisen rearrangements, the most versatile and widely utilized variant of the [3,3] sigmatropic rearrangement, howVer, is limited in this context by the poor *E/Z* selectivity commonly associated with the enolization of simple $\alpha,\alpha-$ disubstituted esters (Figure 30). After the [3,3] sigmatropic rearrangement *via* a critical chair-like transition state, a mixture of two diastereomers is formed.

[95] For selected examples, see: (a) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730-2737. (b) Ziegler, F. E.; Nangia, A.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 3987-3991. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401. (d) Boeckman, R. K. Jr., del Rosario Rico Ferreira, M.; Mitchell, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190-191.
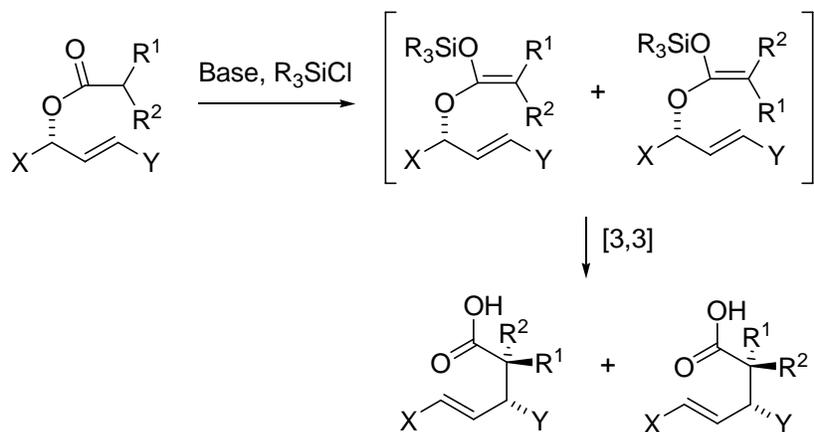
Figure 30. Constructing quaternary carbon stereocenters with Ireland Claisen rearrangements

Some special esters, such as chelated and/or cyclic enolates, provide good control of enolate geometry for α,α-disubstituted esters in advance of Ireland-Claisen rearrangements.[96] For example, α-amino substituted esters afford enolates of high *Z* selectivity because of a strong chelating effect. Highly diastereoselective [3,3]-sigmatropic products have been obtained (Scheme 35).[97]
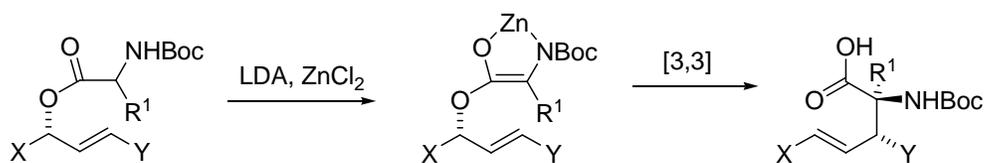
Scheme 35. Ireland –Claisen rearrangement of allyl α-aminoacetate

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[96] For a review, see: (a) *Quaternary Stereocenters* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**, pp. 120-131. For other selected examples, see: (b) Ireland, R. E.; Wipf, P.; Armstrong, III, J. D. *J. Org. Chem.* **1991**, *56*, 650-657. (c) Echavarren, A. M.; de Mendoza, J.; Prados, P.; Zapata, A. *Tetrahedron Lett.* **1991**,*32*, 6421-6424. (d) Gilbert, J. C.; Selliah, R. D. *Tetrahedron* **1994**, *50*, 1651-1664. (e) Enders, D.; Knopp, M.; *Tetrahedron* **1996**, *52*, 5805-5818. (f) Calad, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046-2047.
[97] (a) Kazmaier, U. *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 998-999. (b) Kazmaier, U.; Krebs, A. *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 2012-2014. (c) Kazmaier, U.; Mues, H.; Krebs, A. *Chem. Eur. J.* **2002**, *8*, 1850-1855.

4.1 CONSTRUCTION OF QUATERNARY CARBON CENTERS USING THE ICR REACTION

Based on the olefin isomerization-Claisen rearrangement (ICR) developed before, the ICR strategy, in which highly stereoselective construction of quaternary carbon stereocenters are obtained from chemo- and stereoselective Ir(I)-catalyzed isomerization of 2-substituented and 2,3-disubstituented allylic ethers and *in situ* [3,3] sigmatropic rearrangement of the formed allyl vinyl ethers, are desired (Figure 31).
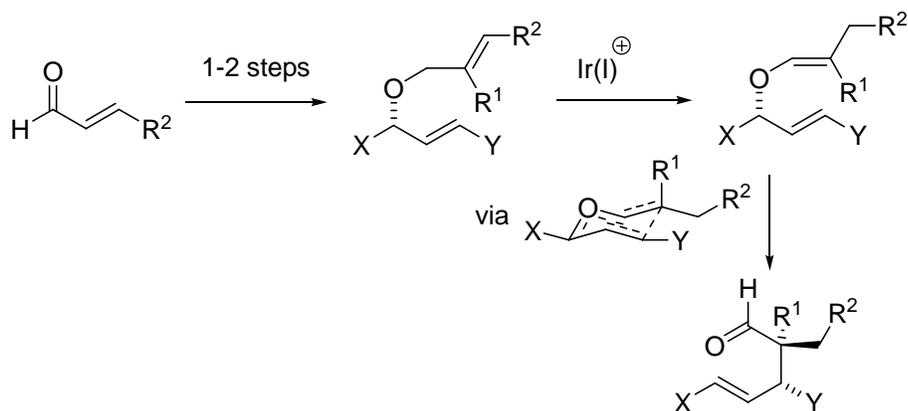
Figure 31. ICR-based strategy for quaternary carbon construction

Rigorous coupling of substrate olefin geometry and transition state organization with reaction stereoselectivity is a defining characteristic of [3,3] sigmatropic rearrangements. Highly stereoselective ICR-based Claisen rearrangements are predicted on controlling vinyl ether geometry during the initial olefin isomerization event. Limited energetic differentiation of the putative *E* or *Z* trisubstituted vinyl ethers constitutes a considerable liability for controlling olefin isomerization and Claisen stereoselectivity. As a result, documenting the capacity of metal-catalyzed isomerization of 2-substituented (**60a,** eq 16) and 2,3-disubstituented (**60b,** eq 17) allylic ethers was an essential component of these investigations. Moreover, enantioselective reaction variants would be predicated on the 2,2-disubstituted vinyl ether moieties causing

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limited disruption of chair-like transition states responsible for efficient transfer of substrate chirality during bond reorganization.

4.1.1 ICR of 1,1-disubstituted allyl ethers for preparing aldehydes with quaternary carbon center

Preliminary efforts addressing these issues employed ethers **60a/b** as representative test substrates for assaying olefin isomerization. Each reaction produced only a single *Z/E* vinyl isomer (**61a/b**) even after long reaction time (eq 16 and 17).
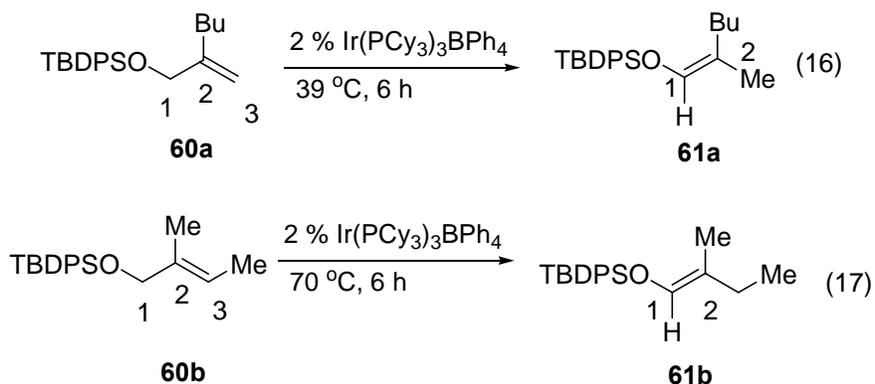
Based on the transition state shown in Figure 32, we assumed that vinyl ether **61a** is the *Z* isomer and **61b** is the *E* isomer. The non-bonding relationship between huge Ir(PCy₃)ₙ with OR makes Ir(I) coordinate with the olefin and insert into the allylic C-H bond from the side opposite from the OR group. Although the isomerization of 2-substituted or 2,3-disubstituted allyl ethers requires more catalyst-loading and longer time at higher temperature than that of simple allyl ethers described before, only one isomer was observed. The result indicated that the *E-Z* vinyl ether transformation is not observed in these reactions.
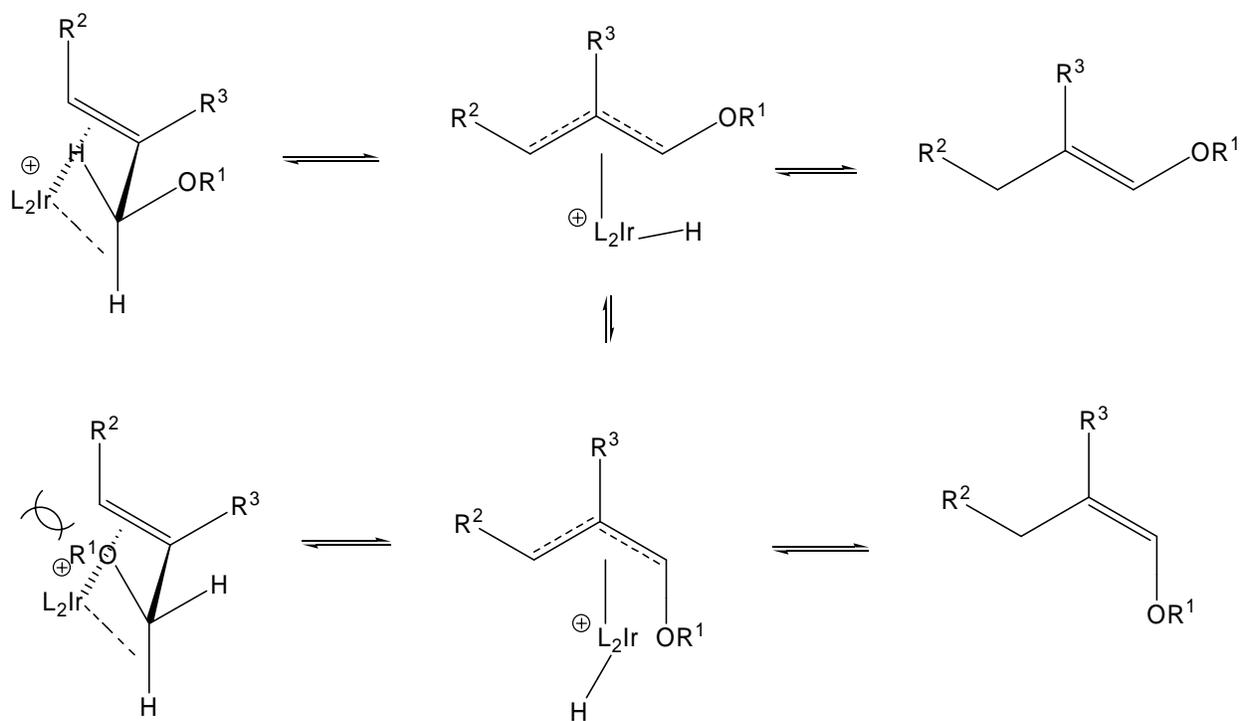
Figure 32. Stereoselectivity of isomerization

Based on this initial result, treating the di(allyl) ether (*E*)-(3-(2-methylenehexyloxy)prop-1-ene-1,3-diyl)dibenzene (**62a**) with 2 mol% Ir(PCy$_3$)$_3$BPh$_4$ at 75 °C elicited a highly selective isomerization and concomitant [3,3] sigmatropic rearrangement to directly generate the 2,2-disubstituted pentenal derivatives **64a** (*d.r.* = 97:3). Converting this aldehyde to the semicarbazide derivative (**64a'**) indicated that the aldehyde **64a** is the 2,3-*anti* isomer (Figure 33). This result confirmed our assumation that the (*Z*)-vinyl ether intermediate (**63a**) was offered from the isomerization.

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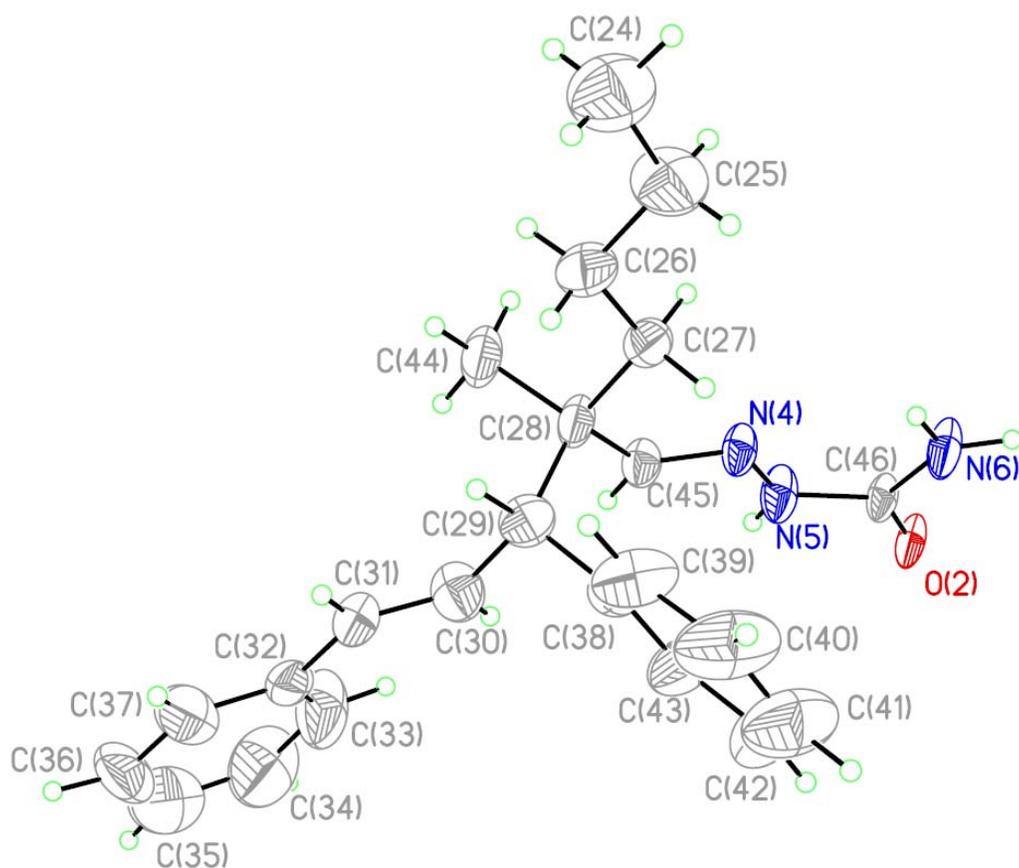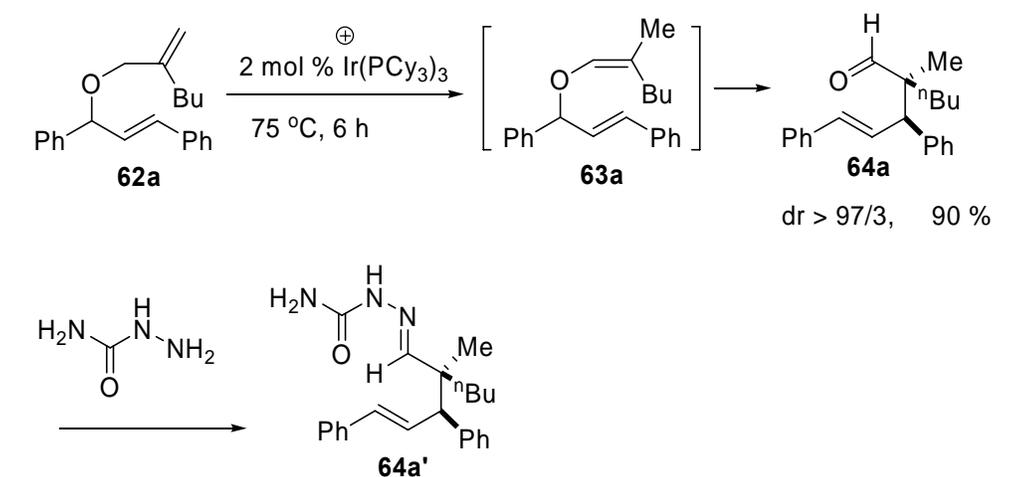
Figure 33. Structure of semicarbazide derivative of Claisen rearrangement product 64a

More 2-substituted di(allyl) ethers (**62a-n**) were prepared to observe the isomerization

reactivity of this new ICR protocol. Some methods were applied to prepare the 2-substituted allyl

alcohols. A two-step sequence from diethyl malonate with alkylation and reduction offered substituted allyl alcohols (Scheme 36).[98]
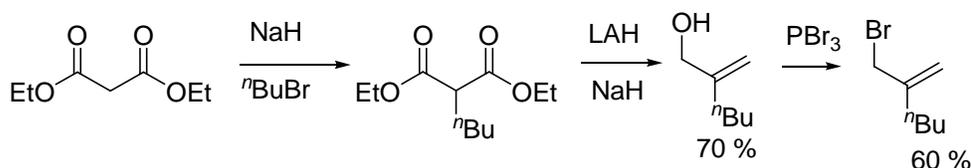
Scheme 36. Allyl alcohol from diethyl malonate

The CuI-catalyzed Grignard reagent addition to propargyl alcohol afforded 2-substituted allyl alcohols in a single step.[99] The first equivalent of Grignard reagent deprotonate the propargyl alcohol and the second equivalent of Grignard reagent (forming RCuMgBrI) attack the triple bond in the presence of copper salt to produce a five-member ring intermediate.[100] The 2-substituted allyl alcohols are obtained after aqueous work-up (eq 18).
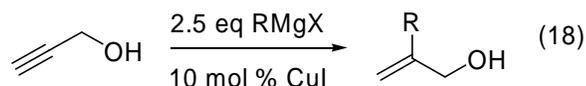
With the substituted allyl alcohol at hand, di(allyl) ether (**62**) was prepared. Generally, the di(allyl) ethers are obtained from the etherification of allyl bromide and sodium alkoxide. In some cases, the strong bases caused side reactions. For example, when R was a benzyl group (in the reaction for preparing **62e**, Scheme 37), the base partially deprotonated the benzyl carbon atom and caused an olefin shift to afford a by-product with a conjugated structures (**62e′**). It was difficult to directly isolate these two ethers. However when the mixture was treated under ICR conditions, the di(allyl) ether **62e′** had no ICR; but the di(allyl) ether **62e** afforded an aldehyde under ICR conditions. Finally, the ether **62e′** and the aldehyde **64e** were isolated. The Pd(0)-catalyzed *O*-allylation prepared the pure di(allyl) ether **62e**.

[98] Yadav, J. S.; Satyanarayana Reddy, P.; Jolly, R. S. *Indian J. Chem. Sect. B.* **1986**, 25, 294-295.
[99] Duboudin *J. Organomet. Chem.* **1979**, *168*, 1-11.
[100] Pd(0)-catalyzed coupling of this five-member ring intermediate affords disubstituted allyl alcohols, see: (a) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989-2992. (b) Lu, Z.; Ma, S. *J. Org. Chem.* **2005**, *71*, 2655-2660.
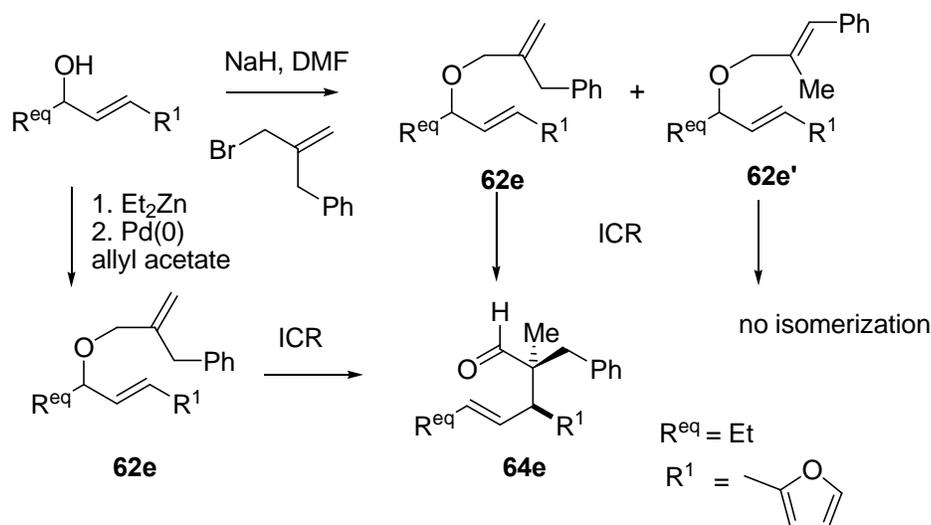
Scheme 37. *O*-allylation of benzyl substituted allyl bromide

The ICR of di(allyl) ethers **62** offered modest to high yields of aldehydes **64.** The results are listed in Table 6. The isomerization proceeded smoothly for most substrates (R = Me, Et, [n]Bu, Bn and Cy). The Claisen rearrangement of the benzyl-substituted allylic ethers **62d/e** served to highlight that olefin isomerization is highly regioselective even when the formation of a resonance-stabilized styrene system is a possible competing pathway (Scheme 38).
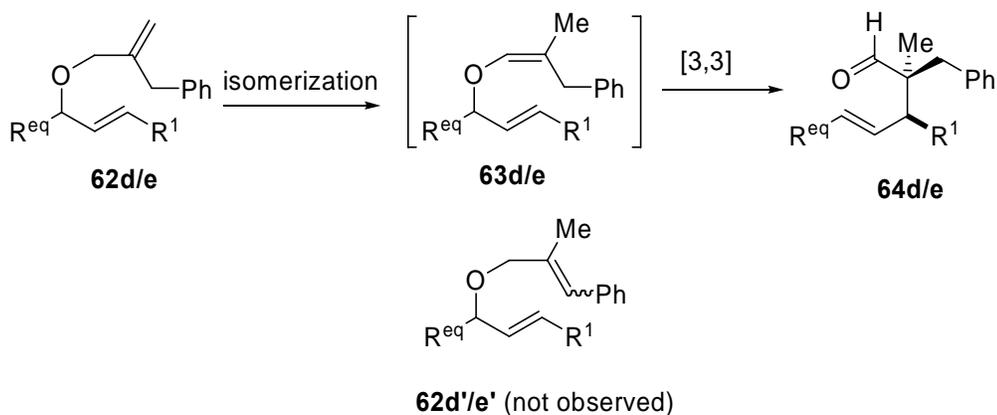
Scheme 38. ICR of benzyl substituted di(allyl) ether

Due to the large $A_{1,2}$ strain between R^2 and the alkoxy group, the isomerization process is retarded and no isomerization was observed when allyl ether (R^2 is [t]Bu, **60c**) was treated in 10 mol% catalyst loading at 80 ^{o}C for 24 h (eq 19). The same explaination accounts for the poor

isomerization of substrates **62f/g** with branched R^2 (cyclohexyl): the isomerization of **62f/g** requires more catalyst loading, a higher temperature and a longer reaction time.

$$RO\diagdown\diagup\hspace{-0.5em}\overset{{}^{t}Bu}{=}\quad\xrightarrow[\text{80 °C, 24 h}]{\text{10 mol \% Ir(PCy}_3)_3^{\oplus}}\quad \text{starting material}\quad (19)$$

60c

R = allyl or TBS
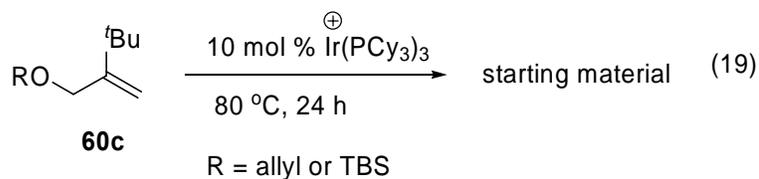
Table 6. ICR of 1,1-Disubstituted Allyl Ethers 62
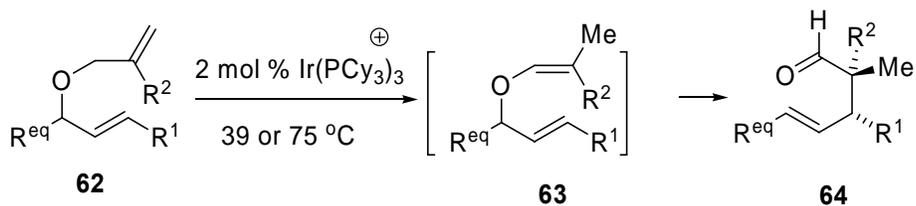
entry	R^{eq}	R^1	R^2	*anti: syn*	% yield
a	Ph	Ph	*n*Bu	97:3	90
b	Ph	Me	*n*Bu	93:7	93
c	*n*Bu	Me	*n*Bu	88:6.2 (6.2% Z isomers)	71
d	*n*Bu	Me	Bn	95:3 (2% Z isomers)	75
e	Et	2-furyl	Bn	96:4	76
f	Et	Ph	Cy	87:13	70
g	*n*Bu	Me	Cy	93:7	50[a]
h	Et	Ph	Et	90:6 (4% Z isomer)	66
i	*tert*-Bu	Me	Me	NA	85
j	Et	Ph	Cl		0
k	Et	Ph	Ph		0

a. The initial reaction time 24 h at ambient temperature, starting material remained.

Some substrates had not isomerization in the Table 6. Stabilized conjugated styrene structure caused no isomerization in entry **62k** (R^2 is Ph). Coordinations between Cl atom and Ir(I) made the isomerization of entry **62j** (R^2 is Cl) to be impossible.

Because there is no epimerization in these α-quaternary center aldehydes (**64a-i**) and the Ir(I)-catalyzed isomerization process is relatively slow at ambient temperature, the direct heating of the reaction mixtures also afforded ideal result. But this convenient procedure afforde good result only in some examples (e.g. R^{eq} = Me, Ph, ^iPr and cyclohexyl). When R^{eq} was Et or ^nBu, a side reaction, which is named post-rearrangement olefin isomerization of Claisen adduct (**64e**), produced a difficultly isolated by product (**65e**) (Scheme 39). To avoid the by product, the lower isomerization temperature and the additive PPh₃ were necessary.
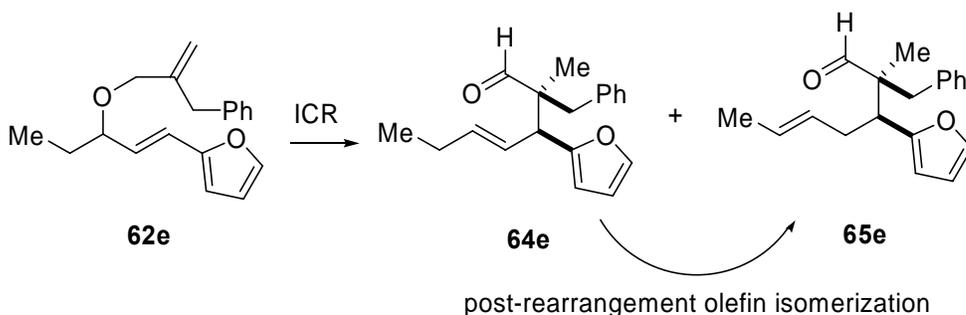
Scheme 39. Post-rearrangement olefin isomerization

4.1.2 ICR of 2,3-disubstituted allyl ether

Based on the ICR of 2-substituted allyl ethers, the ICR of 2,3-disubstituted allyl ethers (**66**) was examined. Suggested from the transition state in Figure 35, the (*E*)-vinyl ethers (**67**) were generated from the isomerization of 2,3-disubstituted allyl ethers **66**. Finaly, 2,3-*syn* aldehydes **68** were obtained followed by Claisen rearrangement.

2,3-Disubstituted allyl ethers were prepared from a convenient sequence: the 2-methyl allyl alcohol was treated with phosphrous bromide to afford a mixture of primary and secondary allylic bromides (about 3 : 1 to 4 : 1). Then sodium alkoxides attacked the mixture through S_N2 or S_N2' reaction to afford the single non-branched di(allyl) ethers with different Z/E selectivity (**66**, Scheme 40).
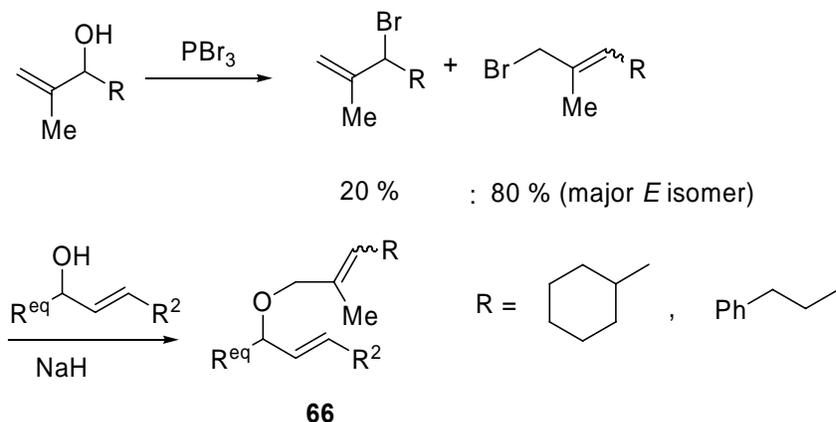
Scheme 40. Preaparation of trisubstituted allyl ethers

The ICR of di(allyl) ethers **66** offered modest to high yields of 2,3-*syn* aldehydes **68.** The results are listed in Table 7. This isomerization is more difficult and slower than that of 2-substituted allyl ethers **62**. Generally, isomerization temperatures were as high as 75 $^{\circ}$C. Upon treatment under ICR conditions, entries **66a-c** (R= Me or CH_2CH_2Ph) afforded *syn*-α-quaternary pentenals **68a-c** with good diastereoselectivity and yield. No desired aldehyde was afforded from the ICR of entry **d** (R = cyclohexyl) due to the large cyclohexyl retarding the Ir(I) complex coordination with the olefin and insertion into the allylic C-H bond.

Table 7. ICR of 2,3-disubstituted allyl ethers 66
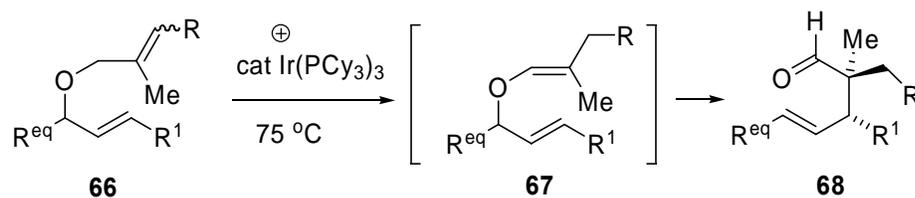
entry	R^{eq}	R^1	R	*syn:anti*	Yield %
a	*n*Bu	Me	Me	96:4	75
b	*n*Bu	Me	CH_2CH_2Bn	94:6	71
c[a]	Et	Ph	Me		60
d	*n*Bu	Me	Cy		0

a. The post-rearrangement olefin isomerization always afforded about 10 % by product in entry **c** (eq 20), but not obviously found in entry **a** and **b.** The possible reason is that the Claisen rearrangement of entry **c** is much easier than that of in entry **a** and **b**.
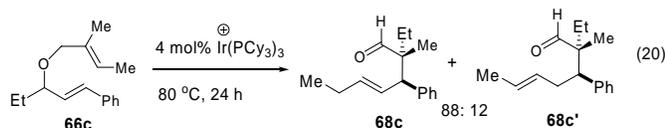
The Overall ICR stereoselectivity was suggestive of Claisen diastereoselection originating from kinetically controlled allyl ether isomerization via the η^3-allyl Ir^{III} intermediates **69a** or **69b** (Figure 34). Kinetic control of vinyl ether geometry is inferred from the eroded olefin stereoselectivity that accompanies extended isomerization reaction times. Moreover, ICR reorganization of **62h** and **66c** afford the diastereomeric Claisen products **64h** and **68c**, respectively (both two diastereomers are different in NMR spectra and HPLC coinjection), indicative of bond reorganization proceeding through stereochemically unique intermediates. Olefin isomerization subject to thermodynamic control would lead to stereoconvergent reactions of vinyl ethers **63h/67c** *via* interconversion of the kinetically-formed η^3-allyl complexes. Claisen rearrangements are characterized by the well-established relationships existing between substrate chirality, olefin geometry, and rearrangement stereoselectivity. Given the regioisomeric

relationship existing between **62h** and **66c**, these results correlate, for the first time, substrate *regiochemistry*, rather than *stereochemistry*, with the stereochemical outcome of the [3,3] sigmatropic rearrangement.
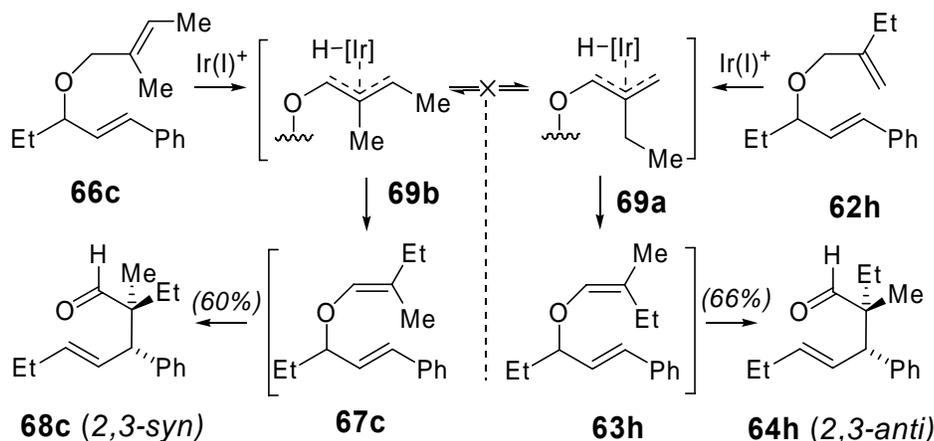
Figure 34. Correlating ICR substrate regiochemistry and Claisen diastereoselectivity

4.1.3 ICR reaction for enantioenriched aldehyde with quaternary center

Among the defining characteristics of these ICR reactions is the flexibility they offer in devising enantioselective reaction variants. First, enantioenriched ICR substrates were prepared in a single step by an amino alcohol-catalyzed asymmetric Et$_2$Zn-aldehyde addition and *in situ* zinc alkoxide allylation under Pd(0) catalysis (Scheme 41). Under the ICR reaction conditions, the enantioenriched 1,1-disubstituted allylic ethers **62e/f** afforded the 2,2-disubstituted-4-pentenals **64e/f** with near perfect chirality transfer.
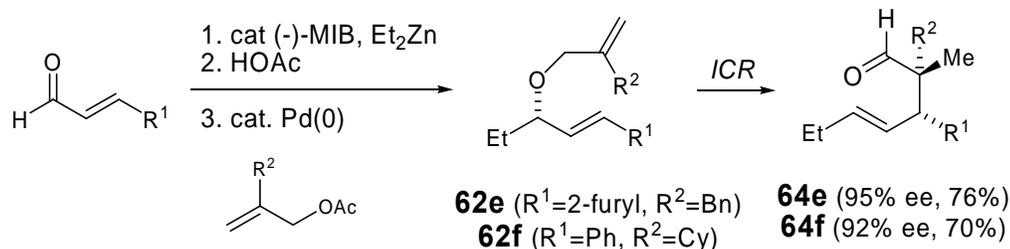
Scheme 41. Catalytic asymmetric di(allyl) ether synthesis

Alternatively, enantioenriched allyl homoallyl ethers as ICR substrates were prepared by asymmetric aldehyde *C*-allylation followed by *O*-alkylation (81% ee, Scheme 42). [101] Enantioenriched allyl homoallyl ether **70** participated in stereoselective tandem olefin isomerization to the corresponding (*E,Z*)-allyl vinyl ether **71** and *in situ* [3,3] sigmatropic rearrangement to afford the 2,3-*anti*-pentenal derivative **72** (81% ee) with near perfect chirality transfer.
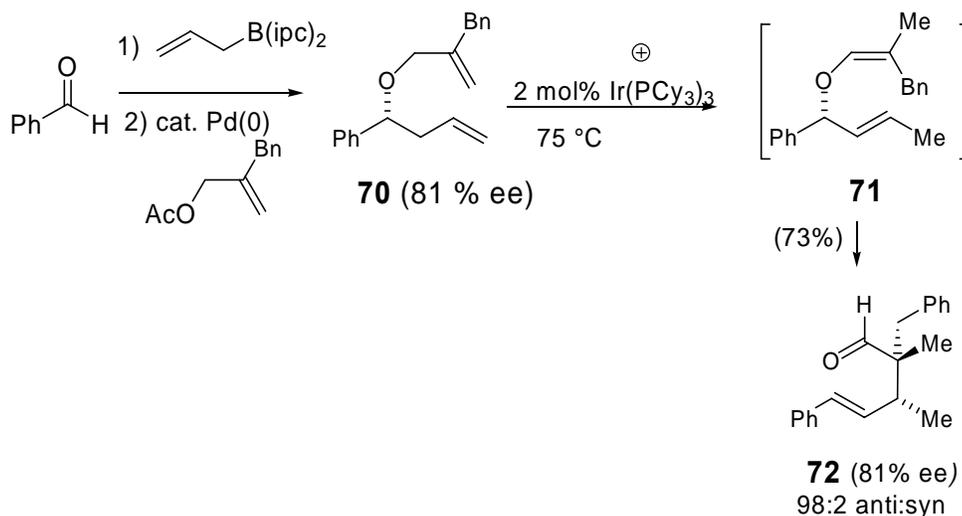
Scheme 42. ICR of asymmetric allyl homoallyl ether for aldehyde with quaternary carbon center

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[101] The enantioenriched homoallylic alcohol was prepared according to the published procedure, see: Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389-2392. The enantioselectivity of the allylation reaction was not optimized.

Finally, an enantioenriched α,α-disubstituted aldehyde lacking β stereocenter (**75**) was prepared by ICR of an enantioenriched di(allyl) ether **73,** which was prepared by enzyme-catalyzed kinetic resolution of racemic 5-phenylpent-1-en-3-ol[102] followed by *O*-allylation. The reaction proceeded without competing terminal olefin isomerization and delivered an aldehyde **75** with faithful chirality transfer but only modest yield (95% ee, 50%, Scheme 43). [103] However, under Pd(II) catalysis (5 mol% (*i*-BuCN)PdCl$_2$, *i*-BuCN/tol), the isolated allyl vinyl ether **74** undergoes bond reorganization with chirality transfer equal to the thermal reaction, albeit with opposite induction, to generate aldehyde **ent-75** in excellent yield (84%).[104]

Conditions: (a) 75 °C; *95% ee* (50% + 8% *Z* olefin)
(b) 5 mol % (*i*BuCN)PdCl$_2$; *93% ee* (84% **ent -75**)
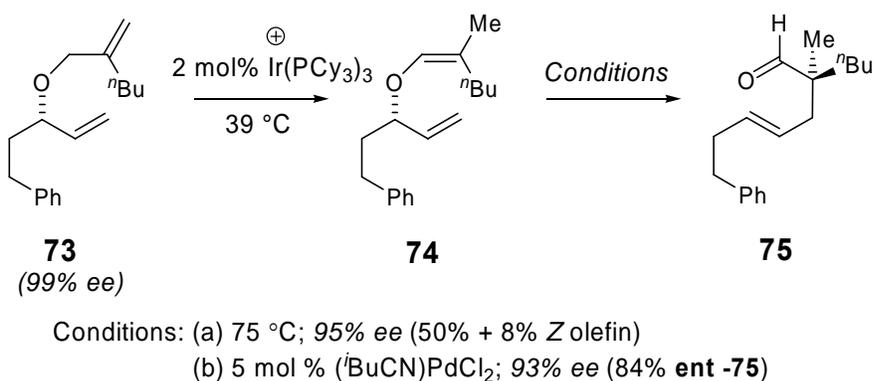
Scheme 43. Thermal and Pd(II)-catalyzed Claisen rearrangement for different enantiomers

In conclusion, the olefin isomerization-Claisen rearrangement reaction provides convenient access to stereodefined all-carbon stereocenters and vicinal quaternary-tertiary stereocenter relationships. The success of these reactions enables a variety of easily accessed strategies for achiVing enantioselective quaternary carbon installation.

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[102] Takagi, Y.; Teramoto, J.; Kihara, H.; Itoh, T.; Tsukube, H. *Tetrahedron Lett.* **1996**, *37*, 4991-4992.

[103] Remaining material is unreacted starting material resulting from incomplete olefin isomerization.

[104] Pd(II)-catalyzed Claisen rearrangements employing nitrile additives suppress the competing vinyl cleavage noted in prVious attempts at Pd(II)-catalyzed Claisen rearrangement of α-unsubstituted vinyl ethers; see: Van der Baan, J. L.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 6267-6270.

4.2   ICR OF DI(ALLYL) ETHER BEARING AN ENOL ETHER-QUATERNARY

CENTER WITH OXYGEN

Based on the result of constructing highly stereodefined all carbon quaternary centers with the ICR protocol, we sought to extend this methodology to prepare stereodefined quaternary α-hydroxy-pent-4-enals (Figure 35).
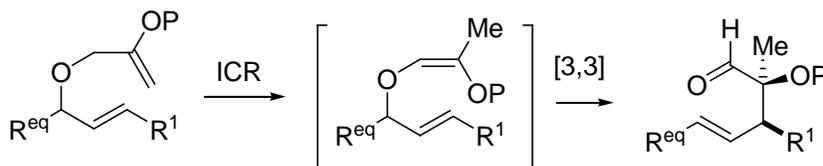
Figure 35. ICR of 2-alkoxy allyl ethers

Some precedents for preparing α-siloxy-pent-4-enals have been reported. The enolates of α-allyoxy ketones (**76**) were trapped with TMSCl to produce allyl vinyl ether intermediates (**77**). The subsequent Claisen rearrangement of **77** afforded α-siloxy-pent-4-enals (**78**) in good yield (70- 92 %).[105] However no aldehyde data, especially diastereoselectivity, were reported. It was suggested that the enolization of **76** afforded the *Z/E* mixture of silyl vinyl ethers (**77**) and caused the poor diastereoselectivity of the [3,3] products. Another problem of the strategy was a competing [2,3] Wittig rearrangement, which afforded by-product α-hydroxycarbonyl compounds **79** (Figure 36).[106]

[105] (a) Kachinski, J. L. C.; Salomon, R. G. *Tetrahedron Lett*. **1977**, 37, 3235-3238. (b) Kachinsky, J. L. C.; Salomon, R. G. *J. Org. Chem.* **1986**, 51, 1393-1401.
[106] (a) Mikami, K.; Takahashi, O.; Tabei, T.; Nakai, T. *Tetrahedron Lett.* **1986**, 27, 4511-4514. (b) Nakai, T.; Mikami, K.; Taya, S.; Kimura, Y.; Mimura, T. *Tetrahedron Lett.* **1981**, 22, 69-72.
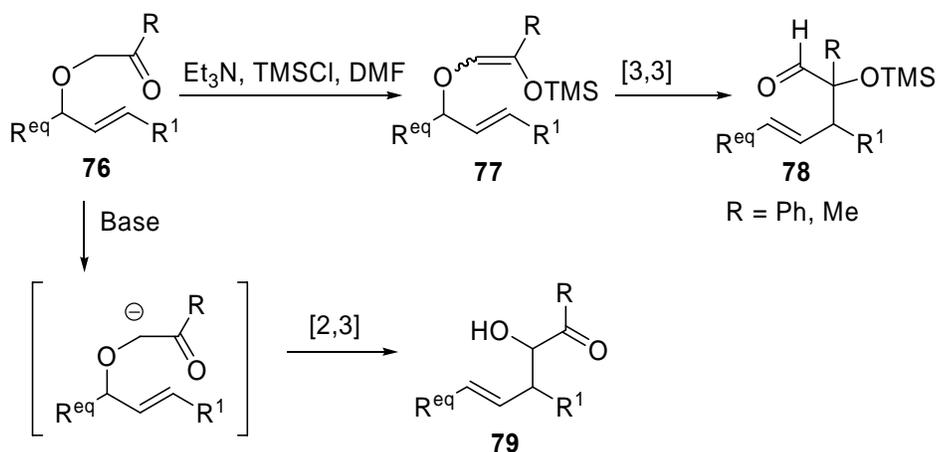
Figure 36. Competing [3,3] and [2,3] rearrangement of 76

Wood has reported a Rhodium carbenoid-initiated Claisen rearrangement for enantioselective synthesis of quaternary center with hydroxyl group (eq 21).[107] High chiral transfer was obtained from this reaction. Another example for preparing Claisen product with quaternary center with hydroxyl group is a Pd(II)-catalyzed ICR of a di(allyl) ether bearing an enol ether (eq 22).[108]
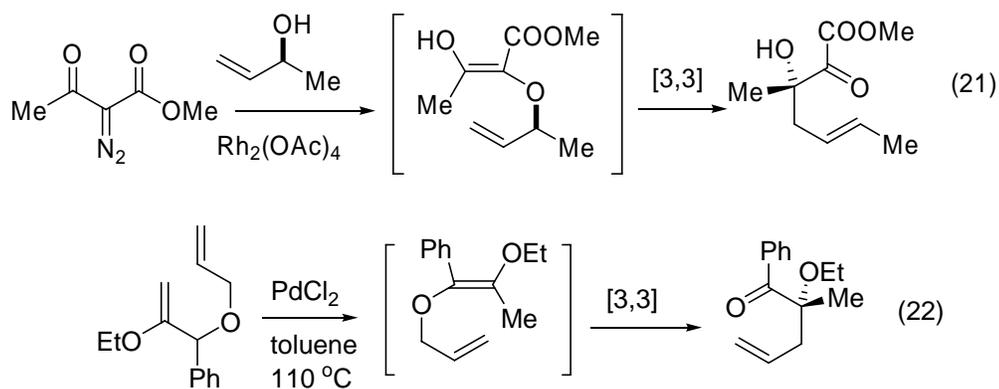
The ICR protocol was focused on preparing α-hydroxy quaternary carbon center with better diastereoselectivity, substrate generality and operational simplicity. Di(allyl) ethers (**81**)

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[107] Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H. J. *J. Am. Chem. Soc*. **1999**, *121*, 1748-1749.
[108] Nevado, C.; Echavarren, A. M. *Tetrahedron* **2004**, *60*, 9735-9744.

were prepared by methylidenation of corresponding alkoxy acetate esters (**80**) with Tebbe's reagent (eq 23).[109]

(23)
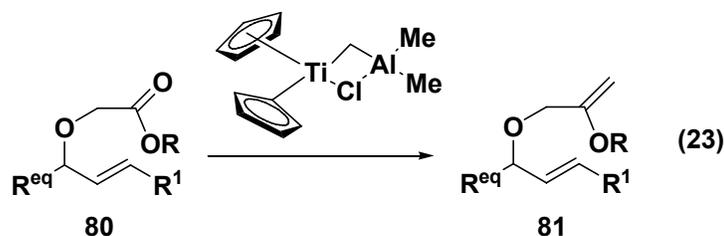
First, upon treatment under ICR conditions, the isomerization of di(allyl) ether **81a** at ambient temperature gave a mixture of 1: 1 *Z/E* isomer of by-product (**81a'**). The conjugation was overcome to form vinyl ether (**81a′**). No desired allyl vinyl ether (**82a**) or aldehyde (**83a**) was observed. The result indicated that the isomerization of 2-alkoxy allyl ether is even more difficult than that of the conjugated cinnamyl ether (eq 24). As a result, more elaborate conditions were required for the desired isomerization.

(24)
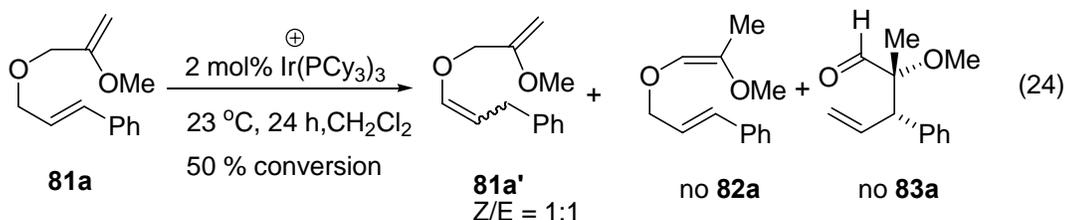
The ICR of substrate **82b** afforded 100 % conversion of rearrangement products (**83b**) with good diastereoselectivity (about 20 : 1). But the post-rearrangement olefin isomerization of **83b** afforded a difficultly isolated aldehydes mixture (**83b′**, about 50%, Figure 37). Considering this high temperature, slow isomerization rate and fast Claisen rearrangement rate, the post-rearrangement olefin isomerization is an essential problem for realizing successful ICR protocol.

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[109] 1.0 equivalent of bis(cyclopentadienyl)titanium (IV) dichloride and 2.0 equivalents of AlMe$_3$ in toluene stir in ambient temperature. See: (a) Pine, S. H.; Kim, G.; Lee, V. *Org. Syn.* **1990**, *69*, 72. Review of Titanium reagents for alkylidenation of carboxylic acid and carbonic acid derivatives, see: Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans. 1,* **2002**, 2763.
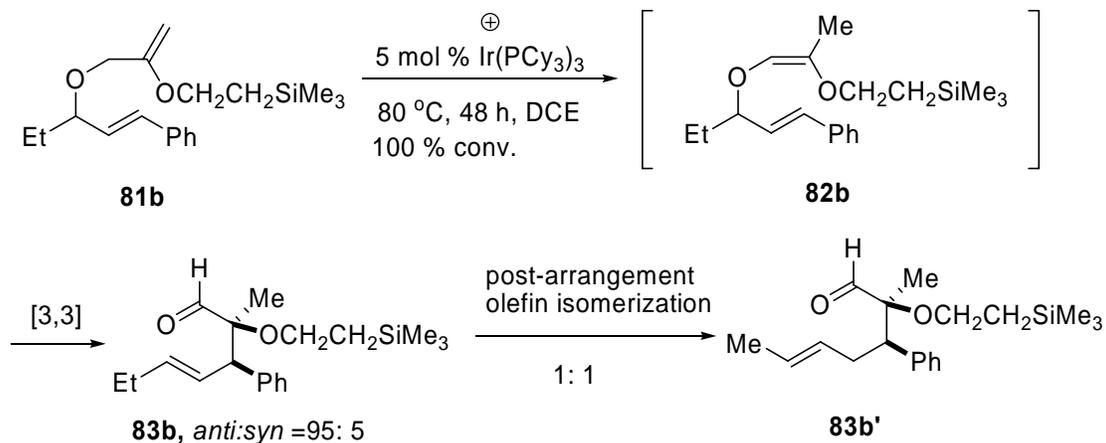
Figure 37. ICR and post-rearrangement olefin isomerization of di(allyl) ether

For minimizing the post-rearrangement olefin isomerization, milder condition was employed. The reaction afforded 50 % conversion of Claisen product (**83b/c**) with good diastereoselectivity in 48 h at 40 $^{\circ}$C, with unreacted starting material and a small amount of post-rearrangement olefin isomerization aldehyde (**83b'/c'**, eq 25).
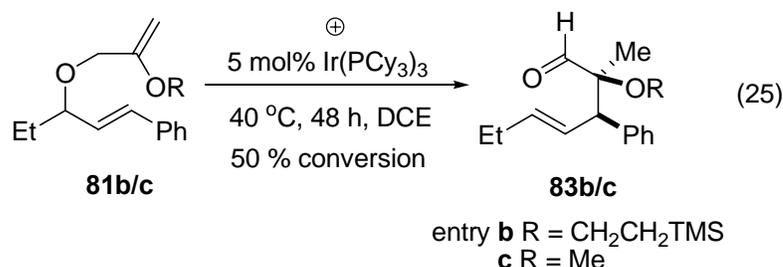
Based on the above observation, the slow isomerization, the fast [3,3]-sigmatropic rearrangement and the high temperature with the ICR protocol will bring post-rearrangement olefin isomerization products. To overcome this conflict, R^{eq} should be chosen from groups, in which no post-rearrangement olefin isomerization in the Claisen product (**83**). Methyl and some aryls and branched alkyls, for example, Ph, ^{i}Pr, ^{t}Bu and cyclohexyl, are good choices. Thus, the substrate **81d** (R^{eq} = Me) was subjected in 5 mol% catalyst loading at 75 $^{\circ}$C for 48 h to give product **83d** with good yield and diastereoselectivity (*anti:syn* = 94: 6) (eq 26). There is no post-rearrangement olefin isomerization in this case.

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$$(26)$$
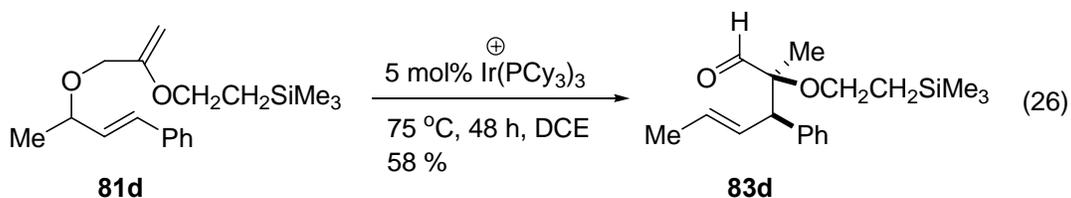
In general, stereoselective quaternary all-carbon stereocenter construction is often not easily achieved from methodologies developed primarily for accessing less substituted stereogenic carbons. Olefin isomerization-Claisen rearrangement (ICR) reactions offer a strategy for recruiting the venerable Claisen rearrangement for asymmetric quaternary carbon construction. Several complementary strategies for enantioselective quaternary carbon synthesis derive directly from the ICR reaction design.

4.3 EXPERIMENTAL SECTION

4.3.1 Experiment of section 4.1

4.3.1.1 ICR for 2-substituted allyl ethers
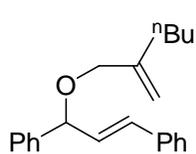
(E)-(3-(2-Methylenehexyloxy)prop-1-ene-1,3-diyl)dibenzene (62a): General Procedure **C** (concentrated H_2SO_4 catalyzed etherification) was followed employing (E)-1,3-diphenyl-2-propen-1-ol (0.489 g, 2.33 mmol) and 2-methylenehexan-1-ol[110] (0.474 ml, 3.49 mmol) in anhydrous THF (1 ml). The crude product was purified by MPLC on silica gel (0-5% EtOAc in hexanes) to afford 0.490 g (69%) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.90 (t, J = 7.2 Hz, 3H), 1.26-1.29 (m,

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[110] Yadav, J. S.; Joshi, B.; Sahasrabubhe, A. *Synth. Comm.* **1985**, *15*, 797-805.

4H), 2.09 (m, 2H), 3.97 (s, 2H), 4.93 (s, 1H), 4.96 (d, J = 7.1 Hz, 1H), 5.06 (s, 1H), 6.30 (dd, J = 16, 7.0 Hz, 1H), 6.62 (d, J = 16 Hz, 1H), 7.20-7.45 (m, 10H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.9, 22.4, 29.8, 32.9, 71.0, 81.3, 111.1, 126.5, 126.8, 127.5, 127.6, 128.4, 128.5, 130.3, 131.2, 136.6, 141.2, 146.3 ppm; MS (EI, 70 V): m/z 306 (M$^{+\cdot}$), 288, 262, 206, 193, 181, 165, 158, 143, 129, 115, 105, 91, 77, 65; HRMS m/z calcd for C$_{22}$H$_{26}$O (M$^{+\cdot}$): 306.1984; found: 306.1984.
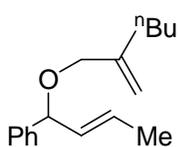
(E)-(1-(2-Methylenehexyloxy)but-2-enyl)benzene (62b): General Procedure **A** was followed employing 1.00 g of (E)-1-phenylbut-2-en-1-ol (6.75 mmol) in THF. The crude product was purified by silica gel (2% EtOAc in hexanes) to afford 1.57 g (95%) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.89 (m, 3H), 1.25-1.46 (m, 4H), 1.71 (d, J = 5.7 Hz, 3H), 2.06 (m, 2H), 3.88 (s, 2H), 4.72 (d, J = 6.7 Hz, 1H), 4.89 (s, 1H), 5.01 (s, 1H), 5.59 (ddd, J = 15, 6.6, 0.9 Hz, 1H), 5.69 (dq, J = 15, 6.2 Hz, 1H), 7.22-7.35 (m, 5H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.8, 17.6, 22.4, 32.9, 70.7, 81.4, 110.9, 126.7, 127.2, 127.8, 128.2, 132.3, 132.4, 141.8, 146.4 ppm; MS (EI, 70 V): m/z 244 (M$^{+\cdot}$), 229, 147, 131, 119, 115, 105, 91, 77, 55; HRMS m/z calcd for C$_{17}$H$_{24}$O (M$^{+\cdot}$): 244.1827; found: 244.1821.
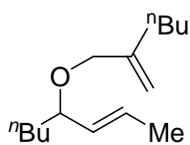
(E)-4-(2-Methylenehexyloxy)oct-2-ene (62c): General Procedure **A** was followed employing 0.961 g of (E)-oct-2-en-4-ol[111] (6.75 mmol) in THF. Purification by MPLC on silica gel(0-5 % ethyl acetate in hexanes) afforded 1.20 g (71 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.89 (m, 3H), 0.91 (m, 3H), 1.20-1.65 (m, 10H), 1.71 (dd, J = 6.4, 1.6 Hz, 3H), 2.04 (m, 2H), 3.58 (dt, J =

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[111] Chamberlin, A, R.; Mulholland, R. L. Jr. *Tetrahedron* **1984**, *40*, 2297.

8.1, 6.3 Hz, 1H), 3.72 (d, J = 13 Hz, 1H), 3.93 (d, J = 13 Hz, 1H), 4.85 (s, 1H), 4.97 (s, 1H), 5.29

(ddq, J = 14, 6.6, 1.6 Hz, 1H), 5.58 (dqd, J = 15, 6.5, 0.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz,

CDCl$_3$): δ 13.9, 14.0, 17.6, 22.5, 22.7, 27.7, 29.8, 33.0, 35.5, 70.5, 80.0, 110.5, 128.1, 132.4,

146.9 ppm; MS (EI, 70 V): m/z 224 (M$^{+\cdot}$), 229, 167, 139, 127, 111, 97, 85, 69, 55; HRMS m/z

calcd for C$_{15}$H$_{28}$O (M$^{+\cdot}$): 224.2140. Found: 224.2141.
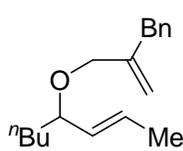
1-(2-((*E*)-Oct-2-en-4-yloxy)methyl)allyl)benzene (62d): **General Procedure A** was followed employing (*E*)-oct-2-en-4-ol (256 mg, 2.0 mmol) and 1-(2-(bromomethyl)allyl)benzene[112] (630 mg, 3.0 mmol) in THF. The crude product

was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to yield 397 mg

(77%) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.18-7.53 (m,

5H), 5.51 (dq, J = 15.2, 6.5 Hz, 1H), 5.28 (ddq, J = 15.2, 8.2, 1.4 Hz, 1H), 5.09 (s, 1H), 4.89 (s,

1H), 3.91 (d, J = 12.6 Hz, 1H), 3.70 (d, J = 12.6 Hz, 1H), 3.58 (dt, J = 8.2, 6.2 Hz, 1H), 3.40 (s,

2H), 1.69 (dd, J = 6.5, 1.4 Hz, 3H), 1.30-1.76 (m, 6H), 0.92 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR

(75 MHz, CDCl$_3$): δ 146.1, 139.3, 132.2, 129.0, 128.3, 128.1, 126.0, 112.9, 79.9, 69.7, 40.0,

35.4, 27.7, 22.6, 17.6, 14.0 ppm; IR (liquid film): 2932, 2859, 1651, 1495, 1453, 1073, 969, 902,

740, 699 cm^{-1}; MS (EI, 70 V): m/z 258 (M$^{+\cdot}$), 240, 201, 131, 91, 70; HRMS m/z calcd for

C$_{18}$H$_{26}$O (M$^{+\cdot}$): 258.1984; found: 258.1988.
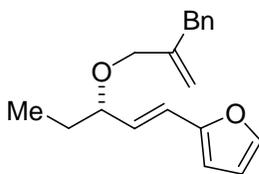
(*S,E*)-2-(3-(2-Benzylallyloxy)pent-1-enyl)furan (62e): General Procedure **D** was applied to (*E*)-3-(2-furyl)acrolein (611 mg, 5.0 mmol)

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[112] 1-(2-(Bromomethyl)allyl)benzene was prepared by by reacting 2-benzylprop-2-en-1-ol with PBr$_3$ in hexanes.

146

and 2-benzylallyl acetate (950 mg, 5.0 mmol)[113]. The crude product was purified by column chromatography on silica gel (2% EtOAc in hexanes) to yield 765 mg (54%) of the title compound as light yellow oil. $[\alpha]_D = -89.7$ (c 5.12, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.27-7.41 (m, 6H), 6.43 (dd, J = 3.2, 1.9 Hz, 1H), 6.34 (d, J = 15.9 Hz, 1H), 6.28 (d, J = 3.2 Hz, 1H), 6.07 (dd, J = 15.9, 7.7 Hz, 1H), 5.19 (s, 1H), 4.99 (s, 1H), 4.04 (d, J = 12.5 Hz, 1H), 3.84 (d, J = 12.5 Hz, 1H), 3.77 (q, J = 6.9 Hz, 1H), 3.48 (s, 2H), 1.60-1.90 (m, 5H), 1.04 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 152.30, 145.90, 141.78, 139.17, 129.00, 128.21, 126.03, 120.32, 113.13, 111.16, 107.70, 80.87, 70.24, 40.00, 28.61, 9.84 ppm; IR (liquid film): 3027, 2964, 2931, 1651, 1494, 1453, 1030, 1013, 963, 736, 699 cm^{-1}; MS (EI, 70 V): m/z 282 (M$^{+\cdot}$), 253, 225, 200, 191, 151, 148, 135, 131, 123, 115; HRMS m/z calcd for C$_{19}$H$_{22}$O$_2$ (M$^{+\cdot}$) 282.1620; found: 282.1608. The allylic alcohol (S,E)-1-(furan-2-yl)pent-1-en-3-ol was purified by column chromatography on silica gel (2% EtOAc in hexanes); $[\alpha]_D = -6.4$ (c 1.74, CHCl$_3$). Separating the enantiomers by chiral HPLC [Daicel Chiracel^{TM} OD-H column, flow rate 0.5 mL/min, 5% i-PrOH, 95% hexanes, T$_r$ 18.69 (R) and 20.52 (S)] provided the enantiomer ratio: 3R: 3S = 2.0: 98.0 (96% ee).
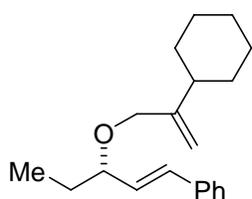
(S,E)-(3-(2-Cyclohexylallyloxy)pent-1-enyl)benzene **(62f)**: General Procedure **D** was followed employing cinnamaldehyde (2.0 mmol, 264 mg) and 2-cyclohexylallyl acetate (2.4 mmol, 437 mg).[114] The crude product was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to yield 341 mg (60%) of the title compound as light yellow oil. $[\alpha]_D = -63.4$ (c 4.51, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20-7.40 (m, 5H), 6.58 (d, J = 15.9 Hz, 1H), 6.14 (dd, J = 15.9, 8.0 Hz, 1H),

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[113] 2-Benzylallyl acetate was prepared by reacting 2-benzylprop-2-en-1-ol with acetic anhydride.
[114] 2-Cyclohexylallyl acetate was prepared by reacting 2-cyclohexylprop-2-en-1-ol with acetic anhydride.

5.09 (s, 1H), 4.96 (s, 1H), 4.14 (d, J = 12.8 Hz, 1H), 3.91 (d, J = 12.8 Hz, 1H), 3.84 (q, J = 6.9

Hz, 1H), 1.98-2.08 (m, 1H), 1.15-1.98 (m, 12H), 1.03 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75

MHz, CDCl$_3$): δ 151.73, 136.71, 132.06, 130.66, 128.49, 127.51, 126.37, 109.05, 81.39, 70.27,

41.10, 32.35, 32.11, 28.71, 26.72, 26.33, 9.90 ppm; IR (liquid film): 2926, 2852, 1449, 1093,

967, 891, 747, 692 cm^{-1}; MS (EI, 70 V): *m/z* 284 (M$^{+\cdot}$), 255, 193, 145, 129, 115, 91; HRMS *m/z*

calcd for C$_{20}$H$_{28}$O (M$^{+\cdot}$): 284.2140; found: 284.2147. The allylic alcohol (S,E)-1-phenylpent-1-

en-3-ol was purified by flash chromatography on silica gel (2% EtOAc in hexanes). Separating

the allylic alcohol enantiomers by chiral HPLC [Daicel Chiracel^{TM} OD-H column, flow rate 1.0

mL/min, 0.5% *i*-PrOH, 99.5% hexanes, T$_r$ 13.4 (R) and 16.3 (S)] provided the enantiomer ratio:

3R: 3S = 3.5:96.5 (93% ee).
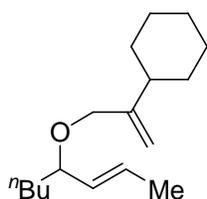
(3-((*E*)-Oct-2-en-4-yloxy)prop-1-en-2-yl)cyclohexane **(62g)**: General

Procedure **A** was followed employing (*E*)-oct-2-en-4-ol (256 mg, 2.0 mmol)

and (3-bromoprop-1-en-2-yl)cyclohexane (447 mg, 2.2 mmol)[115] in THF. The

crude product was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to

yield 355 mg (71%) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ

5.58 (dq, J = 15.3, 6.5 Hz, 1H), 5.30 (ddq, J = 15.3, 8.2, 1.5 Hz, 1H), 4.97 (s, 1H), 4.85 (s, 1H),

3.98 (d, J = 12.8 Hz, 1H), 3.75 (d, J = 12.8 Hz, 1H), 3.60 (dt, J = 8.2, 6.4 Hz, 1H), 1.95 (t, J =

11.1 Hz, 1H), 1.72 (dd, J = 6.5, 1.5 Hz, 3H), 1.07-1.83 (m, 16 H), 0.90 (t, J = 7.4 Hz, 3H) ppm;

^{13}C NMR (75 MHz, CDCl$_3$): δ 152.1, 132.5, 128.3, 109.0, 80.1, 69.9, 41.2, 35.6, 32.5, 32.2, 27.8,

26.9 (overlap of 2 C), 26.5, 22.8, 17.8, 14.2 ppm; MS (EI, 70 V): *m/z* 250 (M$^{+\cdot}$), 209, 193, 137,

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[115] (3-Bromoprop-1-en-2-yl)cyclohexane was prepared by reacting 2-cyclohexylprop-2-en-1-ol with PBr$_3$ in hexanes

123, 109, 111, 95, 86, 83, 69, 67, 55; HRMS *m/z* calcd for $C_{17}H_{30}O$ (M$^{+\cdot}$): 250.2297; found: 250.2306.
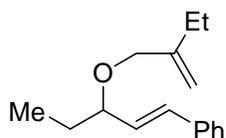
(E)-(3-(2-Methylenebutoxy)pent-1-enyl)benzene **(62h)**: **General Procedure A** was followed employing (*E*)-1-phenylpent-1-en-3-ol (324 mg, 2.0 mmol) and 2-(bromomethyl)but-1-ene (447 mg, 3.0 mmol) in DMF. The crude product was purified by flash chromatography on silica gel (2 % EtOAc in hexanes) to yield 360 mg (78%) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.27-7.49 (m, 5H), 6.59 (d, J = 16.0 Hz, 1H), 6.15 (dd, J = 16.0, 8.0 Hz, 1H), 5.10 9s, 1H), 4.97 (s, 1H), 4.10 (d, J = 12.5 Hz, 1H), 3.91 (d, J = 12.5 Hz, 1H), 3.84 (q, J = 7.4 Hz, 1H), 2.17 (q, J = 7.3 Hz, 2H), 1.62-1.91 (m, 2H), 1.14 (t, J = 7.4 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 148.11, 136.68, 132.09, 130.55, 128.48, 127.50, 126.36, 109.84, 81.29, 71.08, 28.67, 25.96, 11.99, 9.85 ppm; MS (EI, 70 V): *m/z* 230 (M$^{+\cdot}$), 201, 161, 145, 133, 117, 91; HRMS *m/z* calcd for $C_{16}H_{22}O$ (M$^{+\cdot}$): 230.1671; found: 230.1668.
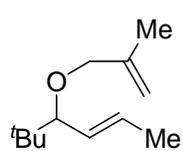
(E)-5,5-Dimethyl-4-(2-methylallyloxy)hex-2-ene (62i): General procedure **A** was followed employing (*E*)-2,2-dimethylhex-4-en-3-ol (640 mg, 5.0 mmol) and 3-chloro-2-methylprop-1-ene (675 mg, 7.5 mmol). The crude product was purified by flash chromatograph on silical gel (2 % EtOAc in hexanes) to yield 819 mg (90 %) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.54 (dq, J = 15.3, 6.4 Hz, 1H), 5.31 (ddq, J = 15.3, 8.6, 1.4 Hz, 1H), 4.92 (s, 1H), 4.81 (s, 1H), 3.87 (d, J = 12.7 Hz, 1H), 3.62 (d, J = 12.7 Hz, 1H), 3.17 (d, J = 8.6 Hz, 1H), 1.72 (dd, J = 6.4, 1.5 Hz, 3H), 1.71 (s, 3H), 0.89 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.09, 129.70, 129.09, 111.08, 88.03, 71.98, 34.62, 26.24, 19.74, 17.77 ppm.
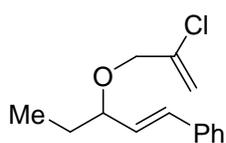
(*E*)-(3-(2-Chloroallyloxy)pent-1-enyl)benzene (62j): General procedure **A** was followed employing (*E*)-1-phenylpent-1-en-3-ol (810 mg, 5.0 mmol) and 2,3-dichloroprop-1-ene (833 mg, 7.5 mmol). The crude product was purified by flash chromatograph on silical gel (2 % EtOAc in hexanes) to yield 1.06 g (90 %) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20-7.42 (m, 5H), 6.53 (d, J = 15.9 Hz, 1H), 6.05 (dd, J = 15.9, 8.1 Hz, 1H), 5.48 (q, J = 1.3 Hz, 1H), 5.35 (q, J = 1.0 Hz, 1H), 4.12 (ddd, J = 14.1, 1.4, 1.1 Hz, 1H), 3.98 (ddd, J = 14.1, 1.2, 0.9 Hz, 1H), 3.82 (q, J = 7.0 Hz, 1H), 1.57-1.84 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H) ppm.
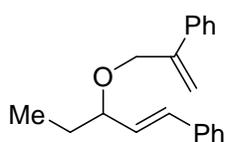
1-(1-((*E*)-1-Phenylpent-1-en-3-yloxy)prop-2-en-2-yl)benzene (62k): General procedure **A** was followed employing (*E*)-1-phenylpent-1-en-3-ol (486 mg, 3 mmol) and 1-(1-bromoprop-2-en-2-yl)benzene[116] (870 mg, 4.5 mmol). The crude product was purified by flash chromatograph on silical gel (2 % EtOAc in hexanes) to yield 667 mg (80 %) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.35-7.65 (m, 10H), 6.70 (d, J = 16.0 Hz, 1H), 6.26 (dd, J = 16.0, 8.0 Hz, 1H), 5.68 (s, 1H), 5.53 (d, J = 1.3 Hz, 1H), 4.64 (d, J = 12.9 Hz, 1H), 4.42 (d, J = 12.9 Hz, 1H), 4.02 (q, J = 6.9 Hz, 1H), 1.68-1.93 (m, 2H), 1.05 (d, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.7, 139.0, 136.1, 132.3, 130.4, 128.6, 128.2, 127.6, 126.4, 126.2, 114.0, 81.5, 69.9, 28.7, 9.9 ppm; MS (EI, 70 V): *m/z* 278 (M$^{+\cdot}$), 249, 231, 220, 205, 187, 145, 131, 116, 103; HRMS *m/z* calcd for C$_{20}$H$_{22}$O (M$^{+\cdot}$) 278.1671. found 278.1675.

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[116] 1-(1-bromoprop-2-en-2-yl)benzene was prepared by reacting 2-phenylprop-2-en-1-ol with PBr$_3$ in hexanes
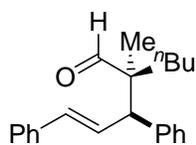
***anti*-2-((*E*)-1,3-Diphenylallyl)-2-methylhexanal (64a)**: **General Procedure D** was followed employing 0.477 g of (*E*)-3-(2-methylenehexyloxy)-1,3-diphenylprop-1-ene (**62a**, 6.21 mmol) in CH$_2$Cl$_2$ at 23 °C. Purifying the crude product mixture by MPLC (0-10% EtOAc in hexanes) afforded 0.430 g (90%) of the title compound as colorless oil (*anti: syn* > 97:3). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.87 (m, 3H), 1.12 (s, 3H), 1.25 (m, 4H), 1.47-1.77 (m, 2H), 3.68 (d, J = 8.7 Hz, 1H), 6.47 (d, J = 16 Hz, 1H), 6.56 (dd, J = 16, 8.7 Hz, 1H), 7.17-7.39 (m, 10H), 9.61 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.9, 16.0, 23.3, 26.3, 34.6, 52.7, 55.7, 126.3, 126.8, 127.4, 127.8, 128.3, 128.5, 129.0, 133.0, 137.1, 140.2, 206.4; MS (EI, 70 V): *m/z* 306 (M$^{+\cdot}$), 250, 193, 178, 165, 115, 91; HRMS *m/z* calcd for C$_{22}$H$_{26}$O (M$^{+\cdot}$): 306.1984; found: 306.1986.
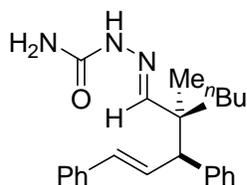
***anti*-(1*E*)-1-((*E*)-2-Butyl-2-methyl-3,5-diphenylpent-4-enylidene)semi carbazide (64a′)**: Semicarbazide hydrochloride (1.11 g, 10 mmol) and dry sodium acetate (1.23 g, 15 mmol) were ground together in a mortar. Ethanol (10 mL) was added and the resulting mixture was heated to boiling. The hot solution was filtered and then cooled to ambient temperature *anti*-2-((*E*)-1,3-diphenylallyl)-2-methylhexanal (**64a**, 153 mg, 0.5 mmol) was added and the mixture was heated at 40 °C for 2.5 h. Water (20 mL) was added and the resulting mixture was extracted with ethyl ether (3 × 20 mL). evaporating the solvent gave 181 mg of the desired product (100 %) that was recrystallized from ethanol to provide crystals suitable for X-ray diffraction analysis. ^{1}H NMR (300 MHz, DMSO-d^6): δ 9.77 (s, 1H), 6.70 (dd, J = 15.6, 10.1 Hz, 1H), 6.43 (d, J = 15.6 Hz, 1H), 6.02 (s, 2H), 3.51 (d, J = 9.9 Hz, 1H), 3.33 (s, 1H), 1.10-1.45 (m, 7H), 1.05 (s, 3H), 0.79 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d^6): δ 156.71, 148.56, 141.41, 137.04, 131.47, 129.86,

129.20, 128.50, 127.80, 127.18, 126.15, 126.10, 57.69, 43.66, 37.06, 25.91, 22.88, 19.21, 13.97

ppm; MS (EI, 70 V): *m/z* 363 (M$^{+\cdot}$), 246, 233, 193, 178, 165, 127, 115, 91; HRMS *m/z* calcd for

C$_{23}$H$_{29}$ON$_3$ (M$^{+\cdot}$): 363.2311; found: 363.2237. See Appendix A for X-ray diffraction data.
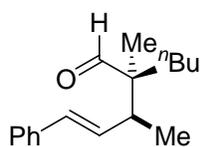
anti-2-Methyl-2-((E)-4-phenylbut-3-en-2-yl)hexanal   **(64b)**:   **General**

Procedure D (CH$_2$Cl$_2$ at 40 °C) was followed employing 0.491 g of 1-((*E*)-1-

(2-methylenehexyloxy)but-2-enyl)benzene (**62b**). Purifying the crude product

mixture by MPLC (0-10% gradient EtOAc in hexanes) afforded 454 mg (93%) of the title

compound as a colorless oil (*anti : syn* = 93 :7). Separating the steoisomers by GLC [Varian CP

Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp

@ 5.00 °C/min to 250 °C, hold for 20.00 min, Tr = 55.4 (ANTI), 55.8 (SYN) min] provided the

diastereomer ratio: 93:7. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.87 (m, 3H), 1.01 (d, J = 5.8 Hz, 3H),

1.03 (s, 3H), 1.03-1.25 (m, 4H), 1.43-1.63 (m, 2H), 2.61 (m, 1H), 6.08 (dd, J = 16, 9.0 Hz, 1H),

6.43 (d, J = 16 Hz, 1H), 7.21-7.40 (m, 5H), 9.50 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.6,

13.9, 16.0, 23.3, 26.1, 34.9, 41.8, 52.2, 126.1, 127.2, 128.5, 130.4, 131.3, 137.2, 206.8; MS (EI,

70 V): *m/z* 244 (M$^{+\cdot}$), 188, 131, 115, 104, 91, 77, 70, 65, 55; HRMS *m/z* calcd for C$_{17}$H$_{24}$O (M$^{+\cdot}$):

244.1827; found: 244.1827.
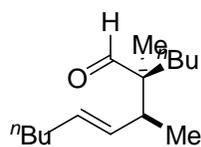
anti-(E)-2-Butyl-2,3-dimethylnon-4-enal (64c): General Procedure **D** (1,2-

DCE, at 80 °C) was followed employing 0.477 g of (*E*)-4-(2-

methylenehexyloxy)oct-2-ene (**62c**). Purification by MPLC (0-10%

EtOAc/hexanes) afforded 0.338 g (71 %) of the title compound as a colorless oil (*anti : syn : Z* =

88 : 6.2 : 6.2). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.86 (m, 3H), 0.90 (m, 3H), 0.93(s, 3H), 1.00-1.57

(m, 10H), 2.00 (m, 2H), 2.36 (dq, J = 8.5, 6.9, 1H), 5.25 (ddt, J = 15, 8.7, 1.2 Hz, 1H), 5.45 (dt, J

= 15, 6.7 Hz, 1H), 9.43 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.5, 13.8, 16.1, 22.1, 23.3, 26.1,

31.6, 32.2, 34.8, 41.2, 51.8, 130.0, 132.3, 207.2; MS (EI, 70 V): *m/z* 224 (M$^{+\cdot}$), 168, 153, 114,

111, 95, 81, 69, 55; HRMS *m/z* calcd for C$_{15}$H$_{28}$O (M$^{+\cdot}$): 224.2140. Found: 224.2143.
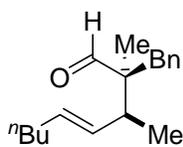
***anti*-(*E*)-2-Benzyl-2,3-dimethylnon-4-enal (64d)**: **General Procedure D** was

followed employing 1-(2-(((*E*)-oct-2-en-4-yloxy)methyl)allyl)benzene (**62d**,

258 mg, 1.0 mmol) and 2 mol% of the Ir(I)-derived catalyst (9.0 mg

[IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$, and 6.8 mg NaBPh$_4$) and stirred 60 h at 75 °C using 1,2-

dichloroethane as solvent. Purifying the crude product mixture by flash chromatography on

silica gel (2.5% Et$_2$O in hexanes) yielded 194 mg (75%) of the title compound as a colorless oil

(*anti : syn : Z* = 95 : 3 : 2). Separating the stereoisomers by GLC [Varian CP Wax 52CB column

(30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to

250 °C, hold for 20.00 min, Tr = 50.4, 50.6, 53.0 and 53.4 min] provided the diastereomer ratio:

Z: syn: anti = 2.6:2.9:94.5. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.61 (s, 1H), 7.04-7.28 (m, 5H), 5.56

(dt, J = 15.2, 6.7 Hz, 1H), 5.38 (ddt, J = 15.2, 8.8, 1.2 Hz, 1H), 3.01 (d, J = 13.8 Hz, 1H), 2.70 (d,

J = 13.8 Hz, 1H), 2.49 (dq, J = 8.6, 7.0 Hz, 1H), 2.06-2.13 (m, 2H), 1.36-1.42 (m, 4H), 0.99 (d, J

= 6.9 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 207.0,

137.2, 133.2, 130.2, 129.9, 128.1, 126.4, 53.3, 41.8, 41.4, 32.3, 31.6, 22.2, 16.4, 13.9, 13.7 ppm;

MS (EI, 70 V): *m/z* 258 (M$^{+\cdot}$), 240, 201, 131, 91, 70; HRMS *m/z* calcd for C$_{18}$H$_{26}$O (M$^{+\cdot}$):

258.1984; found: 258.1988.
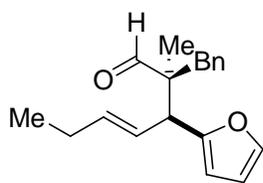
(2S,3S,E)-2-Benzyl-3-(furan-2-yl)-2-methylhept-4-enal (64e): General Procedure D was followed employing di(allyl) ether **62e** (141 mg, 0.5 mmol) and 4 mol% catalyst (9.0 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$, and 6.8 mg NaBPh$_4$) using 1,2-dichloroethane as solvent at 35 °C and an initial reaction time of 12 h. After addition of 15.6 mg PPh$_3$, the reaction was heated at 80 °C for 16 h; (2R,3R):(2S,3R) = 96:4. Purifying the crude product mixture by flash chromatography on silica gel (2.5% Et$_2$O in hexanes) yielded 107 mg (76%) of the title compound as a light yellow oil. [α]$_D$ = +25.0 (c 2.71, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.75 (s, 1H), 7.05-7.40 (m, 6H), 6.32 (dd, J = 3.1, 1.9 Hz, 1H), 6.10 (d, J = 3.1 Hz, 1H), 5.61-5.76 (m, 2H), 3.72 (d, J = 8.2 Hz, 1H), 3.07 (d, J = 13.7 Hz, 1H), 2.75 (d, J = 13.7 Hz, 1H), 2.15 (qd, J = 7.4, 5.0 Hz, 1H), 1.06 (t, J = 7.4 Hz, 3H), 0.99 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.87, 154.44, 141.49, 137.40, 136.72, 130.38, 128.11, 126.48, 123.71, 110.11, 107.33, 53.28, 48.55, 41.05, 25.64, 15.98, 13.64 ppm; IR (liquid film): 2965, 2932, 1723, 1497, 1454, 1148, 1013, 973, 733, 701 cm^{-1}; MS (EI, 70 V): m/z 282 (M$^{+\cdot}$), 253, 225, 200, 191, 151, 148, 135, 131, 123, 115; HRMS m/z calcd for C$_{19}$H$_{22}$O$_2$ (M$^{+\cdot}$): 282.1620; found: 282.1608.
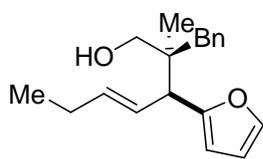
(2S,3S,E)-2-Benzyl-3-(furan-2-yl)-2-methylhept-4-en-1-ol (64e′): 1 M hexanes solution of ^{i}Bu$_2$AlH (0.5 mL, 0.5 mmol) was added to a −78 °C solution of aldehyde **64e** (70 mg, 0.25 mmol) in CH$_2$Cl$_2$. After stirring 30 min at −78 °C, a saturated aqueous sodium tartrate solution (2 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases formed (~1 h). The mixture was extracted with Et$_2$O (3×) and the combined organic extracts were dried (MgSO$_4$), concentrated, and the resulting crude oil was purified by flash chromatography on

silica gel (16% EtOAc in hexanes) to yield 56 mg (80%) of the title compound as a light yellow oil. Separating the enantiomers by chiral HPLC [Daicel Chiracel^{TM} OD-H column, flow rate 0.5 mL/min, 5.0% i-PrOH, 95.0% hexanes, T_r 10.06 (2R, 3R) and 11.12 (2S, 3S)] provided the enantiomer ratio: **64e′**(2R,3R): **64e′**(2S,3S) = 2.4:97.6 (95.2 % ee). [α]$_D$ = +18.1 (c 5.37, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.37 (dd, J = 1.7, 0.6 Hz, 1H), 7.20-7.35 (m, 5H), 6.36 (dd, J = 3.1, 1.7 Hz, 1H), 6.12 (d, J = 3.1 Hz, 1H), 5.80 (dd, J = 15.2, 9.5 Hz, 1H), 5.66 (dt, J = 15.2, 6.0 Hz, 1H), 3.61 (d, J = 9.5 Hz, 1H), 3.19 (d, J = 11.5 Hz, 1H), 3.06 (d, J = 11.5 Hz, 1H), 2.87 (d, J = 13.2 Hz, 1H), 2.63 (d, J = 13.2 Hz, 1H), 2.14 (qd, J = 7.4, 6.0 Hz, 2H), 1.06 (t, J = 7.4 Hz, 3H), 0.73 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 156.34, 140.78, 138.58, 135.81, 130.80, 127.81, 125.89, 125.42, 110.22, 106.52, 66.05, 48.63, 42.86, 40.73, 25.70, 17.70, 13.76 ppm; IR (liquid film): 3590, 3461, 2964, 2247, 1496, 1454, 1147, 1032, 973, 910, 731, 703 cm^{-1}; MS (EI, 70 V): m/z 284 (M$^{+\cdot}$), 193, 148, 135, 121, 117, 107, 91, 79; HRMS m/z calcd for C$_{19}$H$_{24}$O$_2$ (M$^{+\cdot}$): 284.1776; found: 284.1787.

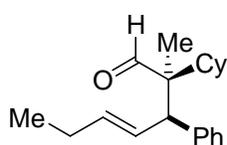**(2S,3S,E)-2-Cyclohexyl-2-methyl-3-phenylhept-4-enal** (**64f**): General Procedure **C** was followed employing di(allyl) ether **62f** (142 mg, 0.5 mmol) and 4 mol% catalyst (9.0 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$, and 6.8 mg NaBPh$_4$) in 1,2-dichloroethane solvent at 50 °C and an initial reaction time of 12 h. After addition of 15.6 mg PPh$_3$, the reaction was heated at 80 °C for 16 h; (2R,3S):(2S,3S) = 87:13. Purifying the crude product mixture by flash chromatography on silica gel (2.5% Et$_2$O in hexanes) yielded 100 mg (70%) of the title compound as light yellow oil. Stereoisomer ratios were determined for corresponding primary alcohol (see below). [α]$_D$ = +17 (c 0.78, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.66 (s, 1H), 7.20-7.40 (m, 5H), 5.66 (dd, J = 15.1, 9.5 Hz, 1H),

5.56 (dt, J = 15.1, 5.8 Hz, 1H), 3.70 (d, J = 9.5 Hz, 1H), 1.98-2.13 (m, 2H), 1.12-1.80 (m, 13 H), 0.99 (s, 3H), 0.98 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 208.33, 141.08, 135.33, 128.99, 128.21, 127.22, 126.49, 54.40, 52.91, 40.99, 28.36, 27.19, 26.80, 26.64, 26.49, 25.63, 13.71, 13.51 ppm; IR (liquid film): 2927, 2853, 1722, 1451, 969, 746, 702 cm^{-1}; MS (EI, 70 V): m/z 284 (M$^{+ \cdot}$), 255, 193, 145, 129, 115, 91; HRMS m/z calcd for C$_{20}$H$_{28}$O (M$^{+ \cdot}$): 284.2140; found: 284.2145.
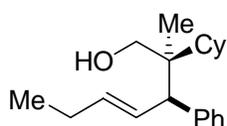
(2S,3S,E)-2-Cyclohexyl-2-methyl-3-phenylhept-4-en-1-ol (64f′): A 1 M hexanes solution of ^{i}Bu$_2$AlH (0.5 mL, 0.5 mmol) was added to a −78 °C solution of aldehyde **64f** (70 mg, 0.25 mmol) in CH$_2$Cl$_2$. After stirring 30 min at −78 °C, a saturated aqueous sodium tartrate solution (2 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases formed (~1 h). The mixture was extracted with Et$_2$O (3×) and the combined organic extracts were dried (MgSO$_4$), concentrated, and the resulting crude oil was purified by flash chromatography on silica gel (16% EtOAc in hexanes) to yield 59 mg (85%) of the title compound as a light yellow oil. Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T$_r$ = 69.8 (syn, E), 70.1 (anti, E), and 70.4 (anti, Z), min] provided the diastereomer ratio: 12.8: 89.4: 3.8. Separating the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.5 ml/min, 4.0% i-PrOH, 96.0% hexanes, T$_r$ 10.6 (2S,3S) and 14.1 (2R,3R) provided the enantiomer ratio: *(2S,3S): (2R,3R)* 3.6: 96:4 (92 % ee). [α] $_D$ = +11.2 (c 2.51, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.18-7.32 (m, 5H), 5.90 (ddt, J = 15.1, 10.0, 1.2 Hz, 1H), 5.50 (dt, J = 15.1, 6.3 Hz, 1H), 3.61 (d, J = 10.0, 1H), 3.46 (dd, J = 11.6, 5.6 Hz, 1H), 3.36

(dd, J = 11.6, 6.7 Hz, 1H), 2.05 (qd, J = 7.4, 6.3 Hz, 2H), 1.10-1.80 (m, 11H), 0.99 (t, J = 7.4 Hz, 3H), 0.84 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.37, 134.17, 129.23, 128.77, 128.19, 126.17, 66.90, 52.40, 43.44, 42.97, 27.98, 27.87, 27.50, 27.40, 26.88, 25.82, 16.82, 13.91 ppm; IR (liquid film): 3467, 2959, 1738, 1451, 1375, 1265, 1032, 973, 739, 704 cm^{-1}; MS (EI, 70 V): m/z 268 (M$^{+\cdot}$–H$_2$O), 255, 146, 123, 117; HRMS m/z calcd for C$_{20}$H$_{28}$ (M$^{+\cdot}$–H$_2$O): 268.2191; found 268.2197.
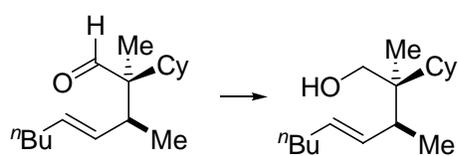
anti-(E)-2-Cyclohexyl-2,3-dimethylnon-4-enol (**64g′**): General Procedure **C** was followed employing 1-(2-(((E)-oct-2-en-4-yloxy)methyl)allyl)benzene **62g** (250 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$, and 6.8 mg NaBPh$_4$) and an initial reaction time of 24 h at 23 °C. After addition of 15.6 mg PPh$_3$, the reaction was heated at 80 °C for 16 h. The reaction was cooled to ambient temperature and the crude product mixture was dissolved in CH$_2$Cl$_2$ (2 mL). The reaction was cooled to −78 °C and a solution of ^{i}Bu$_2$AlH (1.0 M in hexanes, 2.0 mL, 2.0 mmol) was added. After stirring 30 min at −78 °C, a saturated aqueous sodium tartrate solution (8 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases formed (~1 h). The mixture was extracted with Et$_2$O (3×) and the combined organic extracts were dried (MgSO$_4$), concentrated, and the resulting crude oil was purified by flash chromatography on silica gel (16% EtOAc in hexanes) to yield 126 mg (50%, anti : syn= 93 : 7) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.49 (dd, J = 15.4, 7.6 Hz, 1H), 5.39 (dt, J = 15.4, 5.9 Hz, 1H), 3.54 (d, J = 11.5 Hz, 1H), 3.46 (d, J = 11.5 Hz, 1H), 2.39 (dq, J = 7.6, 7.0 Hz, 1H), 2.01 (q, J = 6.4 Hz, 2H), 1.04-1.78 (m, 15H), 1.01 (d, J = 7.0 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 0.69 (s, 3H) ppm; ^{13}C

NMR (75 MHz, CDCl$_3$): δ 133.3, 130.6, 66.7, 41.9, 41.8, 40.4, 32.5, 31.8, 28.0, 27.4 (overlap of 3C), 26.9, 22.2, 16.7, 15.9, 14.0 ppm; MS (EI, 70 V): *m/z* 252 (M$^{+\cdot}$), 227, 193, 181, 169, 127, 109, 95, 67, 57; HRMS *m/z* calcd for C$_{17}$H$_{32}$O (M$^{+\cdot}$): 252.2453; found: 252.2460.
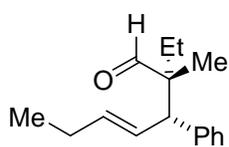
***anti*-(*E*)-2-Ethyl-2-methyl-3-phenylhept-4-enal (64k): General Procedure C** was followed employing (*E*)-(3-(2-methylenebutoxy)pent-1-enyl)benzene (**62k**, 115mg, 0.5 mmol) and 4 mol% catalyst (9.0 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$), and stirred 12 h at 50 °C in 1,2-dichloroethane solvent. At this time, 15 mg of PPh$_3$ was added at the reaction was heated at 80 °C for an additional 12 h. Purifying the crude product mixture by flash chromatography on silica gel (2.0% EtOAc in hexanes) yielded 76 mg (66%) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.58 (s, 1H), 7.27-7.47 (m, 5H), 5.80 (dd, J = 15.2, 9.8 Hz, 1H), 5.61 (dt, J = 15.1, 6.2 Hz, 1H), 3.48 (d, J = 9.7 Hz, 1H), 1.95-2.09 (m, 2H), 1.45-1.80 (m, 2H), 1.04 (s, 3H), 1.01 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 207.0, 140.9, 135.8, 129.3, 128.2, 126.6, 126.5, 55.3, 52.7, 27.2, 25.6, 15.3, 13.6, 8.5; MS (EI, 70 V): *m/z* 230 (M$^{+\cdot}$), 201, 145, 131, 117, 91, 77, 69, 57; HRMS *m/z* calcd for C$_{16}$H$_{22}$O (M$^{+\cdot}$): 230.1671; found 230.1668.
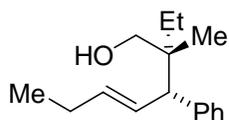
***anti*-(*E*)-2-Ethyl-2-methyl-3-phenylhept-4-enol (64k′):** A 1 M hexanes solution of ^{i}Bu$_2$AlH (0.5 mL, 0.5 mmol) was added to a −78 °C solution of aldehyde **64k** (57 mg, 0.25 mmol) in CH$_2$Cl$_2$. After stirring 30 min at −78 °C, a saturated aqueous sodium tartrate solution (2 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases formed (~1 h). The mixture was

extracted with Et$_2$O (3×) and the combined organic extracts were dried (MgSO$_4$), concentrated, and the resulting crude oil was purified by flash chromatography on silica gel (16% EtOAc in hexanes) to yield 40 mg (70%) of the title compound as a light yellow oil. Separating the isomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T$_r$ = 52.9, 53.2, and 53.7 min] provided the diastereomer ratio: 6 (*syn*): 4 (*Z*): 90 (*anti*). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.21-7.40 (m, 5H), 5.94 (ddt, J = 15.1, 10.1, 1.4 Hz, 1H), 5.59 (ddt, J = 15.1, 10.1, 1.4 Hz, 1H), 3.52 (d, J = 11.3 Hz, 1H), 3.41 (d, J = 11.3 Hz, 1H), 3.35 (d, J = 10.1 Hz, 1H), 1.98-2.10 (m, 2H), 1.20-1.65 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H), 0.82 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 142.7, 134.3, 129.3, 128.6, 127.9, 126.1, 67.2, 54.9, 41.1, 27.1, 25.7, 18.2, 13.7, 8.0 ppm; IR (liquid film): 3392, 2963, 2930, 1601, 1492, 1453, 1376, 1034, 970, 702 cm^{-1}; MS (EI, 70 V): *m/z* 232 (M$^{+.}$), 201, 145, 129, 117; HRMS *m/z* calcd for C$_{16}$H$_{24}$O (M$^{+.}$): 232.1827; found 232.1835.
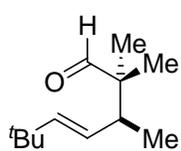
(*E*)-2,2,3,6,6-Pentamethylhept-4-enal (64i): General Procedure **D** was followed employing di(allyl) ether (**62i**, 182 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) and stirred 60 h at 80 °C in dichloroethane solvent. Purification by flash chromatograph on silical gel (2.5 % ethyl ether in hexanes) to yield 155 mg (85 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.43 (s, 1H), 5.46 (d, J = 15.6 Hz, 1H), 5.13 (dd, J = 15.6, 8.8 Hz, 1H), 2.29 (dq, J = 8.8, 7.0 Hz, 1H), 0.96 (s, 9H), 0.95 (s, 3H), 0.94 (s, 3H), 0.90 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 206.9, 143.5, 124.8, 48.7, 41.8, 33.0, 29.7, 19.5, 17.9, 15.6 ppm.

4.3.1.2 ICR for 2,3-disubstituted allyl ethers
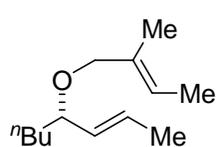
(2E)-4-((E)-2-Methylbut-2-enyloxy)oct-2-ene (66a): General Procedure **A** was followed employing (E)-oct-2-en-4-ol (384 mg, 3.0 mmol) and (E)-1-bromo-2-methylbut-2-ene (671 mg, 4.5 mmol) in THF. The crude product was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to yield 235 mg (40%) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.57 (dq, J = 15.3, 6.4 Hz, 1H), 5.45 (q, J = 6.7 Hz, 1H), 5.29 (ddq, J = 15.3, 8.2, 1.5 Hz, 1H), 3.87 (d, J = 11.2 Hz, 1H), 3.66 (d, J = 11.3 Hz, 1H), 3.55 (q, J = 7.0 Hz, 1H), 1.71 (dd, J = 6.4, 1.5 Hz, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.25-1.46 (m, 6H), 0.89 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 133.4, 132.5, 128.0, 121.8, 79.6, 73.8, 35.5, 27.7, 22.7, 17.6, 14.0, 13.8, 13.1 ppm; MS (EI, 70 V): *m/z* 196 (M[+.]), 181, 139, 110, 81, 71, 69; HRMS *m/z* calcd for C$_{13}$H$_{24}$O (M[+.])196.1827. found 196.1832.
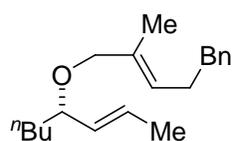
1-((3E)-5-((E)-Oct-2-en-4-yloxy))-4-methylpent-3-enyl)benzene (66b): General Procedure **A** was followed employing (E)-oct-2-en-4-ol (256 mg, 2.0 mmol) and a mixture of 1-((E)-5-bromo-4-methylpent-3-enyl)benzene and 1-(3-bromo-4-methylpent-4-enyl) benzene (~4:1, 714 mg, 3.0 mmol)[117] in THF. The crude product was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to yield 372 mg (65%) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.18-7.53 (m, 5H), 5.55 (dq, J = 15.3, 6.4 Hz, 1H), 5.44 (t, J = 6.8 Hz, 1H), 5.30 (ddq, J = 15.3, 8.2, 1.5 Hz, 1H), 3.89 (d, J = 11.5 Hz, 1H), 3.69 (d, J = 11.5 Hz, 1H), 3.55 (q, J = 7.0 Hz, 1H), 2.69 (t, J = 7.8 Hz, 2H), 2.39 (q, J = 7.4 Hz, 2H), 1.73 (dd, J = 6.2, 1.0 Hz, 3H), 1.63 (s, 3H), 1.24-1.50 (m, 4H),

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[117] The mixture of 1-((E)-5-bromo-4-methylpent-3-enyl)benzene and 1-(3-bromo-4-methylpent-4-enyl)benzene was prepared by reacting 2-methyl-5-phenylpent-1-en-3-ol with PBr$_3$ in hexanes.

0.91 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 142.1, 133.3, 132.4, 128.4, 128.2, 128.1, 126.6, 125.7, 79.4, 73.6, 35.7, 35.4, 31.6, 29.6, 27.7, 22.7, 17.7, 14.1 ppm; MS (EI, 70 V): m/z 286 (M$^{+\cdot}$), 229, 195, 181, 175, 160, 143, 127; HRMS m/z calcd for C$_{16}$H$_{21}$O (M$^{+\cdot}$−C$_4$H$_9$) 229.1592; found: 229.1594.
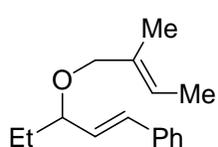
((E)-3-((E)-2-Methylbut-2-enyloxy)pent-1-enyl)benzene (66c): General Procedure **A** was followed employing (E)-1-phenylpent-1-en-3-ol (324 mg, 2.0 mmol) and (E)-1-bromo-2-methylbut-2-ene (447 mg, 3.0 mmol) in DMF. The crude product was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to yield 320 mg (70%) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.21-7.53 (m, 5H), 6.62 (d, J = 16.0 Hz, 1H), 6.18 (dd, J = 16.0, 7.9 Hz, 1H), 5.61 (q, J = 5.7 Hz, 1H), 4.07 (d, J = 11.2 Hz, 1H), 3.88 (d, J = 11.2 Hz, 1H), 3.83 (q, J = 7.0 Hz, 1H), 1.79 (s, 3H), 1.75 (d, J = 5.7 Hz, 3H), 1.61-1.91 (m, 2H), 1.07 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.76, 133.19, 131.90, 130.77, 128.50, 127.49, 126.36, 122.12, 80.95, 74.31, 28.67, 13.75, 13.13, 9.94 ppm; IR (liquid film): 2965, 2931, 2859, 1493, 1450, 1063, 968, 747, 693 cm^{-1}; MS (EI, 70 V): m/z 230 (M$^{+\cdot}$), 201, 161, 145, 133, 117, 91; HRMS m/z calcd for C$_{16}$H$_{22}$O (M$^{+\cdot}$): 230.1671; found 230.1668.
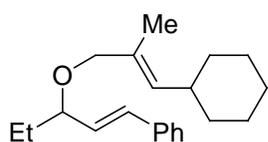
1-((1E)-3-   ((E)-3-Cyclohexyl-2-methylallyloxy)pent-1-enyl)benzene (66d): General procedure **A** was followed employing (E)-1-phenylpent-1-en-3-ol (486 mg, 3.0 mmol) and mixture of 1-((E)-5-bromo-4-methylpent-3-enyl)benzene and 1-(3-bromo-4-methylpent-4-enyl) benzene (about 4: 1, 1.3 g, 6.0 mmol). The crude product was purified by flash chromatograph on silical gel (2 % EtOAc in

hexanes) to yield 715 mg (80 %) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20-7.46 (m, 5H), 6.49 (d, J = 16.0 Hz, 1H), 6.07 (dd, J = 16.0, 8.0 Hz, 1H), 5.23 (d, J = 9.1 Hz, 1H), 3.95 (d, J = 11.5 Hz, 1H), 3.76 (d, J = 11.5 Hz, 1H), 3.71-3.75 (m, 1H), 2.12-2.28 (m, 1H), 1.26-1.80 (m, 12H), 1.68 (d, J = 1.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 136.7, 134.3, 132.0, 130.7, 130.3, 128.5, 127.5, 126.3, 80.6, 74.4, 36.6, 33.1, 32.9, 28.7, 26.0, 25.94, 25.91, 14.0, 10.04 ppm; MS (EI, 70 V): m/z 298 (M$^{+\cdot}$), 269, 240, 226, 161, 145, 133, 117, 95, 81; HRMS m/z calcd for C$_{21}$H$_{30}$O (M$^{+\cdot}$) 298.2297. found 298.2305.
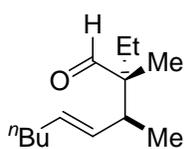
syn-(E)-2-Ethyl-2,3-dimethylnon-4-enal (68a): **General Procedure C** was followed employing (2E)-4-((E)-2-methylbut-2-enyloxy)oct-2-ene (**66a**, 196 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$, and 6.8 mg NaBPh$_4$) and stirred 60 h at 75 °C in 1,2-dichloroethane solvent. Purifying the crude product mixture by flash chromatography on silica gel (2.5% Et$_2$O in hexanes) yielded 147 mg (75%) of the title compound as a colorless oil (syn:anti= 96:4). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.45 (s, 1H), 5.43 (dt, J = 15.2, 6.4 Hz, 1H), 5.27 (dd, J = 15.2, 8.4 Hz, 1H), 2.39 (dq, J = 8.4, 6.9 Hz, 1H), 2.34-2.44 (m, 1H), 1.94-2.00 (m, 2H), 1.27-1.73 (m, 6H), 0.97 (d, J = 6.9 Hz, 3H), 0.94 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H) ppm; ^{13}C (75 MHz, CDCl$_3$): 207.3, 132.0, 130.9, 51.9, 41.6, 32.2, 31.6, 26.6, 22.1, 14.8, 14.2, 13.9, 8.4 ppm; MS (EI, 70 V): m/z 196 (M$^{+\cdot}$), 181, 139, 110, 81, 71, 69; HRMS m/z calcd for C$_{13}$H$_{24}$O (M$^{+\cdot}$): 196.1827; found 196.1820.
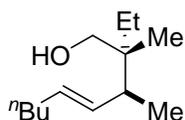
syn-(E)-2-Ethyl-2,3-dimethylnon-4-enol (68a'): A 1 M hexanes solution of ^{i}Bu$_2$AlH (0.5 mL, 0.5 mmol) was added to a −78 °C solution of aldehyde **68a** (49 mg, 0.25 mmol) in CH$_2$Cl$_2$. After stirring 30 min at −78 °C, a saturated

aqueous sodium tartrate solution (2 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases formed (~1 h). The mixture was extracted with Et_2O (3×) and the combined organic extracts were dried ($MgSO_4$), concentrated, and the resulting crude oil was purified by flash chromatography on silica gel (16% EtOAc in hexanes) yielded 29 mg (60 %) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.41-5.45 (m, 2H), 3.41 (s, 2H), 2.11-2.21 (m, 1H), 1.97-2.01 (m, 2H), 1.37 (q, J = 7.6 Hz, H), 1.26-1.36 (m, 4H), 0.97 (d, J = 6.9 Hz, 3H), 0.94 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H), 0.80 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.2, 130.5, 68.0, 41.4, 39.7, 32.3, 31.8, 27.5, 22.2, 17.4, 15.2, 13.9, 7.9 ppm; MS (EI, 70 V): *m/z* 198 (M[+.]), 180, 167, 111, 83, 69; HRMS *m/z* calcd for $C_{13}H_{26}O$ (M[+.]): 198.1984; found 198.1975.
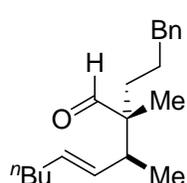
syn-(*E*)-2,3-Dimethyl-2-(3-phenylpropyl)non-4-enal (**68b**): General Procedure **C** was followed employing 1-((*3E*)-5-((*E*)-oct-2-en-4-yloxy)-4-methylpent-3-enyl)benzene (**66b,** 143 mg, 0.5 mmol) and 2 mol% catalyst (4.5 mg [$IrCl(C_8H_{14})_2$]$_2$, 8.4 mg PCy_3 and 3.4 mg $NaBPh_4$) and stirred 60 h at 75 °C in 1,2-dichloroethane solvent. Purifying the crude product mixture by flash chromatography on silica gel (2.5% Et_2O in hexanes) yielded 102 mg (71%) of the title compound as a colorless oil (*syn:anti* = 95:5). Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T_r = 60.1 and 61.0 min] provided the diastereomer ratio: *anti: syn* = 5.8:94.2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.15-7.31 (m, 5H), 5.42 (dt, J = 15.2, 6.5 Hz, 1H), 5.26 (dd, J = 15.2, 8.5 Hz, 1H), 2.57-2.61 (m, 2H), 2.24-2.48 (m, 2H), 1.93-1.98 (m, 3H), 1.24-1.75 (m, 6H), 0.96 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75

MHz, CDCl$_3$): δ 207.1, 142.0, 132.2, 130.7, 128.32, 128.25, 125.8, 51.6, 41.8, 36.5, 33.7, 32.2, 31.6, 29.7, 25.9, 22.1, 14.9, 13.9 ppm; MS (EI, 70 V): *m/z* 286 (M$^{+\cdot}$), 258, 256, 245, 229, 192, 163, 145, 117, 111, 104, 91, 69; HRMS *m/z* calcd for C$_{20}$H$_{30}$O (M$^{+\cdot}$); 286.2297; found 286.2288.

syn-(E)-2,3-Dimethyl-2-(3-phenylpropyl)non-4-enol (68b′): A 1 M hexanes solution of ^{i}Bu$_2$AlH (0.5 mL, 0.5 mmol) was added to a −78 °C solution of aldehyde **68b** (72 mg, 0.25 mmol) in CH$_2$Cl$_2$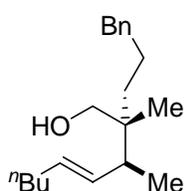. After stirring 30 min at −78 °C, a saturated aqueous sodium tartrate solution (2 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases formed (~1 h). The mixture was extracted with Et$_2$O (3×) and the combined organic extracts were dried (MgSO$_4$), concentrated, and the resulting crude oil was purified by flash chromatography on silica gel (16% EtOAc in hexanes) yielded 65 mg (90 %) of the title compound as a light yellow oil. Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m × 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T$_r$ = 64.6 and 68.9 min] provided the diastereomer ratio: *anti: syn* = 3.7:96.3; ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.15-7.31 (m, 5H), 5.39-5.41 (m, 2H), 3.41 (d, J = 11.4 Hz, 1H), 3.37 (d, J = 11.4 Hz, 1H), 2.58 (t, J = 7.7 Hz, 2H), 2.12-2.19 (m, 1H), 1.95-2.05 (m, 2H), 1.52-1.74 (m, 3H), 1.26-1.46 (m, 6H), 0.90 (d, J = 6.9 Hz, 3H), 0.89(t, J = 7.4 Hz, 3H), 0.75 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 143.0, 133.4, 130.9, 128.7, 128.6, 126.0, 68.8, 42.0, 40.1, 37.2, 35.5, 32.6, 32.1, 25.8, 22.5, 18.4, 15.5, 14.2 ppm; MS (EI, 70 V): *m/z* 288 (M$^{+\cdot}$), 270, 257, 176, 159, 145, 117, 104, 91; HRMS *m/z* calcd for C$_{20}$H$_{32}$O (M$^{+\cdot}$): 288.2453; found 288.2459.
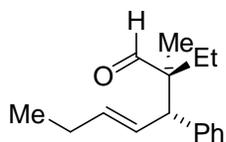
***syn*-(*E*)-2-Ethyl-2-methyl-3-phenylhept-4-enal (68c): General Procedure D** was followed employing ((*E*)-3-((*E*)-2-methylbut-2-enyloxy)-pent-1-enyl)benzene (**66c**, 115mg, 0.5 mmol) and 4 mol% catalyst (9.0 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$), and stirred 24 h at 80 °C in 1,2-dichloroethane solvent. The crude product mixture contained aldehyde **68c** and aldehyde syn-(*E*)-2-ethyl-2-methyl-3-phenylhept-5-enal **68c″** resulting from post-rearrangement olefin isomerization as a 90:10 mixture. Purifying the crude product mixture by flash chromatography on silica gel (2.0% EtOAc in hexanes) yielded 68 mg (60%) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.58 (s, 1H), 7.27-7.47 (m, 5H), 5.81 (dd, J = 15.2, 9.3 Hz, 1H), 5.60 (dt, J = 15.2, 6.2 Hz, 1H), 3.52 (d, J = 9.3 Hz, 1H), 1.95-2.09 (m, 2H), 1.45-1.80 (m, 2H), 1.05 (s, 3H), 1.00 (t, J = 7.5 Hz, 3H), 0.78 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.8, 140.4, 135.6, 129.3, 128.2, 127.2, 126.7, 55.0, 53.1, 27.6, 25.6, 14.4, 13.6, 8.3 ppm; MS (EI, 70 V): *m/z* 230 (M$^{+\cdot}$), 201, 145, 131, 117, 91, 77, 69, 57; HRMS *m/z* calcd for C$_{16}$H$_{22}$O 230 (M$^{+\cdot}$): 230.1671; found 230.1668.
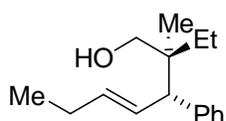
***syn*-(*E*)-2-Ethyl-2-methyl-3-phenylhept-4-enal (68c'):** A 1 M hexanes solution of ^{i}Bu$_2$AlH (0.5 mL, 0.5 mmol) was added to a −78 °C solution of aldehyde **68c** (57 mg, 0.25 mmol) in CH$_2$Cl$_2$. After stirring 30 min at −78 °C, a saturated aqueous sodium tartrate solution (2 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases formed (~1 h). The mixture was extracted with Et$_2$O (3×) and the combined organic extracts were dried (MgSO$_4$), concentrated, and the resulting crude oil was purified by flash chromatography on silica gel (16% EtOAc in hexanes) to yield 40 mg (70%) of the title compound as a light yellow oil. Separating the

isomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T_r = 53.7, 54.6 min] provided the stereoisomer ratio: *syn: anti* = 88:12. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.21-7.40 (m, 5H), 5.91 (ddt, J = 15.1, 10.1, 1.4 Hz, 1H), 5.57 (ddt, J = 15.1, 10.1, 1.4 Hz, 1H), 3.35 (d, J = 11.2 Hz, 1H), 3.35 (d, J = 10.1 Hz, 1H), 3.27 (d, J = 11.2 Hz, 1H), 1.98-2.10 (m, 2H), 1.20-1.65 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H), 0.80 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 142.5, 134.1, 129.4, 128.9, 127.9, 126.0, 67.1, 54.9, 41.1, 27.3, 25.6, 18.0, 13.7, 7.9 ppm; IR (liquid film): 3392, 2963, 2930, 1601, 1492, 1453, 1376, 1034, 970, 702 cm^{-1}; MS (EI, 70 V): *m/z* 232 (M$^{+\cdot}$), 201, 145, 129, 117; HRMS *m/z* calcd for C$_{16}$H$_{24}$O (M$^{+\cdot}$): 232.1927; found 232.1835.

Diastereomers Proof for Claisen Adducts 64h and 68c: The relative stereochemistry for **64h** and **68c** was determined for the corresponding primary alcohols **64h′** and **68c′**. HPLC analysis of the **64h′** and **68c′** racemates provided the retention times 6.6/7.1 (50:50) and 7.0/8.4 min (50:50), respectively (Daicel Chiracel^{TM} OD-H column, flow rate 0.8 ml/min, 4.0% *i*-PrOH, 96.0% hexanes). HPLC analysis of a 1:1 mixture of (±)-**64h′** and (±)-**68c′** was separated using the same method (Daicel Chiracel^{TM} OD-H column, flow rate 0.8 ml/min, 4.0% *i*-PrOH, 96.0% hexanes) to afford the retention times 6.6, 7.2, and 8.6 min peaks in a ratio of 25:50:25 indicating that **64h′** and **68c′** are unique diastereomers.

4.3.1.3 Asymmetric quaternary ICR reaction
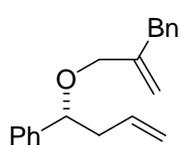
1-(2-(((*R*)-1-Phenylbut-3-enyloxy)methyl)allyl)benzene (70): General Procedure **A** was followed employing (*R*)-1-phenylbut-3-en-1-ol (81% ee, 296

mg, 2.0 mmol)[118] and (2-(bromomethyl)allyl)benzene (630 mg, 3.0 mmol) in THF. The crude product was purified by flash chromatography on silica gel (2% EtOAc in hexanes) to yield 450 mg (81%) of the title compound as light yellow oil. +10.8 (c 1.07, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.27-7.46 (m, 10H), 5.88-6.04 (m, 1H), 5.07-5.22 (m, 3H), 5.00 (s, 1H), 4.39 (dd, J = 7.4, 5.8 Hz, 1H), 3.94 (d, J = 12.4 Hz, 1H), 3.76 (d, J = 12.4 Hz, 1H), 3.54 (d, J = 15.0 Hz, 1H), 3.47 (d, J = 15.0 Hz, 1H), 2.62-2.82 (m, 1H), 2.48-2.60 (m, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ; IR (liquid film): 3027, 2908, 2856, 1642, 1601, 1494, 1453, 1087, 913, 699 cm^{-1}; MS (EI, 70 V): m/z 278 (M$^{+\cdot}$), 237, 147, 131, 129, 115, 107; HRMS m/z calcd for C$_{20}$H$_{22}$O (M$^{+\cdot}$): 278.1671; found 278.1675.
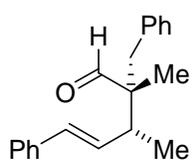
(2S,3R,E)-2-Benzyl-2,3-dimethyl-5-phenylpent-4-enal **(72)**: General Procedure **D** was followed employing 1-(2-(((R)-1-phenylbut-3-enyloxy)methyl)allyl)benzene **70** (81 % ee, 139 mg, 0.5 mmol) and 2 mol% catalyst Ir(PCy$_3$)$_3$BPh$_4$ (4.5 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 8.4 mg PCy$_3$, and 3.4 mg NaBPh$_4$) and stirred 60 h at 60 °C in 1,2-dichloroethane solvent. The crude product mixture was purified by flash chromatography on silica gel (2.5% Et$_2$O in hexanes) to yield 101 mg (73%) of the title compound as colorless oil: *anti: syn* > 98: 2). Separating the enantiomers by chiral HPLC Daicel Chiracel^{TM} OD-H column, flow rate 0.8 mL/min, 0.8% *i*-PrOH, 99.2% hexanes, T$_r$ 30.55 (2R, 3S) and 36.09 (2S, 3R) provided the enantiomer ratio: (2R,3S) : (2S,3R) = 9.1:89.4 (82% ee). [α]$_D$ = −74.6 (c 5.09, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.68 (s, 1H), 7.06-7.42 (m, 10H), 6.53 (d, J = 15.8 Hz, 1H), 6.19 (dd, J = 15.8, 9.1 Hz, 1H), 3.09 (d, J = 13.8 Hz, 1H), 2.77 (d, J = 13.8 Hz,

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[118] The enantioenriched homoallylic alcohol was prepared according to the published procedure, see: Brown, H. C. *J. Am. Chem. Soc.* **1990**, *112*, 2389. The enantioselectivity of the allylation reaction was not optimized.

1H), 2.74 (dq, J = 9.1, 6.9 Hz, 1H), 1.11 (d, J = 6.9 Hz, 3H), 1.02 (s, 3H) ppm; ^{13}C NMR (75

MHz, CDCl$_3$): δ 206.6, 137.0, 136.8, 132.0, 130.2, 128.6, 128.1, 127.4, 126.5, 126.2, 53.4, 42.3,

41.8, 16.2, 14.0 ppm; MS (EI, 70 V): *m/z* 278 (M$^{+\cdot}$), 263, 249, 187, 146, 131, 115, 105, 91, 77,

65; HRMS *m/z* calcd for C$_{20}$H$_{22}$O (M$^{+\cdot}$): 278.1671; found 278.1662.
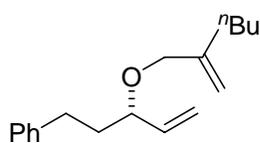
1-((S)-3-(2-Methylenehexyloxy)pent-4-enyl)benzene (73): General Procedure A was followed employing 1.01 g of (S)-5-phenylpent-1-en-3-ol (6.21 mmol, >99% ee).[119] Purifying the crude product mixture by flash chromatography

(flushing with 400 mL of hexanes then eluting with 2.5% EtOAc in hexanes) afforded 1.39 g

(86%) of the title compound as colorless oil. Separating the enantiomers by chiral HPLC (Daicel

Chiracel^{TM} OD-H column, flow rate 1.0 mL/min, 0.5% *i*-PrOH, 95.5% hexanes, T$_r$ 8.3 (S) and

11.0 (R) provided only one enantiomer (>99% ee). [α]$_D$ = +1.73 (c 6.57, CHCl$_3$); ^{1}H NMR (300

MHz, CDCl$_3$): δ 0.91 (t, J = 7.2 Hz, 3H), 1.27-1.50 (m, 4H), 1.74-2.02 (m, 2H), 2.07 (m, 2H),

2.72 (m, 2H), 3.68 (dt, J = 5.8, 7.4 Hz, 1H), 3.75 (d, J = 13 Hz, 1H), 3.97 (d, J = 13 Hz, 1H), 4.88

(s, 1H), 5.01 (s, 1H), 5.17 (m, 1H), 5.22 (m, 1H), 5.72 (m, 1H), 7.15-7.30 (m, 5H); ^{13}C NMR (75

MHz, CDCl$_3$): δ 13.8, 22.4, 29.8, 31.6, 33.0, 37.1, 71.0, 79.7, 110.7, 116.8, 125.6, 128.2, 128.4,

139.0, 142.1, 146.6; MS (EI, 70 V): *m/z* 258 (M$^{+\cdot}$− H), 235, 229, 215, 187, 171, 161, 144, 129,

117, 105, 97, 91, 55; HRMS *m/z* calcd for C$_{18}$H$_{27}$O (M$^{+\cdot}$): 259.2062; found: 259.2061.
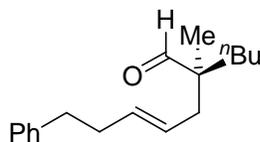
(S,E)-2-Butyl-2-methyl-7-phenylhept-4-en-1-al (75): General Procedure D was followed employing di(allyl) ether (**73**, 258 mg, 1.0 mmol) and 2 mol% catalyst (9.0 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$, and 6.8 mg NaBPh$_4$) and

[119] Takagi, Y.; Teramoto, J.; Kihara, H.; Itoh, T.; Tsukube, H. *Tetrahedron Lett.* **1996**, *37*, 4991-4992.

stirred 60 h at 80 °C in 1,2-dichloroethane solvent. The crude product mixture was purified by flash chromatography on silica gel (2.5% EtOAc in hexanes) to yield 129 mg (50%) of (S,E)-2-butyl-2-methyl-7-phenylhept-4-en-1-al (**75**) and 21 mg (8%) of (*S,Z*)-2-butyl-2-methyl-7-phenylhept-4-en-1-al (**Z-75**)as an inseperable mixture. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.42 (s, J = 2.4 Hz, 1H), 7.17-7.35 (m, 5H), 5.50 (dt, J = 15.2, 6.6 Hz, 1H), 5.31 (dt, J = 15.1, 7.3 Hz, 1H), 2.68 (t, J = 7.3 Hz, 2H), 2.34 (dt, J = 7.6, 7.1 Hz, 2H), 2.08-2.22 (m, 2H), 1.07-1.55 (m, 6H), 0.97 (s, 3H), 0.90 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 206.6, 141.7, 133.4, 128.4, 128.2, 125.7, 125.1, 49.1, 38.5, 35.8, 34.9, 34.2, 26.1, 23.3, 18.3, 13.9 ppm; MS (EI, 70 V): *m/z* 258 (M$^{+\cdot}$), 240, 202, 183, 167, 154, 98, 91; HRMS *m/z* calcd for C$_{18}$H$_{26}$O (M$^{+\cdot}$): 258.1984. found: 258.1979.
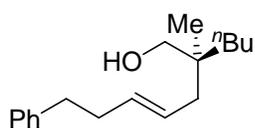
(*S,E*)-2-Butyl-2-methyl-7-phenylhept-4-en-1-ol (**75′**): To a −78 °C solution of aldehyde **75** (65 mg, 0.25 mmol) in CH$_2$Cl$_2$ was added ^{i}Bu$_2$AlH (1.0 M in hexanes, 0.5 mL, 0.5 mmol). After stirring 30 min at −78 °C, a saturated aqueous sodium tartrate solution (2 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases formed (~1 h). The mixture was extracted with Et$_2$O (3×) and the combined organic extracts were dried (MgSO$_4$), concentrated, and the resulting crude oil was purified by flash chromatography on silica gel (16% EtOAc in hexanes) to yield 46 mg (70%) of the title compound as a light yellow oil. Separating the isomers by GLC [Varian CP Wax 52CB column (30 m × 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T$_r$ = 65.7, 66.1 min] provided the isomer ratio: E:Z = 93.7:6.3. Separating the enantiomers by chiral HPLC [Daicel Chiracel^{TM} AD column, flow rate 1.0 mL/min, 2.0% *i*-PrOH, 98.0% hexanes, T$_r$ 11.1 (R)

and 12.2 (S)] provided the enantiomer ratio: (R):(S) = 2.3:97.7 (95% ee). $[\alpha]_D$ = +2.0 (c 2.32, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.17-7.35 (m, 5H), 5.50 (dt, J = 15.2, 5.6 Hz, 1H), 5.43 (dt, J = 15.2, 6.0 Hz, 1H), 3.28 (s, 2H), 2.70 (t, J = 7.6 Hz, 2H), 2.33-2.43 (m, 2H), 1.95 (d, J = 6.0 Hz, 2H), 1.19-1.30 (m, 6H), 0.92 (t, J = 7.4 Hz, 3H) 0.80 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.9, 132.1, 128.4, 128.3, 127.2, 125.7, 69.8, 40.1, 37.9, 36.3, 36.0, 34.3, 25.6, 23.6, 21.5, 14.1 ppm; MS (EI, 70 V): m/z 260 (M$^{+\cdot}$), 242, 229, 185, 162, 151, 146, 138, 131, 117, 114, 104, 97, 91; HRMS m/z calcd for C$_{18}$H$_{28}$O (M$^{+\cdot}$): 260.2140; found: 260.2127.

4.3.2 Experiment of section 4.2
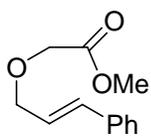
Methyl 2-(cinnamyloxy)acetate (81a′): General procedure **G** for methyl allyoxyacetate: Add (*E*)-3-phenylprop-2-en-1-ol (1.34 g, 10 mmol, 1.0 equiv.) in NaH (1.2 g, 50 mmol, 5.0 equiv.) slurry in THF (10 ml, 1.0 M), and 2-chloroacetic acid (945 mg,10 mmol, 1.0 equiv.) in THF (10 ml, 0.5 M at last) was added dropwise at 0 °C. Then warm to reflux 6 h. Add water 20 ml dropwise to quench the reaction and extracted with ether 20 ml X 3, then extracted organic phase with water 20 ml X 2, combine water phase and add 1.0 M HCl to acidify the solution to pH = 2. Extracted the solution with ether 20 ml X 3, combine the organic phase and drying with MgSO$_4$. After solvent evaporation afford crude 2-(cinnamyloxy)acetic acid. The acid can by purified with chromatography on silica (50 % ethyl acetate in hexanes) or using directly without purification. To a solution of 2-(cinnamyloxy)acetic acid (768 mg, 4.0 mmol), K$_2$CO$_3$ (2.76 g, 20 mmol) in DMF (10 ml) add methyl iodide (1.7 g, 12.0 mmol) and stir 12 h at ambient temperature. Add water 50 ml and extracted with ether 20 ml X 3, combine the organic phase, the solvent was evaporated and the crude product mixture

was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to yield 600 mg (72 %) of the title compound as a light yellow oil.
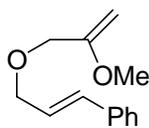
(E)-(3-(2-Methoxyallyloxy)prop-1-enyl)benzene (81a): General procedure **H** for methylidenation with Tebbe's reagent: To a −40 °C solution of ester (**81a′**, 515 mg, 2.5 mmol) in 10 ml THF-pyridine (4:1) was added Tebbe's reagent (2.5 equiv., 6.3 mmol, 12.6 mL of 0.5 M toluene solution).[120] Once addition was complete, the reaction mixture was warmed to ambient temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of 0.5 M aq. NaOH. The resulting mixture was filtered through a celite pad, washing the filter cake with Et$_2$O. The solvents were Vaporated and the crude oil was purified by column chromatography on basic alumina (10% Et$_2$O in hexanes) to give 332 mg of the title product (65%) as colorless oil. ^{1}H NMR (300 MHz, C$_6$D$_6$): δ 6.99-7.21 (m, 5H), 6.53 (d, J = 16.0 Hz, 1H), 6.16 (dt, J = 16.0, 5.7 Hz, 1H), 4.34 (s, 1H), 3.99 (dd, J = 5.7, 1.5 Hz, 2H), 3.99 (s, 1H), 3.95 (s, 2H), 3.21 (s, 3H) ppm; ^{13}C NMR (75 MHz, C$_6$D$_6$): δ 161.11, 137.31, 132.06, 128.74, 127.68, 126.78, 126.69, 82.21, 71.03, 70.40, 54.40 ppm.
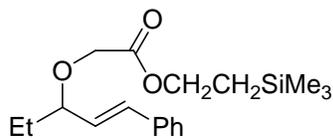
(E)-2-(Trimethylsilyl)ethyl 2-(1-phenylpent-1-en-3-yloxy)acetate (81b′): General procedure **G** for esterfication with DCC and DMAP. To a 2 ml CH$_2$Cl$_2$ solution of (E)-2-(1-phenylpent-1-en-3-yloxy)acetic acid (880 mg, 4.0 mmol), 2-(trimethylsilyl)ethanol (472 mg, 4.0 mmol) added DCC (1030 mg, 5.0 mmol) and DMAP (43 mg, 0.4 mmol). Stirred 24 h at ambient

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[120] For the in situ preparation of Tebbe's reagent: Pine, S. H.; Kim, G.; Lee, V. *Org. Syn.* **1990**, *69*, 72.

temperature, after Vaporation of solvent, the crude product was purified by flash chromatograph on silical gel (10 % ethyl acetate in hexanes) to yield 1024 mg (80 %) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.21-7.38 (m, 5H), 6.51 (d, J = 16.0 Hz, 1H), 6.03 (dd, J = 16.0, 8.3 Hz, 1H), 4.20 (dd, J = 9.5, 8.7 Hz, 1H), 4.08 (d, J = 16.4 Hz, 1H), 4.02 (d, J = 16.4 Hz, 1H), 3.86 (q, J = 7.1 Hz, 1H), 1.57-1.92 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H), 0.96 (t, J = 9.0 Hz, 2H), 0.02 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 170.72, 136.15, 133.18, 129.06, 128.37, 127.65, 126.33, 83.07, 65.50, 62.69, 28.36, 17.12, 9.64 ppm; IR (liquid film): 2933, 2119, 1752, 1250, 1115, 837, 749, 693 cm^{-1}; MS (EI, 70 V): m/z 292 (M$^{+\cdot}$-CH$_2$=CH$_2$), 263, 219, 161, 233, 145, 129, 115, 73; HRMS m/z calcd for C$_{16}$H$_{24}$O$_3$Si (M$^{+\cdot}$-CH$_2$=CH$_2$): 292.1495. found 292.1498.
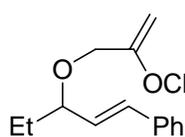
(E)-Trimethyl (2-(3-(1-phenylpent-1-en-3-yloxy)prop-1-en-2-yloxy) ethyl)silane (81b): General procedure **H** was followed employing ester **81b′** (320 mg, 1 mmol), the crude product was purified by column chromatography at basic alumina gel (10 % ethyl ether in hexanes) to give the title product 239 mg (75 %) as colorless oil. ^{1}H NMR (300 MHz, C$_6$D$_6$): δ 7.03-7.23 (m, 5H), 6.45 (d, J = 16.0 Hz, 1H), 6.05 (dd, J = 16.0, 7.8 Hz, 1H), 4.43 (t, J = 0.69 Hz, 1H), 4.17 (d, J = 7.3 Hz, 1H), 4.09 (d, J = 1.5 Hz, 1H), 3.94 (d, J = 7.3 Hz, 1H), 3.78 (q, J = 7.0 Hz, 1H), 3.74 (t, J = 7.8 Hz, 2H), 1.76-1.99 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H), 0.93 (t, J = 7.8 Hz, 3H), 0.14 (s, 9H) ppm; ^{13}C NMR (75 MHz, C$_6$D$_6$): δ 160.70, 137.16, 132.55, 130.86, 128.73, 126.85, 111.86, 82.25, 81.97, 68.95, 64.77, 29.20, 17.33, 10.03, -1.36 ppm; IR (liquid film): 2957, 1662, 1250, 1067, 837, 748, 693 cm^{-1}; MS (EI, 70 V): m/z 290 (M$^{+\cdot}$-CH$_2$=CH$_2$), 217, 205, 145, 129, 115, 91,

79; HRMS *m/z* calcd for $C_{19}H_{30}O_2Si$ (M$^+$) 318.2016, found 318.2031; and $C_{17}H_{26}O_2Si$ (M$^{+\cdot}$-CH$_2$=CH$_2$): 290.1702. found 290.1706.
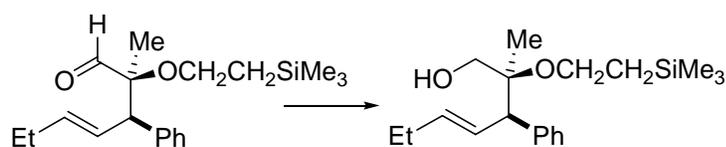
***anti*-(*E*)-2- Methyl-3-phenyl-2-(2-(trimethylsilyl)ethoxy) hept-4-enol (83b′)**: General Procedure **D** was followed employing **83b** (145 mg, 0.5 mmol) and 5 mol% catalyst (11.3 mg Ir-dimer, 21.0 mg PCy$_3$ and 8.5 mg NaBPh$_4$) and stirred 48 h at 40 °C in dichloroethane solvent to afford *anti*-(*E*)-2-methyl-3-phenyl-2-(2-(trimethylsilyl)ethoxy)hept-4-enal **83b** (*syn: anti* = 96: 4). the crude product was purified by flash chromatograph on silical gel (5 % Et$_2$O in hexanes) to yield 64 mg (44 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.73 (s, 1H), 5.93 (ddt, J = 15.3, 9.4, 1.6 Hz, 1H), 5.48 (dt, J = 15.3, 6.1 Hz, 1H), 3.54 (td, J = 9.0, 6.4 Hz, 1H), 3.40 (td, J = 9.0, 6.9 Hz, 1H), 1.98-2.05 (m, 2H), 1.10 (s, 3H), 0.95 (t, J = 6.9 Hz, 3H), 0.87-0.96 (m, 2H), 0.02 (s, 9H) ppm. Then DIBAL-H reduction procedure was followed employing aldehydes **83b** (64 mg, 0.2 mmol), the crude product was purified by flash chromatograph on silical gel (16 % Et$_2$O in hexanes) to yield 51 mg (80 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.21-7.40 (m, 5H), 6.05 (ddt, J = 15.3, 8.9, 1.4 Hz, 1H), 5.64 (dt, J = 15.3, 6.3 Hz, 1H), 3.45-3.65 (m, 5H), 2.09-2.19 (m, 2H), 2.01 (s, 1H), 1.22 (s, 3H), 1.07 (t, J = 7.5 Hz, 3H), 0.99 (td, J = 8.5, 2.8 Hz, 3H), 0.13 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.79, 134.50, 129.43, 128.19, 127.92, 126.26, 79.01, 66.07, 59.12, 54.66, 25.72, 18.85, 17.64, 13.64, -1.27 ppm; IR (liquid film): 3454, 2958, 1453, 1248, 1053, 971, 837, 701 cm^{-1}; MS (EI, 70 V): *m/z* 289 (M$^{+\cdot}$-CH$_2$OH), 261, 218, 171, 145, 131, 101, 73; HRMS *m/z* calcd for $C_{18}H_{29}OSi$ (M$^{+\cdot}$-CH$_2$OH) 289.1988, found 289.1989.

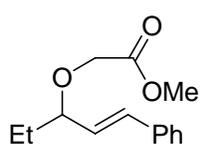**(E)-Methyl 2-(1-phenylpent-1-en-3-yloxy)acetate (81c')**: General procedure **G** was followed employing (E)-1-phenylpent-1-en-3-ol (3.24 g, 20 mmol). the crude product was purified by column chromatography at silica gel (10 % ethyl ether in hexanes) to give the title product 2.34 g (50 %) in two steps as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.27-7.44 (m, 5H), 6.56 (d, J = 16.0 Hz, 1H), 6.07 (dd, J = 16.0, 8.3 Hz, 1H), 4.18 (d, J = 16.4 Hz, 1H), 3.89 (d, J = 16.4 Hz, 1H), 3.74 (s, 3H), 1.59-1.99 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H) ppm.
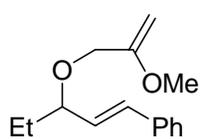
(E)-(3-(2-Methoxyallyloxy)pent-1-enyl)benzene (81c): General procedure **H** was followed employing ester **81c'** (585 mg, 2.5 mmol), the crude product was purified by column chromatography at basic alumina gel (10 % ethyl ether in hexanes) to give the title product 435 mg (75 %) as colorless oil. ^{1}H NMR (300 MHz, C$_6$D$_6$): δ 7.00-7.21 (m, 5H), 6.43 (d, J = 16.0 Hz, 1H), 6.02 (dd, J = 16.0, 7.8 Hz, 1H), 4.39 (s, 1H), 4.12 (d, J = 13.0 Hz, 1H), 3.99 (d, J = 1.8 Hz, 1H), 3.89 (d, J = 13.0 Hz, 1H), 3.74 (q, J = 6.8 Hz, 1H), 3.21 (s, 3H), 1.53-1.80 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, C$_6$D$_6$): 161.64, 137.14, 132.54, 130.79, 128.73, 126.84, 81.98, 81.89, 68.60, 54.35, 29.17, 10.00 ppm.
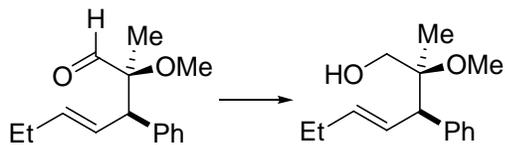
anti-(E)-2- Methoxy-2-methyl-3-phenylhept-4-en-1-ol (83c'): General Procedure **D** was followed employing (E)-(3-(2-Methoxyallyloxy)pent-1-enyl)benzene (81c, 116 mg, 0.5 mmol) and 5 mol% catalyst (11.3 mg Ir-dimer, 21.0 mg PCy$_3$ and 8.5 mg NaBPh$_4$) and stirred 48 h at 40 °C in dichloroethane solvent to afford *anti*-(E)-2-

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methoxy-2-methyl-3-phenylhept-4-en-1-ol **83c** (*syn : anti* = 96 : 4). DIBAL-H reduction procedure was followed, the crude product was purified by flash chromatograph on silical gel (16 % Et$_2$O in hexanes) to yield 68 mg (58 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, C$_6$D$_6$): δ 7.20-7.29 (m, 5H), 5.94 (ddt, J = 15.3, 8.9, 1.5 Hz, 1H), 5.56 (dt, J = 15.3, 6.3 Hz, 1H), 3.57 (d, J = 8.8 Hz, 1H), 3.39-3.53 (m, 2H), 3.30 (s, 3H), 2.01-2.11 (m, 2H), 1.12 (s, 3H), 0.98 (t, J = 7.4 Hz, 3H) ppm.

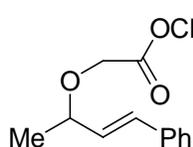**(*E*)-2- (Trimethylsilyl)ethyl-2-(4-phenylbut-3-en-2-yloxy)acetate (81d′):** To a solution of (*E*)-2-(4-phenylbut-3-en-2-yloxy)acetic acid (824 mg, 4.0 mmol)[121] and 2-(trimethylsilyl)ethanol (472 mg, 4.0 mmol) in CH$_2$Cl$_2$ (2 mL) was added DCC (1.030 g, 5.0 mmol) and DMAP (43 mg, 0.4 mmol) and the reaction was stirred for 24 h. The solvent was Vaporated and the crude product mixture was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to yield 980 mg (80%) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.30-7.40 (m, 5H), 6.53 (d, J = 16.0 Hz, 1H), 6.10 (dd, J = 16.0, 8.0 Hz, 1H), 4.23 (t, J = 8.5 Hz, 2H), 4.13 (dq, J =8.0, 6.3 Hz, 1H), 4.10 (d, J = 16.5 Hz, 1H), 4.08 (d, J = 16.5 Hz, 1H), 1.42 (d, J = 6.3 Hz, 3H), 0.98 (t, J = 8.5 Hz, 2H), 0.04 (s, 9H) ppm; MS (EI, 70 V): *m/z* 278 (M$^{+\cdot}$-C$_2$H$_4$), 263, 219, 105, 147, 131, 117, 91, 73; HRMS *m/z* calcd for C$_{15}$H$_{22}$O$_3$Si (M$^{+\cdot}$−C$_2$H$_4$): 278.1338; found: 278.1330.
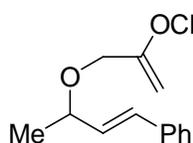
(*E*)- Trimethyl(2-(3-(4-phenylbut-3-en-2-yloxy)prop-1-en-2-yloxy)ethyl)silane (81d): To a −40 °C solution of ester (**81d′**, 612

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[121] Prepared by reacting (*E*)-4-phenylbut-3-en-2-ol (1.0 equiv.) with NaH (5.0 equiv.), and 2-chloroacetic acid (1.0 equiv.) in THF at reflux.

mg, 2.0 mmol) in 10 mL THF-pyridine (4:1) was added Tebbe's reagent (2. 5 equiv, 5.0 mmol, 10 mL of 0.5 M toluenesolution).[122] Once addition was complete, the reaction mixture was warmed to ambient temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and quenched by dropwise addition of 0.5 M aq. NaOH. The resulting mixture was filtered through a celite pad, washing the filter cake with Et$_2$O. The solvents were Vaporated and the crude oil was purified by column chromatography on basic alumina (10% Et$_2$O in hexanes) to give 460 mg of the title product (75%) as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.12-7.31 (m, 5H), 6.53 (d, J = 16.0 Hz, 1H), 6.17 (dd, J = 16.0, 7.5 Hz, 1H), 4.53 (d, J = 0.5 Hz, 1H), 4.19 (s, 1H), 4.22 (d, J = 12.8 Hz, 1H), 4.04 (d, J = 12.8 Hz, 1H), 4.10 (dq, J = 7.5, 6.3 Hz, 1H), 3.83 (t, J = 7.8 Hz, 2H), 1.41 (d, J = 6.3 Hz, 3H), 1.02 (t, J = 7.8 Hz, 2H), 0.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 159.7, 136.6, 131.5, 131.2, 128.4, 127.5, 126.3, 82.5, 76.0, 68.6, 64.7, 21.6, 17.1, -1.5 ppm; IR (liquid film): 2954, 1663, 1250, 1071, 837, 749, 693 cm^{-1}; MS (EI, 70 V): *m/z* 276 (M$^+$-C$_2$H$_4$), 219, 186, 157, 147, 131, 115, 91, 84, 73; HRMS *m/z* calcd for C$_{16}$H$_{24}$O$_2$Si (M$^+$−C$_2$H$_4$): 276.1546; found: 276.1548.
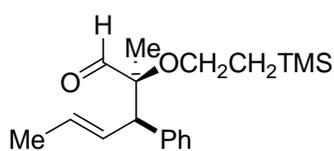
anti-(*E*)-2-   Methyl-3-phenyl-2-(2-(trimethylsilyl)ethoxy)hex-4-enal (83d): General Procedure **D** was followed employing di(allyl) ether (**81d**, 152 mg, 0.5 mmol) and 4 mol% catalyst (9.0 mg [IrCl(C$_8$H$_{14}$)$_2$]$_2$, 16.8 mg PCy$_3$, and 6.8 mg NaBPh$_4$) and stirred 60 h at 80 °C in 1,2-dichloroethane solvent; *anti:syn* = 94:6. Purifying the crude product mixture by flash chromatography on silica gel (2.5% Et$_2$O in hexanes) yielded 88 mg (58%) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.77 (s, 1H), 6.00 (ddq, J = 15.2, 9.4, 1.6

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[122] For the in situ preparation of Tebbe's reagent: Pine, S. H.; Kim, G.; Lee, V. *Org. Syn.* **1990**, *69*, 72.

Hz, 1H), 5.47 (dq, J = 15.2, 6.5 Hz, 1H), 3.57 (td, J = 9.1, 6.4 Hz, 1H), 3.43 (td, J = 9.1, 6.7 Hz, 1H), 3.39 (d, J = 9.4 Hz, 1H), 1.68 (dd, J = 6.4, 1.6 Hz, 3H), 1.13 (s, 3H), 0.96-1.08 (m, 2H), 0.07 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 208.0, 140.2, 129.3, 129.2, 128.0, 127.9, 126.7, 84.0, 61.8, 56.8, 18.9, 17.9, 16.7, −1.3 ppm; IR (liquid film): 2953, 1732, 1452, 1378, 1249, 1056, 970, 860, 837, 700 cm^{-1}. MS (EI, 70 V): *m/z,* 276 (M$^{+\cdot}$−C$_2$H$_4$), 219, 186, 157, 147, 131, 115, 91, 84, 73; HRMS *m/z* calcd for C$_{16}$H$_{24}$O$_2$Si (M$^{+\cdot}$): 276.1546; found: 276.1548.

5.0 LEWIS ACID-PROMOTED CLAISEN REARRANGEMENT AND CASCADE REACTIONS BASED ON ICR

Reactivity in the thermal Claisen rearrangement, which depends on the structure of allyl vinyl ether substrates, was poor in some cases. Thus, additives or catalysts were required for promoting the rearrangement. In general, there are two kinds of chemicals used to promote Claisen rearrangement: late transition metals[123] and hard Lewis acids. They have different activation mechanisms to produce products with different stereoselectivities. Late transition metal (such as Pd, Au, Hg) complexes coordinate the allyl olefin first and allow the vinyl ether nucleophile to attack the activated olefin to complete the Claisen rearrangement *via* a boat transition state. The (*i*BuCN)PdCl$_2$-catalyzed Claisen rearrangement for preparing high stereoselectivity 2,3-*anti* disubstituted aldehydes was developed in Nelson group (Figure 38).[124]

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[123] Palladium-catalyzed Claisen rearrangement of allyl vinyl ether, see: (a) J. L. Van der Baan, F. Bickelhaupt, *Tetrahedron Lett.* **1986**, *27*, 6267-6270; (b) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879; (c) Hayashi, T.; Yamamoto, A.; Ito, Y. *Synth. Commun.*, **1989**, *19*, 2109; Au-catalyzed Claisen rearrangement of propargyl vinyl ethers, see: (d) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc*. **2004**, *126*, 15978-15979.

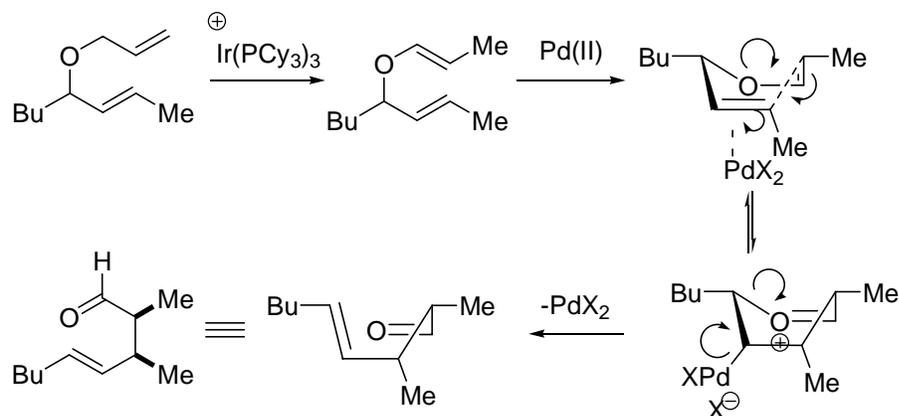[124] Nelson, S. G.; Kerrigen, N.; Bungard, C. J. unpublished result.

Figure 38. Pd(II)-catalyzed ICR reactions

The hard Lewis acid-mediated Claisen rearrangement may be *via* a concerted or an ionicic intermediate mechanism.[125] In the concerted mechanism, Lewis acids coordinate with oxygen to decrease the the activated energy for the Claisen rearrangement, so the reaction becomes much easier. In the ionic intermediate mechanism, the carbon-oxygen bond cleavage to form an allyl carbonium ion and a vinyl oxide anion, so two regioisomers are formed after recombination: one is a normal [3,3] product and the other is a [1,3] rearrangement product.[126] But the [1,3] rearrangement can also be explained as an allyl ether migration followed by [3,3] rearrangement (Figure 39). In general, Lewis acids coordinate the Claisen products carbonyl groups much stronger than the Claisen starting material allyl vinyl ethers. As a result, it is difficult to remove the Lewis acid from the Claisen product to the starting material and start a new catalytic cycle. In most conditions, excess Lewis acids are required for promoting Claisen rearrangement.[127]

[125] (a) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc*. **1990**, *112*, 316-322. (b) Nonoshita, K.; Maruoka, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 541-545. (c) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1981**, *22*, 3985-3988. (d) Chiral Lewis acid-mediated asymmetric Claisen rearrangement, see: Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc*. **1995**, *117*, 1165-1166.
[126] Cu(OTf)$_2$ catalyzed [1,3] rearrangement of allyl vinyl ether, see: Nasveschuk, C. G.; Rovis, T. *Org. Lett*. **2005**, *7*, 2173-2176.
[127] Lewis acid Cr(TPP)Cl-catalyzed Claisen rearrangement, see: Takanami, T.; Hayashi, M.; Iso, K.; Nakamoto, H.; Suda, K. *Tetrahedron* **2006**, *62*, 9467-9474.
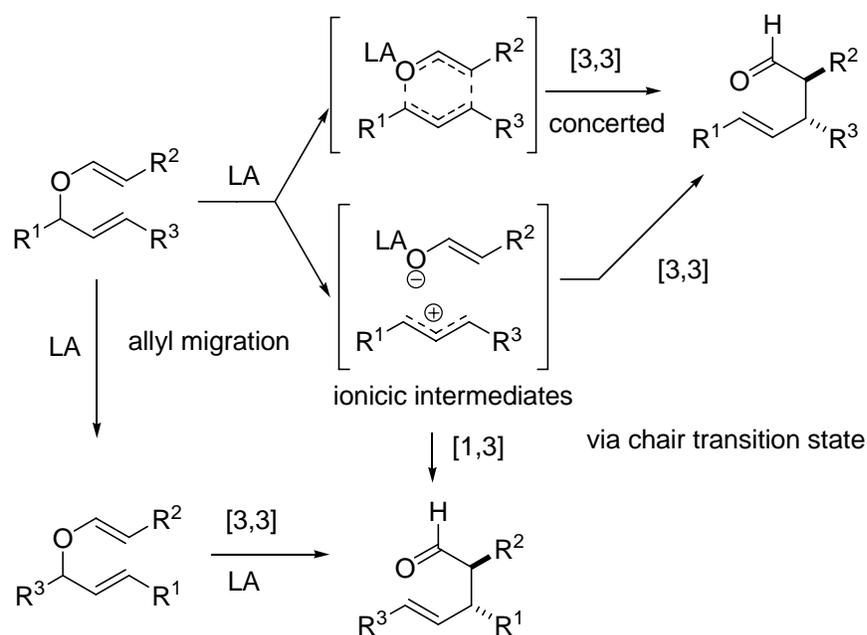
Figure 39. Lewis acid-promoted [3,3] and [1,3] rearrangement

5.1   ORGANOALUMINUM-PROMOTED CLAISEN REARRANGEMENT

In general, the Lewis acid-promoted Claisen rearrangement affords the same diastereoselectivity as the thermal Claisen rearrangement. Thus when the thermal Claisen rearrangement is sluggish, the Lewis acid-promoted reaction may promote it. As we know, the Claisen rearrangement of allyl vinyl ethers bearing an alkene group in am ring seems difficult in common thermal conditions because the reaction is *via* a boat transition state.[128] For example, the thermal Claisen rearrangement of 3-(vinyloxy)cyclohex-1-ene requires 190 ^{o}C (eq 27).[129]

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[128] (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1981**, *46*,479-485. (b) Bartlett, P. A.; Pizzo, C. F. *J. Org. Chem.* **1981**, *46*. 3896-3900.
[129] Dulcere, J. P.; Rodriguez, J. *Synthesis* **1993**, *4*, 399-405.

$$\text{(27)}$$
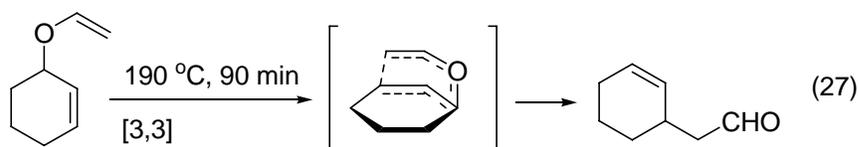
Microwave oven-promoted reactions help us realize these conditions. The cyclic (*E*)-allyl vinyl ether **86a** was easily obtained from selective isomerization of di(allyl) ether **85a** with 1 mol% Ir(PCy$_3$)$_3$BPh$_4$; the internal ring olefin is not isomerized. After addition of 3 mol% PPh$_3$, thermolysis of the crude (*E*)-allyl vinyl ether (**86a**) at 150 ^{o}C in a microwave oven in DCE for 1 h affords 40 % conversion of aldehydes (**87a**, *syn : anti* = 1 : 1) and 60 % of unreacted allyl vinyl ether **86a**, which becomes a mixture of *Z* and *E* isomers (ratio 1:1). Considering the perhaps side reactions caused by residue of iridium salts, the crude allyl vinyl ether **86a** was purified by short Florisil plug. Thermolysis of the purified (*E*)-allyl vinyl in 180 ^{o}C microwave oven for 2 h give excellent conversion to aldehydes (**87a**) with good diastereoselectivity (*anti : syn* = 90 : 10); only trace starting materials remain (Scheme 44). This result indicates that the residue of iridium salt still erodes selectivity at high temperature even it is quenched with PPh$_3$.
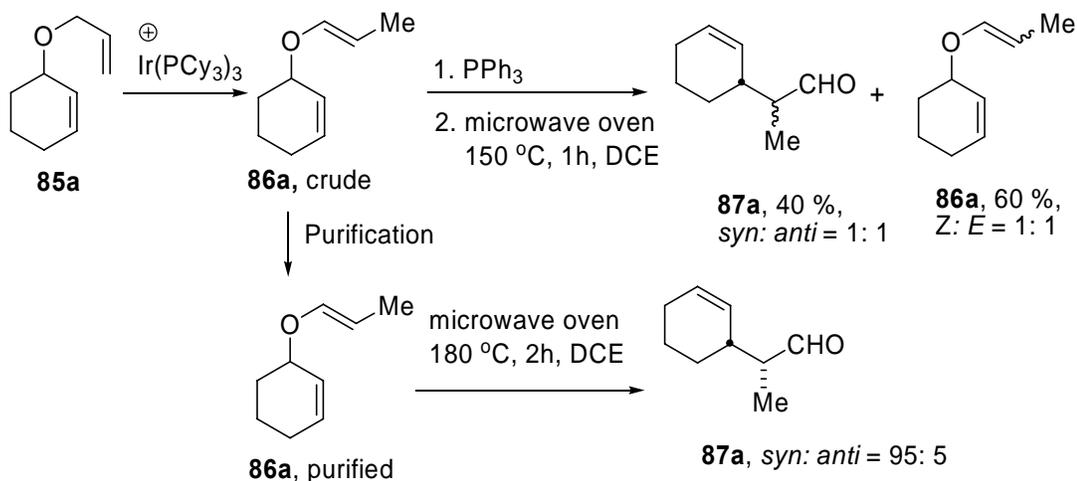
Scheme 44. Thermal Claisen rearrangement of allyl vinyl ether 86a

Because the thermal Claisen rearrangement of the allyl vinyl ether **86a** required elaborate conditions, the Lewis acid condition was examined. Treat the **86a** with 1.5 equivalent Me$_2$AlCl at -40 ^{o}C, after some minutes, the starting material disappeared to afford aldehyde **87a** with a poor diastereoselective (*anti: syn* = 6: 1, depending on the reaction time). The one of possible reasons for poor diastereoselectivity is that strong Lewis acid epimerize Claisen adduct **87a.** As a result, the formed aldehyde should be trapped *in situ* to avoid epimerization. Therefore, we try to use DIBAL-H to promote the Claisen rearrangement and reduce the formed aldehyde to primary alcohol. The alcohol **88a** (*anti : syn* = 96 : 4) was obtained with good yield and diastereoselectivity. Considering purified allyl vinyl ether is not necessary for this cascade reaction, but acetone as a co-solvent of isomerization reaction consumes the DIBAL-H. T`he solvent was removed in vacuum and add fresh CH$_2$Cl$_2$ before treated with DIBAL-H, the same result was obtained (Scheme 45).
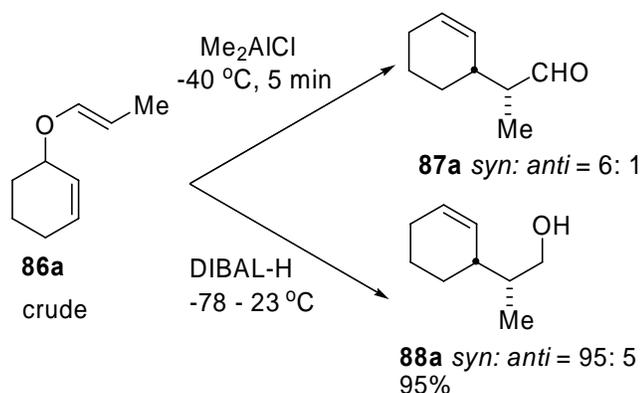
Scheme 45. Organoaluminum-promoted Claisen rearrangement of allyl vinyl ether 86a

The Claisen products of substrates **89** have **α**-quaternary carbon center, so the organoaluminum-promoted ICR reaction afforded good result (Table 8). First, the Ir(I)-catalyzed isomerization of di(allyl) ethers **89** afforded allyl vinyl ethers **90**. Then treatment the crude allyl vinyl ethers (**90**, solvent was changed to pure CH$_2$Cl$_2$) with Me$_2$AlCl (1.0 equivalent, −40 °C) afforded aldehydes **91** with good diastereoselectivity. Diisobutylaluminum hydride proved to be

an equally efficient Lewis acid promoter, generating the alcohols **92** with good diastereoselectivity, thereby affording direct entry to alcohol-containing Claisen adducts without resorting to a separate aldehyde reduction step.

Table 8. Lewis acid-promoted ICR for preparing quaternary carbon
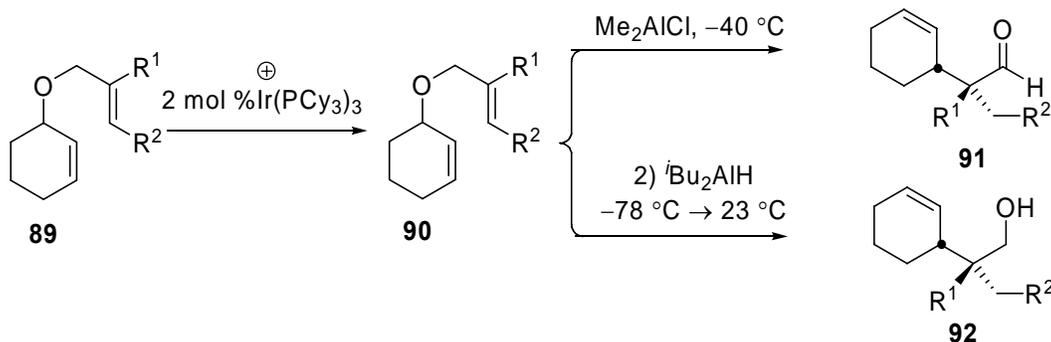
entry	R^1	R^2	d.r.	yield (compound)
a	Me	nC_6H_{13}	100:0	57 (**91**)
b	Me	nC_6H_{13}	98:2	71 (**92**)
c	Et	nC_5H_{11}	94:6	62 (**92**)
d	Me	H	NA	70 (**91**)
e	Me	H	NA	76 (**92**)

Next the organoaluminum-promoted ICR reactions of 6,6-disubstituted-di(allyl) ether **93** was examined. The thermal Claisen rearrangements of corresponding allyl vinyl ether **94** required elaborate conditions. For example, the thermal Claisen rearrangement of **94a** required reflux in toluene for long time, but only modest conversion was observed and the diastereoselectivity was in the long reaction time (eq 28). The thermal Claisen rearrangement of allyl vinyl ether **94b** required a temperature as high as 150 °C in a microwave oven (eq 29). In

addition, purified allyl vinyl ethers are recommended in thermal Claisen rearrangement to avoid epimerization. As a result, the thermal Claisen was not convenient for these reactions.

93a   **94a**   **95a (**syn: anti = 87: 13**)**   (28)

93b   **94b**   **95b** (syn: anti = 19: 1)   (29)
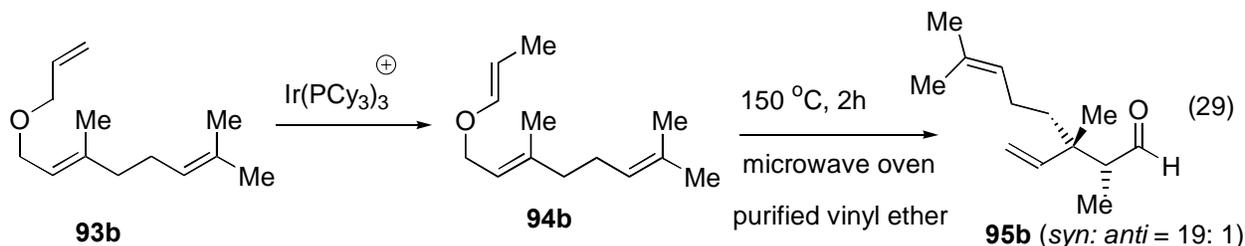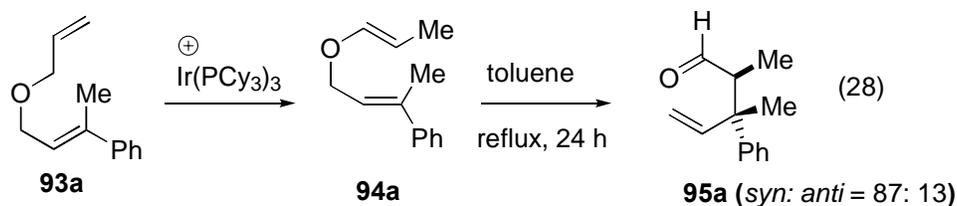
Treatment of the crude allyl vinyl ether (**94b**) with DIBAL-H offered a good stereoselective alcohol **96b** (eq 30).[130] However, poorer selectivity was observed in eq 31: a mixture of alcohols **96c** was obtained. Two major isomers were observed from the GC-trace; maybe they were diastereomers or *E/Z* isomers or a combination of both. A high yield of alcohol with a 2,3-bisquaternary center **96d** was observed from the ICR reaction of the di(allyl) ether **93d** (eq 32).

93b   **96b** (syn: anti = 90: 10)   (30)

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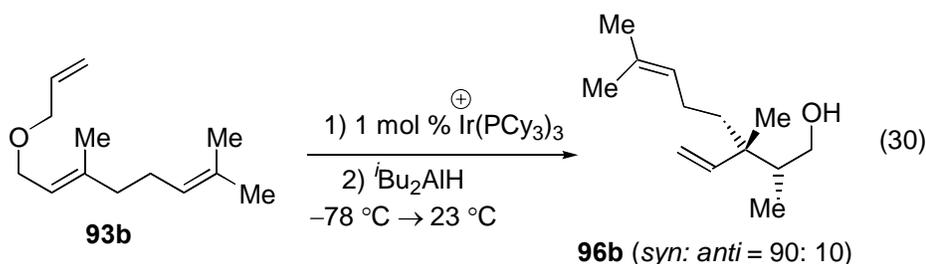
[130] The ratio and following ratio are determined from crude proton NMR and the GC trace.

$$\text{(31)}$$

96c (isomer ratio = 78: 22)

$$\text{(32)}$$
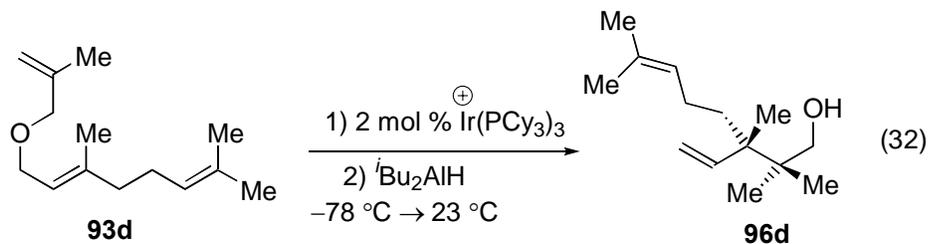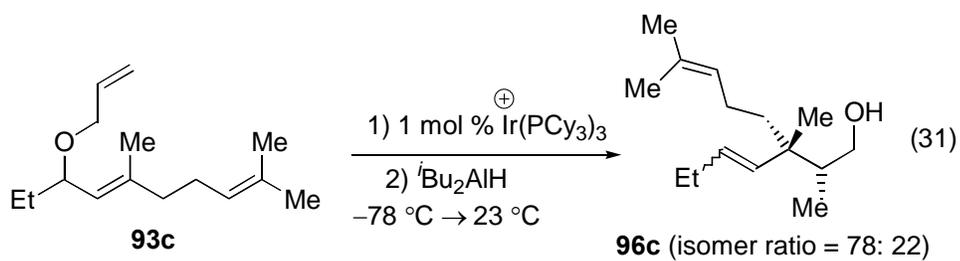
Three other substrates with good thermal Claisen reactivity were examined in this ICR/reduction procedure. Poor selectivity was observed from substrates **93e/f** (eq 33, 34), and good diastereoselectivity was afforded to substrates **93g** (eq 35). As a comparison, the thermal Claisen rearrangement of these substrates always showed far better diastereoselectivity.

$$Bu \overset{O \diagup \diagdown}{\underset{93e}{\diagup}} Me \quad \xrightarrow[\substack{2) \ ^iBu_2AlH \\ -78\ ^\circ C \rightarrow 23\ ^\circ C}]{1)\ 1\ mol\ \%\ \overset{\oplus}{Ir(PCy_3)_3}} \quad Bu \overset{Me\quad OH}{\underset{Me}{\diagup\diagdown}} \qquad (33)$$

93e   **96e** (isomer ratio = 40: 40: 10: 10)

$$Et \overset{O \diagup \diagdown}{\underset{Me}{\diagup}} Ph \quad \xrightarrow[\substack{2) \ ^iBu_2AlH \\ -78\ ^\circ C \rightarrow 23\ ^\circ C}]{1)\ 1\ mol\ \%\ \overset{\oplus}{Ir(PCy_3)_3}} \quad Et \overset{Ph\quad OH}{\underset{Me\ Me}{\diagup\diagdown}} \qquad (34)$$

93f   **96f** (isomer ratio = 42: 29: 16: 13)

$$Me\overset{O \diagup \diagdown}{\underset{Me}{\diagup}} Me \quad \xrightarrow[\substack{2) \ ^iBu_2AlH \\ -78\ ^\circ C \rightarrow 23\ ^\circ C}]{1)\ 1\ mol\ \%\ \overset{\oplus}{Ir(PCy_3)_3}} \quad Me \overset{Me\ Me\ OH}{\underset{Me}{\diagup\diagdown}} \qquad (35)$$

93g   **96g** (*syn: anti* = 95: 5)
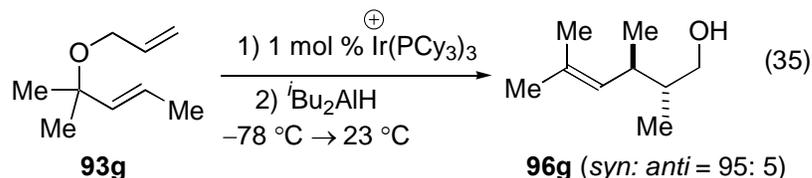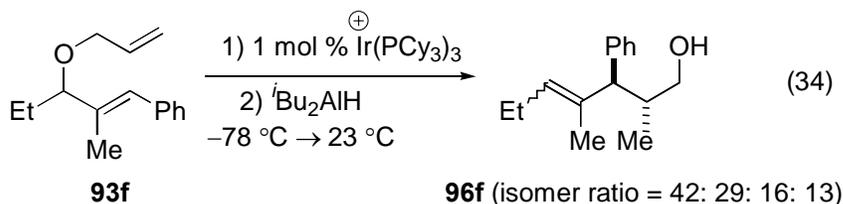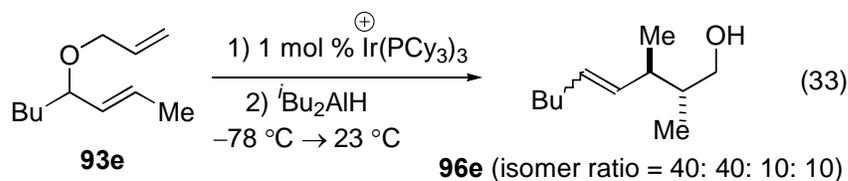
The DIBAL-H promoted cascade Claisen rearrangement/reduction reaction of acyclic substrates did not offer products with good diastereoselectivity, but no [1,3] rearrangement products were observed in these cases.

5.2   CASCADE REACTION BASED ON ICR REACTION

5.2.1 Cascade Claisen/ene reaction

The DIBAL-H reduction trapping the formed aldehyde was discussed in the previous section. Besides this strategy, the Lewis acid-mediated ene reaction traps the formed Claisen adducts in some cases to provide synthetically valuable compounds in single step. Stoltz has reported a

cascade Claisen rearrangement/ene reaction of a vinyl ether, derived from geraniol, with good yield and diastereoselectivity (Scheme 46).[131]
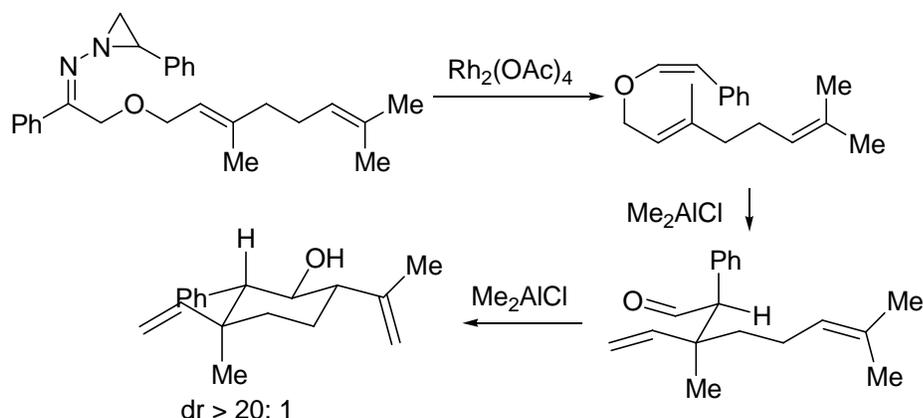
Scheme 46. Cascade Claisen/ene reaction

The Stoltz's conditions were followed employing our allyl vinyl ether substrates, which were derived from isomerization of di(allyl) ethers. This Me$_2$AlCl-mediated cascade Claisen/ene reaction of vinyl ethers (**94b-d**) derived from olefin isomerization of easily prepared di(allyl) ether (**93b-d**) was examined. Treatment of the allyl vinyl ether (**94b**) with 1.1 equivalents of Me$_2$AlCl at -40 °C caused the Claisen/ene cascade reaction (Figure 40). But the stereoselectivity was very poor (Two major isomers **97b1**: **97b2** = 66 %: 22 % were derived from 2,3-*syn* aldehyde **95b1**; another two minor isomers 9 % **97b3** and 2 % **97b4** were derived from 2,3-*anti* aldehyde **95b2**). The reason for obtaining the poorer stereoselectivity in our reaction than in the precedent (Scheme 46) was that two transition states (route **a** and **b**) existed in the ene reaction for the major diastereomer of the Claisen adduct (**95b1**). There was not much energy difference between these two transition states (route **a** and route **b**) where the α-Me assumed in the axial or equtorial position. But in the Scheme 46, due to the large energy difference between two possible

[131] (a) May, J. A.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12426-12427. The aldehyde was derived from Ireland Claisen rearrangement followed by reduction and oxidation, then the aldehyde was treated with Lewis acid condition. see: (b) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 93-196. The cascade oxy-cope/Claisen/ene reaction, see: (c) Sauer, E. L. O.; Barriault, L. *J. Am. Chem. Soc.* **20024**, *126*, 8569-8575.

transition states where α-Ph assumed in the axial or equtorial position, a better selectivity (20:1) was obtained.
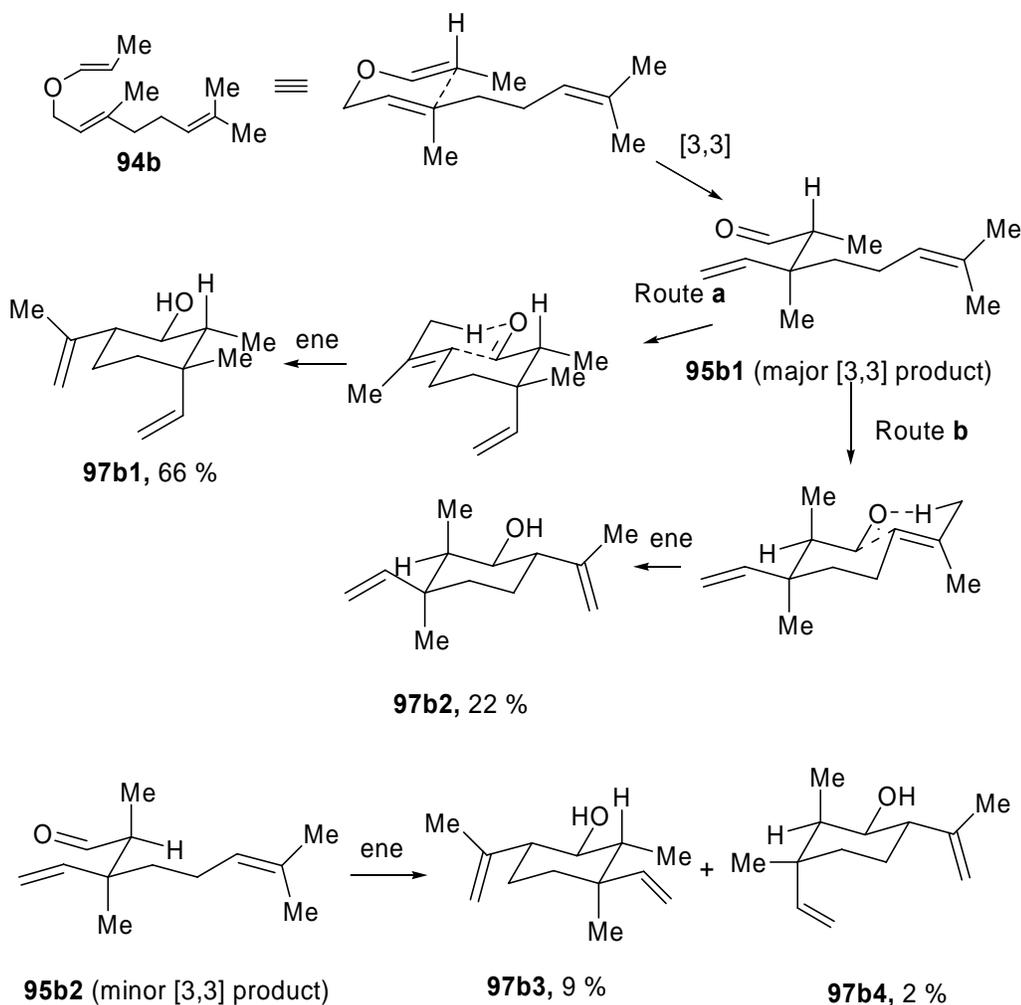
Figure 40. Me₂AlCl promoted ICR-ene reaction

Then two substrates with similar structure (Scheme 47/48) were subjected to same conditions. Both of the reactions afforded very poor selectivity. In Scheme 47, a cascade isomerization-Claisen rearrangement-ene reaction of di(allyl) ether **93c** afforded four major isomers in a ratio of 46: 30: 16: 8 (according to the GC trace and proton NMR spectrum). The two major isomers **97c1** and **97c2** were derived from the major Claisen product **95c1**. In Scheme 48, although the ICR of di(allyl) ether **93d** produced only one Claisen product **95d**, the

diasteroselectivity of the ene reaction was very poor between two isomers of cyclohexanol (**97d1** and **97d2**) in a ratio of 33: 67. Although poor selectivity was obtained in this cascade isomerization/Claisen/ene reaction, polyfunctionallized cyclohexanols were prepared in a single operation from simple starting materials. The procedure could be useful in organic synthesis upon optimization.

Scheme 47. Isomerization-Claisen/ene reaction of di(allyl) ether 93c

Scheme 48. Isomerization-Claisen/ene reaction of di(allyl) ether 93d

5.2.2 Cascade isomerization/Claisen/Wittig/Cope reaction

Another cascade reaction discussed here is cascade isomerization-Claisen-Wittig-Cope reactions. Due to the formed α-chiral aldehyde tend to epimerize in high temperature, Wittig reaction was desired to trap the formed aldehyde to avoid epimerization. Heating the mixture of crude allyl vinyl ether **86a** with Ph₃PCHCOOMe at 180 °C in microwave oven afforded high diastereoselective Wittig product **98a** (*anti: syn* = 91: 9) (Scheme 49). When Ph₃PCHCHO instead Ph₃PCHCOOMe was used in this reaction, no any enal but simple aldehyde **87a** (*anti: syn* = 50: 50) was observed, the possible reason for no desired product is the decomposition of Ph₃PCHCHO in high temperature.
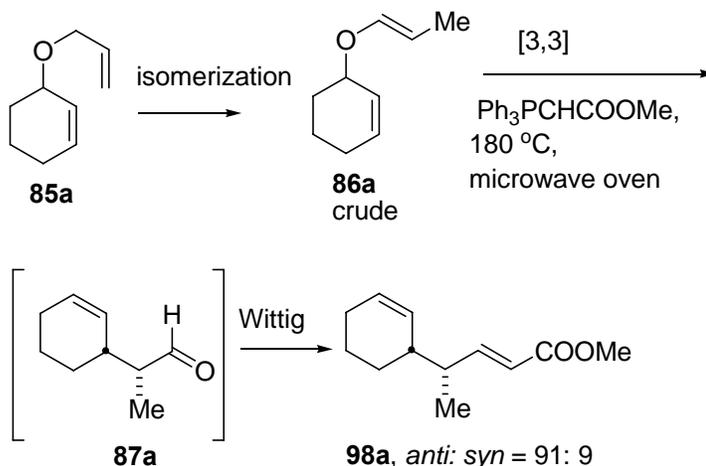
Scheme 49. Cascade isomerization/Claisen/Wittig reaction of di(allyl) ether 85a

When the allyl vinyl ether **86b** was treated in the same condition, the unexpected product **99b**, which was formed *via* the Cope rearrangement of the Wittig products α,β-unsaturated ester **98b,** was observed (Scheme 50). [132]

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[132] The Cope rearrangement of α,β-unsaturated ester was reported, see: (a) Davies, H. M.; Jin, Q. *J. Am. Chem. Soc.* **2004**, *126*, 10862-10863. (b) Davies, H. M.; Beckwith, R. E. *J. Org. Chem.* **2004**, *69*, 9241-9247. (c) Davies, H. M.; Jin, Q. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5472-5475.
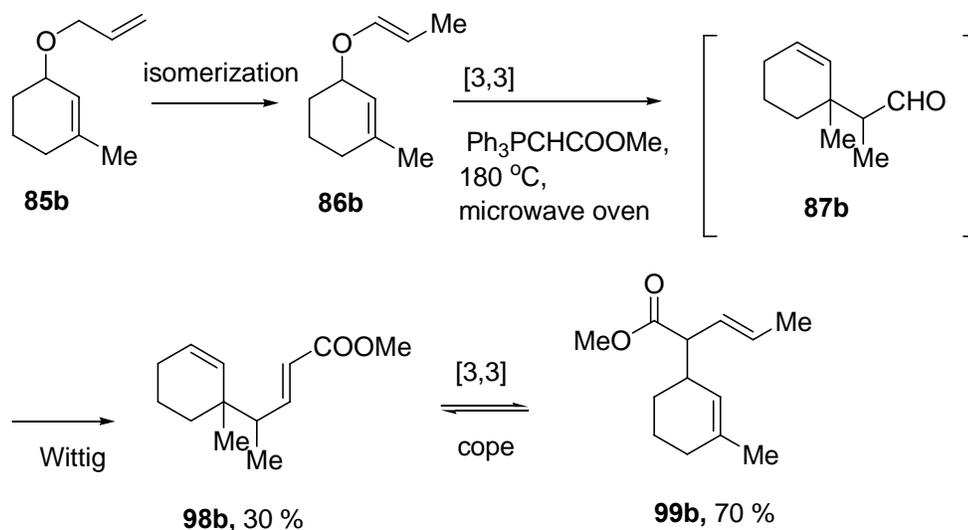
Scheme 50. Cascade isomerization-Claisen-Wittig-Cope reaction of di(allyl) ether 85b

Treatment of the acyclic allyl vinyl ether **94b** under the above conditions afforded Cope rearrangement product **99c** along with Wittig product **98c** (the ratio is 80:20, eq 36). From the above two examples, an equilibrium exists in the Cope rearrangement between two isomers. It is suggested that the β-quaternary center in unconjugated esters (**98b/c**) is an important driving force for the Cope rearrangement to get more thermodynamic favored conjugated **99b/c**. Further studies will let us know the optimized conditions and the limitations of this cascade reaction. The procedure could be useful in organic synthesis upon optimization.

(36)
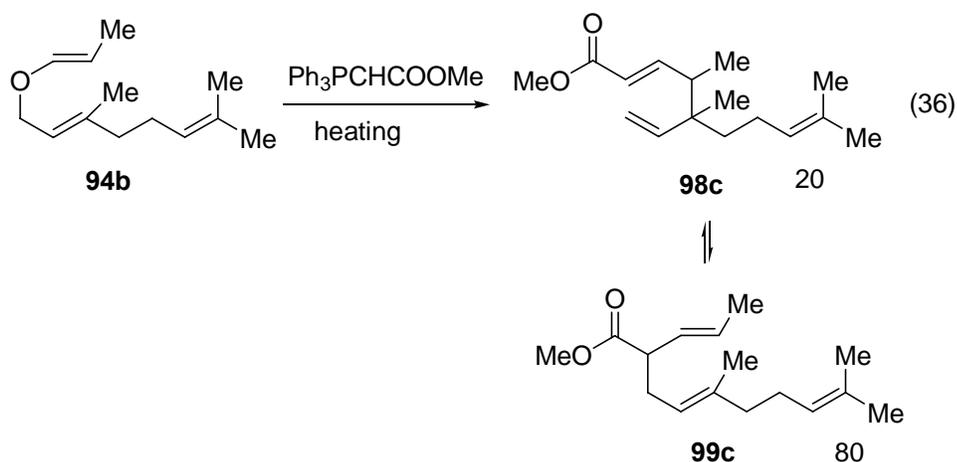
5.2.3 Cascade tetrahydropyran rings formation

Besides Claisen rearrangement, some other reactions for vinyl ethers are useful in organic synthesis. Nucleophilic electron-rich vinyl ethers take part in many reactions to form C-C bonds. Recently, Rychnovsky has reported a cascade tetrahydropyran ring formation through a Mukaiyama-Michael cascade reaction.[133] The reaction uses a vinyl ether as a nucleophilic reagent to attack an unsaturated carbonyl compound which is activated by TiBr$_4$. After [3,3] sigmatropic rearrangement and cyclization, tetrahydropyran rings are formed with highly stereoselectivity (Figure 41).

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[133] Bolla, M. L.; Patterson, B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 16044-16045.
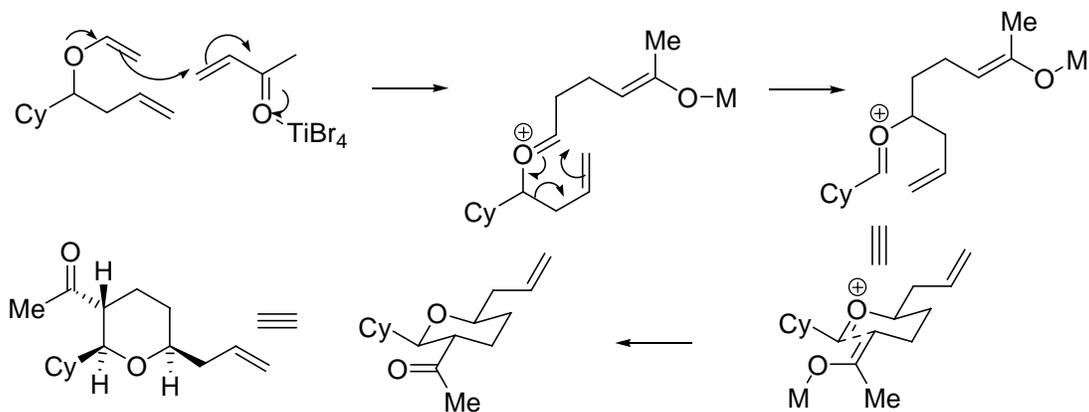
Figure 41. Cascade reaction to form tetrahydropyran rings from homoallyl vinyl ether

Our isomerization protocol is a useful reaction to obtain the substituted homoallyl vinyl ethers. Subsequent treatment of the homoallyl vinyl ethers under the cascade reaction conditions (methyl vinyl ketone, TiBr$_4$, and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in CH$_2$Cl$_2$ at -78 °C) should afford more substituted tetrahydropyran rings. Treating the homoallyl vinyl ether **101a** under the cascade reaction conditions afforded a mixture of epimers (**102a**, 81: 19, Scheme 51).
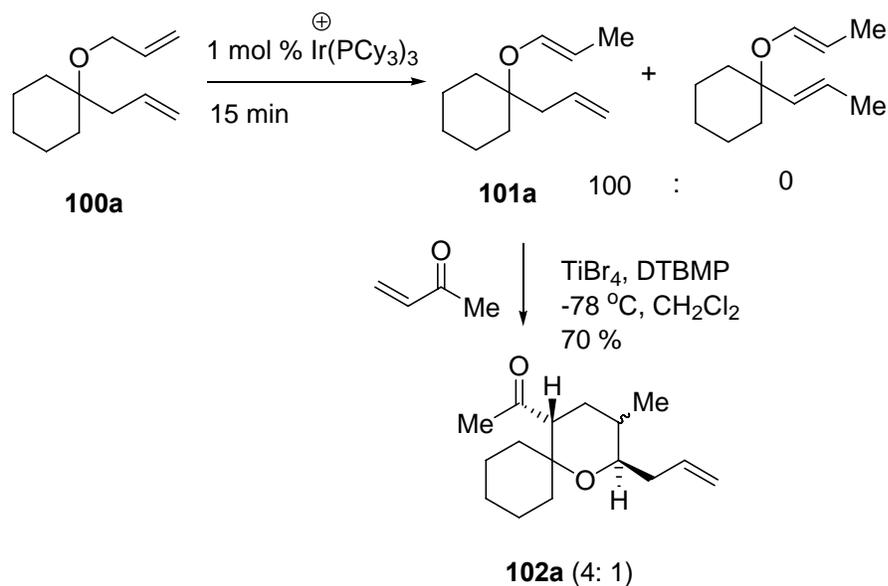
Scheme 51. Tetrahydropyran rings fromation

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Another di(allyl) ethyl (**100b**) was treated under the same condition. After isomerization and a cascade reaction, a poorer ratio (**102b,** ratio 58: 42, eq 37) was obtained. There was no selectivity for the vinyl ether addition to vinyl methyl ketone. Other Lewis acids, bases, ligands or reaction conditions should optimize this cascade reaction for obtaining highly complex products with good yield and stereoselectivity in a single step from simple starting materials.
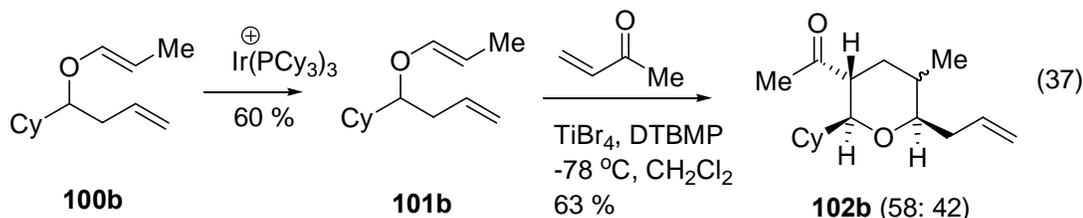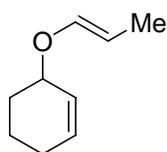

Some reactions were discussed in this chapter. First, the Me$_2$AlCl or DIBAL-H were used to promote the Claisen rearrangement. Next, some ICR based cascade reactions were discussed. All of these reactions require more work to be optimized and applied in organic synthesis.

5.3   EXPERIMENTAL SECTION

5.3.1 Experiment of section 5.1

 (*E*)-3-(Prop-1-enyloxy)cyclohex-1-ene (86a): General Procedure **D** was followed employing 3-(allyloxy)cyclohex-1-ene[134] (**85a,** 552 mg, 4.0 mmol) and 0.5 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloromethane for 30 min. Add pentane 5 ml and pass the solution to a short Florisil plug, after solvent

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[134] Ghosh, S.; Raychaudhuri, S. R.; Salomon, R. G. *J. Org. Chem.* **1987**, 52, 83-90.

evaporation, 496 mg (90 %) of the title compound as a colorless oil was yielded. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.12 (dq, J = 12.3, 1.5 Hz, 1H), 5.89 (dt, J = 10.1, 1.2 Hz, 1H), 5.75 (d, J = 10.1 Hz, 1H), 4.90 (dd, J = 12.3, 6.9 Hz, 1H), 4.17-4.20 (m, 1H), 1.90-2.10 (m, 2H), 1.60-1.85 (m, 4H), 1.54 (dd, J = 6.9, 1.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 144.93, 131.60, 126.66, 100.73, 73.06, 28.45, 24.96, 18.89, 12.48 ppm; IR (liquid film): 2936, 1725, 1674, 1655, 1160, 728 cm^{-1}.
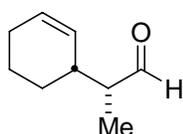
anti-**2-(Cyclohex-2-enyl)propanal (87a)**: A solution of purified (*E*)-3-(prop-1-enyloxy)cyclohex-1-ene (**86a**, 138 mg, 1.0 mmol) in 2 ml anhydrous dichloroethane in seal tube was heated at 180 ^{o}C in microwave oven for 2 h to afford aldehydes (*anti: syn* = 90 : 10). Purification by flash chromatograph on Iatrobeads neutral (pH7) silica gel (2.5 % ethyl ether in hexanes) yield 124 mg (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.67 (d, J = 1.59 Hz, 1H), 5.77 (dq, J = 10.2, 3.3 Hz, 1H), 5.50 (d, J = 10.2 Hz, 1H), 2.51-2.59 (m, 1H), 2.29-2.40 (m, 1H), 1.94-2.03 (m, 2H), 1.69-1.77 (m, 2H), 1.47-1.57 (m, 1H), 1.23-1.36 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 205.34, 129.46, 127.74, 50.55, 36.07, 26.67, 24.93, 21.65, 10.08 ppm; IR (liquid film): 2930, 1726, 1455, 1070, 723 cm^{-1}; MS (EI, 70 V): *m/z* 138 (M$^{+.}$), 123, 109; HRMS *m/z* calcd for C$_9$H$_{14}$O (M$^{+.}$): 138.1045; found 138.1041.
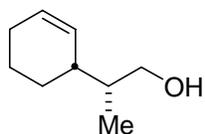
anti-**2-(Cyclohex-2-enyl)propanal (88a)**: General Procedure **I** for DIBAL-H promoted cascade Claisen rearrangement/reduction reaction: A solution of crude allyl vinyl ether (*E*)-3-(prop-1-enyloxy)cyclohex-1-ene (**86a**), which is obtained from di(allyl) ether (**85a**, 138 mg, 1.0 mmol) as general procedure **D**, in 2 ml dichloromethane and add

DIBAL-H (1.0 M in hexanes, 1.5 ml, 1.5 mmol) dropwise at -78 °C, slow warm the solution to ambient temperature for 12 h. Add saturated sodium tartrate solution 6 ml to quench the reaction and extraction with ether. Purification by flash chromatograph on silica gel (16 % ethyl ether in hexanes) yield 132 mg (95 %) of the title compound as colorless oil (*anti: syn* = 95: 5). ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.71 (dq, J = 10.2, 3.3 Hz, 1H), 5.55 (d, J = 10.2 Hz, 1H), 3.60 (dd, J = 10.6, 5.2 Hz, 1H), 3.44 (dd, J = 10.6, 6.9 Hz, 1H), 2.17-2.25 (m, 1H), 1.91-1.98 (m, 2H), 1.46-1.79 (m, 5H), 0.88 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 129.55, 128.15, 65.94, 39.90, 37.30, 26.24, 25.26, 22.22, 13.70 ppm; IR (liquid film): 3332, 2928, 1447, 1037, 721 cm^{-1}; MS (EI, 70 V): *m/z* 140 (M$^{+\cdot}$), 122, 107; HRMS *m/z* calcd for C$_9$H$_{16}$O (M$^{+\cdot}$): 140.1201; found 140.1208.
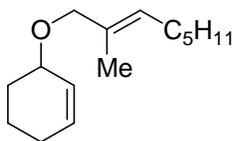
(*E*)-3-(2-Methyloct-2-enyloxy)cyclohex-1-ene (89a): **General Procedure A** was followed employing 0.49 g of cyclohex-2-enol (5.0 mmol), 240 mg NaH (10.0 mmol) and 1.03 g of a 4:1 mixture of (*E*)-1-bromo-2-methyloct-2-ene and 3-bromo-2-methyloct-1-ene (5.0 mmol)[135] in THF. Purifying the crude product mixture by flash chromatography (2% EtOAc in hexanes) gave 440 mg (40%) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.83 (d, J = 10.1 Hz, 1H), 5.75 (d, J = 10.1 Hz, 1H), 5.41 (t, J = 6.8 Hz, 1H), 3.93 (d, J = 11.4 Hz, 1H), 3.87 (d, J = 11.4 Hz, 1H), 3.83-3.87 (m, 1H), 1.90-2.03 (m, 4H), 1.29-1.79 (m, 10H), 1.65 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 132.44, 130.47, 128.21, 128.06, 74.32, 71.27, 31.53, 29.13, 28.33, 27.63, 25.20, 22.53, 19.27, 14.02, 13.92 ppm; MS (EI, 70 V): *m/z* 222 (M$^{+\cdot}$), 207, 179, 127, 107, 97, 81, 69; HRMS *m/z* calcd for C$_{15}$H$_{26}$O (M$^{+\cdot}$): 222.1984; found: 222.1978.

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[135] The mixture of (E)-1-bromo-2-methyloct-2-ene and 3-bromo-2-methyloct-1-ene was prepared by reacting 2-methyloct-1-en-3-ol with PBr$_3$ in hexanes.
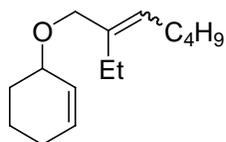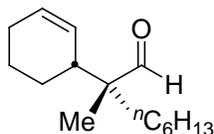
3-(2-Ethylhept-2-enyloxy)cyclohex-1-ene (89c): General Procedure **A** was followed employing 0.20 g of cyclohex-2-enol (2.0 mmol), 144 mg NaH (6.0 mmol), and 715 mg of a mixture of (*E/Z*)-3-(bromomethyl)oct-3-ene and 4-bromo-3-methyleneoctane (3.0 mmol)[136] in THF. Purifying the crude product mixture by flash chromatography (2% EtOAc/hexanes) gave 176 mg (40%) of the title compound as a mixture of E and Z isomers (*E:Z* = 1: 3). ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.83 (dt, J = 10.2, 3.5 Hz, 1H), 5.76 (d, J = 10.2 Hz, 1H), 5.38 (t, J = 7.2 Hz, 1H), 3.97 (d, J = 11.6 Hz, 1H), 3.89 (d, J = 11.6 Hz, 1H), 1.20-2.10 (m, 14H), 0.90 (t, J = 7.4 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H) ppm; MS (EI, 70 V): *m/z* 222 (M$^{+\cdot}$), 124, 95, 85, 81, 69; HRMS *m/z* calcd for C$_{15}$H$_{26}$O (M$^{+\cdot}$): 222.1984; found 222.1978.
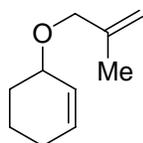
3-(2-Methylallyloxy)cyclohex-1-ene (89d): General Procedure **A** was followed employing 0.98 g of cyclohex-2-enol (10.0 mmol), 480 mg NaH (20.0 mmol) and 1.8 g 3-chloro-2-methylprop-1-ene (20.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes) gave 1.42 g (94 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.84 (dtd, J = 10.1, 3.4, 1.2 Hz, 1H), 5.76 (d, J = 10.1 Hz, 1H), 4.97 (s, 1H), 4.86 (s, 1H), 3.96 (d, J = 12.6 Hz, 1H), 3.90 (d, J = 12.6 Hz, 1H), 3.84 -3.86 (m, 1H), 1.74 (s, 3h), 1.69-1.81 (m, 6H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 142.41, 130.19, 127.59, 111.33, 71.64, 71.52, 28.01, 24.87, 19.15, 18.90 ppm; IR (liquid film): 2937, 1654, 1451, 1087, 899, 729 cm^{-1}; MS (EI, 70 V): *m/z* 152 (M$^{+\cdot}$), 137, 100; HRMS *m/z* calcd for C$_{10}$H$_{16}$O (M$^{+\cdot}$): 152.1201; found 152.1207.

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[136] The mixture of (E/Z)-3-(bromomethyl)oct-3-ene and 4-bromo-3-methyleneoctan was prepared by reacting 3-methyleneoctan-4-ol with PBr$_3$ inhexanes.

***syn*-2-(Cyclohex-2-enyl)-2-ethylheptanal (91a): General Procedure D** was followed employing (*E*)-3-(2-methyloct-2-enyloxy)cyclohex-1-ene (**89a**, 111 mg, 0.5 mmol) a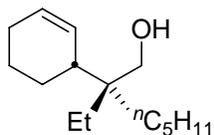nd 4 mol% catalyst (9.0 mg $[IrCl(C_8H_{14})_2]_2$, 16.8 mg PCy_3, and 6.8 mg $NaBPh_4$) and stirred 48 h at 80 °C in 1,2-dichloroethane. After cooling the reaction mixture to ambient temperature, the solvent was evaporated and the resulting residue was dissolved in 1,2-dichloroethane (2 mL) and cooled to −40 °C. A 1.0 M hexanes solution of Me_2AlCl (1.0 mL, 1.0 mmol) was added and the reaction was stirred for 10 min. A saturated sodium tartrate solution (4 mL) was added and the mixture was warmed to ambient temperature and stirred until two homogeneous phases resulted (~1 h). The mixture was extracted with Et_2O (3×) and the combined organic extracts were dried over anhydrous $MgSO_4$. Purifying the crude product mixture by flash chromatography on silica gel (2.5% ethyl ether in hexanes) yielded 63 mg (57%, 100% de) of the title compound as a light yellow oil. Analysis of the crude product mixture by ^{1}H NMR and GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T_r = 38.9 min] provided Vidence of only one diastereomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.49 (s, 1H), 5.81 (dq, J = 10.3, 3.1 Hz, 1H), 5.59 (dt, J = 10.3, 3.5 Hz, 1H), 2.38-2.48 (m, 1H), 1.82-2.10 (m, 2H), 1.20-1.90 (m,1 3H), 0.97 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.1, 130.0, 126.2, 40.4, 33.8, 31.6, 30.0, 25.1, 24.5, 24.0, 22.6, 22.3, 14.8, 14.1 ppm; MS (EI, 70 V) *m/z* 222 (M$^{+\cdot}$), 207, 193, 179, 142, 137, 81; HRMS *m/z* calcd for $C_{15}H_{26}O$ (M$^{+\cdot}$): 222.1984; found 222.1977.
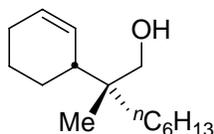
*syn*-2-(Cyclohex-2-enyl)-2-methyloctan-1-ol (92b): General Procedure **D** was followed employing di(allyl) ether **89a** (111 mg, 0.5 mmol) and 4 mol% catalyst (9.0 mg [IrCl(C_8H_{14})$_2$]$_2$, 16.8 mg PCy$_3$, and 6.8 mg NaBPh$_4$) and stirred 48 h at 80 °C in 1,2-dichloroethane solvent. After cooling the reaction mixture to ambient temperature the solvent was Vaporated and the resulting residue was dissolved in dichloromethane (2 mL) and cooled to −78 °C. A 1.0 M hexanes solution of *i*-Bu$_2$AlH (1.0 mL, 1.0 mmol) was added and the reaction was warmed to ambient temperature and stirred 12 h. A saturated sodium tartrate solution (4 mL) was added and the mixture was stirred 1 h. The mixture was extracted with Et$_2$O (3×) and the combined organic extracts were dried over anhydrous MgSO$_4$. Purifying the crude product mixture by flash chromatography on silica gel (16% EtOAc in hexanes) yielded 78 mg (71%) of the title compound as a light yellow oil. Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T_r = 47.1 and 50.0 min] provided the diastereomer ratio: syn:anti = 1.0:99.0. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.69-5.81 (m, 2H), 3.54 (d, J = 11.1 Hz, 1H), 3.39 (d, J = 11.1 Hz, 1H), 2.15-2.25 (m, 1H), 1.90-2.00 (m, 2H), 1.65-1.88 (m, 2H), 1.20-1.62 (m, 13H), 0.89 (t, J = 6.5 Hz, 3H), 0.85 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 128.70, 128.64, 68.21, 40.39, 39.70, 35.18, 31.89, 30.35, 25.22, 23.84, 23.35, 22.83, 22.69, 19.23, 14.09 ppm; MS (EI, 70 V): 224 (M$^{+ \cdot}$), 206, 193, 143, 121, 109; HRMS *m/z* calcd for C$_{15}$H$_{28}$O (M$^{+ \cdot}$) 224.2140, found: 224.2131.

*syn*-2-(Cyclohex-2-enyl)-2-ethylheptanal (92c): General Procedure **C** was followed employing di(allyl) ether **89c** (67 mg, 0.3 mmol) and 4 mol% catalyst (5.4 mg [IrCl(C_8H_{14})$_2$]$_2$, 10.1 mg PCy$_3$, and 4.1 mg NaBPh$_4$) and stirred 48 h at 80 °C in

1,2-dichloroethane solvent. After cooling the reaction mixture to ambient temperature, the solvents were evaporated and the resulting residue was dissolved in dichloromethane (2 mL). The reaction mixture was cooled to −78 °C and a 1.0 M hexanes solution of *i*-Bu$_2$AlH (0.6 mL, 0.6 mmol) was added and the reaction was warmed to ambient temperature and stirred for 12 h. A saturated sodium tartrate solution (4 mL) was added and the mixture was warmed to ambient temperature and stirred for 1 h. The mixture was extracted with Et$_2$O (3×) and the combined organic extracts were dried over anhydrous MgSO$_4$. Purifying the crude product mixture by flash chromatography on silica gel (16% EtOAc in hexanes) yielded 42 mg (62%) of the title compound as a light yellow oil. Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T_r = 46.3 and 48.8 min] provided the diastereomer ratio: *anti: syn* = 3.8:96.2. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.86 (d, J = 10.4 Hz, 1H), 5.75 (dq, J = 10.4, 3.2 Hz, 1H), 3.59 (d, J = 11.1 Hz, 1H), 3.39 (d, J = 11.1 Hz, 1H), 2.15-2.25 (m, 1H), 1.95-2.05 (m, 2H), 1.72-1.89 (m, 3H), 1.21-1.67 (m, 12H), 0.89 (t, J = 7.5 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 129.30, 128.69, 67.19, 42.18, 39.94, 32.94, 31.79, 31.58, 25.34, 24.26, 23.99, 22.96, 22.79, 14.12, 7.92 ppm; MS (EI, 70 V): 224 (M$^{+\cdot}$), 206, 195, 193, 177, 163, 153, 149, 143, 142, 135, 125, 109, 95, 83, 69, 55; HRMS *m/z* calcd for C$_{15}$H$_{28}$O (M$^{+\cdot}$): 224.2140; found: 224.2138.
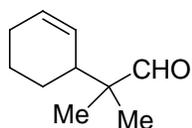

2-(Cyclohex-2-enyl)-2-methylpropanal (91d): Same Procedure as preparation of compound **91a** was followed employing 3-(2-methylallyloxy)cyclohex-1-ene (**89d,** 152 mg, 1 mmol), Purifying the crude product mixture by flash chromatography on silica gel (5 % EtOAc in hexanes) yielded 106 mg (70 %) of the title compound as a light yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$): δ 9.52 (s, 1H), 5.80 (dq, J = 10.3, 3.4 Hz, 1H), 5.49 (d, J = 10.3 Hz, 1H), 2.35-2.42 (m, 1H), 1.97-1.98 (m, 2H), 1.24-1.57 (m, 4H), 1.03 (s, 6H) ppm; MS (EI, 70 V): *m/z* 152 (M$^{+\cdot}$), 137, 123,; HRMS *m/z* calcd for C$_{10}$H$_{16}$O (M$^{+\cdot}$): 152.1201; found 152.1208.
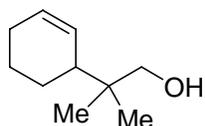
2-(Cyclohex-2-enyl)-2-methylpropan-1-ol (92e): General Procedure **D** was followed employing 3-(2-methylallyloxy)cyclohex-1-ene (**89d**, 152 mg, 1 mmol) and 2 mol% catalyst loading, the initial reaction time is 6 h at 40 °C. After DIBAL-H (1.0 M in hexanes, 1.5 ml, 1.5 mmol) promoted reaction. Purification by flash chromatograph on silica gel (16 % ethyl ether in hexanes) yield 117 mg (76 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.71-5.80 (m, 1H), 5.68 (dt, J = 10.4, 1.5 Hz, 1H), 3.45 (d, J = 10.9 Hz, 1H), 3.39 (d, J = 10.9 Hz, 1H), 2.05-2.15 (m, 1H), 1.85-1.97 (m, 2H), 1.69-1.82 (m, 2H), 1.65 (brs, 1H), 1.38-1.55 (m, 1H), 1.19-1.35 (m, 1H), 0.88 (s, 3H), 0.86 (s, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 128.6, 128.5, 70.3, 41.3, 37.5, 25.1, 24.0, 22.7, 22.1, 21.5 ppm; MS (EI, 70 V): *m/z* 154 (M$^{+\cdot}$), 136, 123, 107, 81, 73, 67, 55; HRMS *m/z* calcd for C$_{10}$H$_{18}$O (M$^{+\cdot}$): 154.1358; found 154.1362.
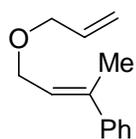
(*E*)-(4-(allyloxy)but-2-en-2-yl)benzene (93a): The General Procedure **A** was applied to (*E*)-3-phenylbut-2-en-1-ol (1.48 g, 10.0 mmol). The crude product was purified by column chromatography on silical gel (2 % ethyl acetate in hexanes) to yield 1.80 g (95 %) of the title compound as light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.23-7.54 (m, 5H), 6.02-6.15 (m, 2H), 5.43 (d, J = 17.2 Hz, 1H), 5.32 (d, J = 10.4 Hz, 1H), 4.32 (d, J = 6.5 Hz, 2H), 4.15 (d, J = 5.7 Hz, 2H), 2.18 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 142.85, 138.20, 134.81, 128.16, 127.12, 125.71, 124.24, 117.13, 71.20, 67.05, 16.13 ppm.
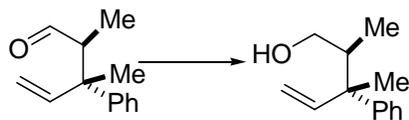
syn-**2,3-Dimethyl-3-phenylpent-4-enol** **(96a)**: General procedure **D** was followed employing (*E*)-(4-(allyloxy)but-2-en-2-yl)benzene (**116a**, 188 mg, 1.0 mmol) and 1 mol% catalyst (4.5 mg Ir-dimer, 8.4 mg PCy$_3$ and 3.4 mg NaBPh$_4$) in dichloromethane and an initial reaction time of 30 min before quenched with 7.8 mg PPh$_3$ (0.03 mmol). Dichloromethane was removed and add 5 ml dry toluene and reflux 24 h to afford *syn*-2,3-dimethyl-3-phenylpent-4-enal **95a** (*syn: anti* = 87: 13). General Diisobutylaluminum hydride (2.0 ml, 1.0 M in hexanes, 2.0 mmol) reduction of **95a** followed by purification by flash chromatography (15 % EtOAc/hexanes) gave 158 mg (85 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.20-7.37 (m, 5H), 6.18 (dd, J = 17.5, 10.9 Hz, 1H), 5.20 (dd, J = 10.9, 0.9 Hz, 1H), 5.12 (dd, J = 17.5, 0.9 Hz, 1H), 3.74 (dd, J = 10.6, 4.2 Hz, 1H), 3.33 (dd, J = 10.6, 8.3 Hz, 1H), 2.20-2.31 (m, 1H), 1.58 (s, 1H), 1.36 (s, 3H), 0.85 (d, J = 6.7 Hz, 3H) ppm.
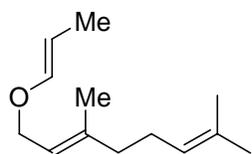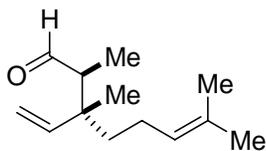
(*E*)-3,7-Dimethyl-1-((*E*)-prop-1-enyloxy)octa-2,6-diene **(94b)**: General Procedure **D** was followed employing (*E*)-1-(allyloxy)-3,7-dimethylocta-2,6-diene[137] (**93b**, 785 mg, 4.0 mmol) and 0.5 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloromethane for 30 min. Add pentane 5 ml, pass the solution to a short Florisil plug and evaporate the solvent to yield 706 mg (90 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.24 (dq, J = 12.5, 1.5 Hz, 1H), 5.38 (tq, J = 6.7, 1.2 Hz, 1H), 5.08-5.12 (m, 1H), 4.80 (dq, J = 12.6, 6.7 Hz, 1H), 4.19 (d, J = 6.7 Hz, 1H), 2.02-2.13 (m, 4H), 1.69 (s, 6H), 1.61 (s, 3H), 1.56 (dd, J = 6.7, 1.5 Hz, 3H) ppm; ^{13}C

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[137] Vyglazov, O. G.; Chuiko, V. A.; Izotova, L. V. *Russ. J. Gen. Chem. En.* **2003**, 73, 933-939.

NMR (300 MHz, CDCl$_3$): δ 146.2, 140.6, 131.6, 123.8, 119.7, 98.6, 65.7, 39.4, 26.2, 25.3, 17.6 16.4, 12.5 ppm; IR (liquid film): 2925, 1657, 1443, 1178, 931 cm^{-1}.

***syn*-2,3,7-Trimethyl-3-vinyloct-6-enal (95b):** A solution of purified (*E*)-3,7-dimethyl-1-((*E*)-prop-1-enyloxy)octa-2,6-diene (**94b**, 196 mg, 1.0 mmol) in 2 ml anhydrous dichloroethane in seal tube was heated at 150 °C in microwave oven for 2 h to afford aldehydes (*anti: syn* = 95: 5). ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.71 (d, J = 2.5 Hz, 1H), 5.88 (dd, J = 17.5, 10.9 Hz, 1H), 5.18 (dd, J = 10.9, 1.1 Hz, 1H), 5.03 (dd, J = 17.5, 1.1 Hz, 1H), 5.03-5.13 (m, 1H), 2.34 (qd, J = 6.9, 2.5 Hz, 1H), 2.03-2.11 (m, 2H), 1.85-1.93 (m, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.02 (s, 3H), 1.01 (d, J = 6.9 Hz, 3H) ppm.
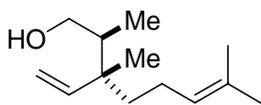
***syn*-2,3,7-Trimethyl-3-vinyloct-6-enol (96b)**: General Procedure **I** was followed employing di(allyl) ether (**93b**, 785 mg, 4.0 mmol) and 0.5 mol% catalyst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloromethane for 30 min. Then and DIBAL-H (1.0 M in hexanes, 6.0 ml, 6.0 mmol). Purification by flash chromatograph on silica gel (16 % ethyl ether in hexanes) yields 705 mg (90 %) of the title compound as colorless oil. Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T$_r$ = 39.2 and 39.9 min] provided the diastereomer ratio: *syn: anti* = 89.5: 10.5. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.75 (dd, J = 17.6, 10.9 Hz, 1H), 5.00-5.08 (m, 1H), 5.04 (dd, J = 10.9, 1.4 Hz, 1H), 4.93 (dd, J = 17.6, 1.4 Hz, 1H), 3.68 (dd, J = 10.6, 4.2 Hz, 1H), 3.23 (dd, J = 10.6, 8.3 Hz, 1H), 2.30 (brs, 1H), 1.83 (q, J = 7.9 Hz, 1H), 1.65 (s, 3H), 1.55 (s,

3H), 1.16-1.39 (m, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.88 (s, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 146.28, 131.04, 124.76, 112.52, 65.17, 43.28, 41.30, 39.51, 25.57, 22.36, 17.56, 17.47, 11.75 ppm; MS (EI, 70 V): *m/z* 165 (M$^+$-CH$_2$OH), 153, 137, 121, 109, 95; HRMS *m/z* calcd for C$_{12}$H$_{21}$ (M$^+$-CH$_2$OH): 165.1643; found 165.1640.
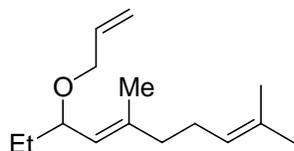
**(E)-8-(Allyloxy)-2,6-dimethyldeca-2,6-diene (93c)**: General Procedure **A** was followed employing 0.91 g of (E)-5,9-dimethyldeca-4,8-dien-3-ol (5.0 mmol), 240 mg NaH (10.0 mmol) and 0.75 ml allyl bromide (10.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes) gave 1.0 g (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.91 (dddd, J = 15.3, 12.8, 6.2, 5.1 Hz, 1H), 5.27 (dq, J = 15.3, 1.7 Hz, 1H0, 5.07-5.16 (m, 2H), 5.01 (d, J = 9.2 Hz, 1H), 4.01 (ddt, J = 12.8, 5.1, 1.3 Hz, 1H), 3.89 (q, J = 6.9 Hz, 1H), 3.80 (ddt, J = 12.8, 6.2, 1.3 Hz, 1H), 2.01-2.12 (m, 4H), 1.68 (s, 3H), 1.64 (d, J = 1.3 Hz, 3H), 1.61 (s, 3H), 1.34-1.51 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 139.0, 135.7, 131.4, 126.2, 124.0, 116.2, 76.4, 68.5, 53.6, 39.7, 28.6, 26.3, 25.6, 17.6, 16.5, 9.7 ppm; IR (liquid film): 2966, 2929, 1450, 1377, 1071, 920 cm^{-1}; MS (EI, 70 V): 193 (M$^+$-C$_2$H$_5$), 164, 135, 123, 99, 81, 69, 57.
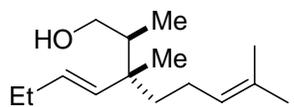
(2S,3R,E)-3-(But-1-enyl)-2,3,7-trimethyloct-6-en-1-ol (96c): General Procedure **I** was followed employing (E)-8-(allyloxy)-2,6-dimethyldeca-2,6-diene (**93c,** 222 mg, 1 mmol), 1 mol% catalyst loading and DIBAL-H (1.0 M in hexanes, 2 ml, 2 mmol). Purification by flash chromatograph on silica gel (16 % ethyl ether in hexanes) yield 165 mg (75 %) of the title compound as colorless oil. Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00

min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T_r = 41.8, 41.9, 42.3 and 42.8 min]

provided the diastereomer ratio: 2.4: 0.5: 75.8: 21.4. Data of the major isomer. ^{1}H NMR (300

MHz, CDCl$_3$): δ 5.30-5.45 (m, 2H), 5.08 (t, J = 6.5 Hz, 1H), 3.72 (dd, J = 10.7, 4.8 Hz, 1H), 3.29

(dd, J = 10.7, 7.7 Hz, 1H), 2.00-2.07 (m, 2H), 1.87 (q, J = 7.9 Hz, 2H), 1.67 (s, 3H), 1.58 (s, 3H),

1.22-1.40 (m, 2H), 1.49-1.60 (m, 1H), 0.98 (t, J = 7.6 Hz, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (300

MHz, CDCl$_3$): δ 137.1, 135.9, 131.1, 130.1, 125.0, 65.8, 65.3, 44.2, 43.8, 40.3, 40.2, 40.1, 39.1,

34.6, 31.6, 25.9, 25.7, 22.6, 22.5, 20.5, 18.2, 17.5, 14.2, 14.1, 12.3, 11.9 ppm.
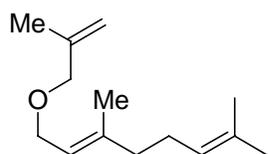
(E)-3,7-Dimethyl-1-(2-methylallyloxy)octa-2,6-diene (93d): General Procedure **A** was followed employing 1.54 g of (E)-3,7-dimethylocta-2,6-dien-1-ol (10.0 mmol), 480 mg NaH (20.0 mmol) and 1.8 g 3-chloro-2-methylprop-1-ene (20.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes)

gave 1.87 g (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.36 (d,

J = 6.7 Hz, 1H), 5.09 (d, J = 6.3 Hz, 1H), 4.95 (s, 1H), 4.88 (s, 1H), 3.95 (d, J = 6.8 Hz, 2H), 3.87

(s, 2H), 1.95-2.12 (m, 4H), 1.74 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR

(300 MHz, CDCl$_3$): δ 142.4, 139.9, 131.5, 123.9, 120.9, 112.0, 73.8, 66.2, 39.5, 26.3, 25.6, 19.4,

17.6, 16.3 ppm; MS (EI, 70 V): 208 (M[+·]), 193, 136, 123, 109, 93, 81, 69, 55; HRMS m/z calcd

for C$_{14}$H$_{24}$O (M[+·]): 208.1827; found 208.1835.
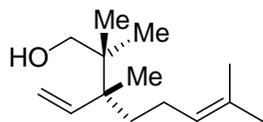
2,2,3,7-Tetramethyl-3-vinyloct-6-en-1-ol (96d): General Procedure **I** was followed employing di(allyl) ether (**93d**, 208 mg, 1 mmol) and 2

mol% catalyst loading, the initial reaction time is 6 h at 40 °C. After DIBAL-H (1.0 M in

hexanes, 2.0 ml, 2 mmol) promoted reaction. Purification by flash chromatograph on silica gel

(16 % ethyl ether in hexanes) yield 154 mg (74 %) of the title compound as colorless oil. ^{1}H

NMR (300 MHz, CDCl$_3$): δ 5.89 (dd, J = 17.6, 10.9 Hz, 1H), 5.12 (dd, J = 10.9, 1.6 Hz, 1H),

5.08 (t, J = 7.1 Hz, 1H), 4.95 (dd, J = 17.6, 1.6 Hz, 1H), 3.52 (d, J = 11.1 Hz, 1H), 3.38 (d, J =

11.1 Hz, 1H), 1.67 (s, 3H), 1.57 (s, 3H), 1.71-1.81 (m, 4H), 1.28-1.47 (m, 2H), 0.98 (s, 3H), 0.91

(s, 3H), 0.85 (s, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 144.8, 131.1, 125.1, 113.6, 69.5, 43.9,

40.7, 34.7, 25.7, 23.0, 20.4, 20.1, 17.6, 16.4 ppm; MS (EI, 70 V): 210 (M$^+$), 195, 179, 167, 137,

123, 109, 95, 81, 69, 55; HRMS m/z calcd for C$_{14}$H$_{26}$O (M$^+$): 210.1984, found 210.1990.

5.3.2 Experiment of section 5.2

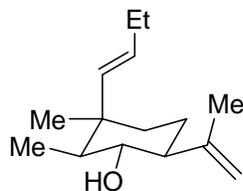### 5.3.2.1 Cascade isomerization-Claisen rearrangement-ene reaction
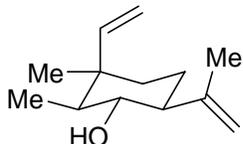
2β,3β-dimethyl-6β-(prop-1-en-2-yl)-3α-vinylcyclohex-β-anol **(97b1):**
General Procedure **J** for cascade olefin isomerization/Claisen
rearrangement/ene reaction: General Procedure **D** was followed employing

(E)-1-(allyloxy)-3,7-dimethylocta-2,6-diene (**93b**, 194 mg, 1.0 mmol) with 1 mol% catalyst

(iridium dimer 4.5 mg, PCy$_3$ 8.4 mg and NaBPh$_4$ 3.4 mg), after isomerization, remove the

solvent in vacuum. A solution of crude allyl vinyl ether (**94b**) in dichloromethane (0.5 M) was

added Me$_2$AlCl (1.0 M in hexanes, 1.5 ml, 1.5 mmol) dropwise at -40 °C, allow the reaction

warm to ambient temperature over 12 h. Add saturated sodium tartrate solution 6 ml to quench

the reaction and extraction with ether. After drying with MgSO$_4$ and solvent Vaporation, crude

proton NMR show three isomers ratio is 64: 29: 7. Separating the stereoisomers in crude mixture

products by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min,

method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T$_r$ = 28.2, 28.9,

29.5 and 31.2 min] provided the diastereomer ratio: 22 (**97b2**): 9 (**97b3**): 2 (**97b4**): 66 (**97b1**). The purification by flash chromatograph on silica gel (3 % ethyl acetate in hexanes) yields 95 mg (49 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.02 (dd, J = 17.5, 11.1 Hz, 1H), 4.87 (s, 1H), 4.90 (s, 1H), 5.03 (dd, J = 17.5, 1.3 Hz, 1H), 5.09 (dd, J = 11.1, 1.3 Hz, 1H), 3.29 (t, J = 10.1 Hz, 1H), 2.04 (ddd, J = 12.3, 10.2, 4.3 Hz, 1H), 1.25-1.79 (m, 5H), 1.72 (s, 3H), 1.06 (s, 3H), 1.01 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 146.9, 141.5, 113.6, 113.0, 71.9, 54.8, 47.6, 40.8, 39.1, 27.3, 25.6, 19.0, 11.6 ppm; IR (liquid film): 3462, 3079, 2974, 2934, 1639, 1456, 1373, 1075, 909 cm^{-1}; MS (EI, 70 V): m/z 194 (M$^{+\cdot}$), 179, 176, 161, 147, 135, 123, 111, 107, 95, 81, 68, 55; HRMS m/z calcd for C$_{13}$H$_{22}$O (M$^{+\cdot}$): 194.1671; found 194.1676.
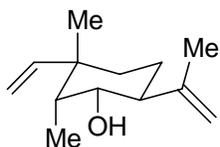
2α,3α-dimethyl-6β-(prop-1-en-2-yl)-3β-vinylcyclohex-β-anol (97b2): The purified **97b2** is isolated as minor product with **97b1**. yields 30 mg (15 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ5.80 (dd, J = 17.6, 10.9 Hz, 1H), 4.93 (dd, J = 10.9, 1.3, 1H), 4.92 (s, 1H), 4.87 (dd, J = 17.6, 1.3 Hz, 1H), 4.87 (s, 1H), 3.94 (dd, J = 10.9, 4.8 Hz, 1H), 2.16 (td, J = 10.8, 5.8 Hz, 1H), 1.84 (qd, J = 7.1, 4.8 Hz, 1H), 1.75 (s, 3H), 1.46-1.73 (m, 3H), 1.12 (s, 3H), 0.86 (s, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 148.8, 146.7, 113.1, 109.9, 68.8, 47.1, 42.3, 40.4, 28.0, 25.6, 24.9, 19.0, 9.0 ppm; IR (liquid film): 3462, 3079, 2974, 2934, 1639, 1456, 1373, 1075, 909 cm^{-1}; MS (EI, 70 V): m/z 194 (M$^{+\cdot}$), 179, 176, 161, 147, 135, 123, 111, 107, 95, 81, 68, 55; HRMS m/z calcd for C$_{13}$H$_{22}$O (M$^{+\cdot}$): 194.1671; found 194.1676.
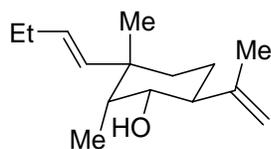
(E)-3α- (But-1-enyl) -2β, 3β-dimethyl-6β-(prop-1-en-2-yl) cyclohexanol

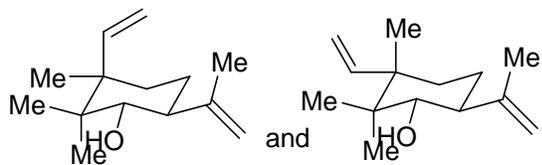**(97c1)**: General Procedure **J** for cascade olefin isomerization/Claisen rearrangement/ene reaction was followed employing (E)-8-(allyloxy)-2,6-dimethyldeca-2,6-diene (**93c**, 222 mg, 1.0 mmol), 1 mol% catalyst loading and Me$_2$AlCl (1.0 M in hexanes, 1.5 ml, 1.5 mmol). Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T$_r$ = 32.5, 33.5, 35.7 and 36.9 min] provided the diastereomer ratio: 30.6 (**97c2**): 16.0, 7.6: 45.8 (**97c1**). Purification by flash chromatograph on silica gel (16 % ethyl ether in hexanes) yields 85 mg (38 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.58 (d, J = 15.8 Hz, 1H), 5.44 (dt, J = 15.8, 6.2 Hz, 1H), 4.90 (s, 1H), 4.87 (s, 1H), 3.29 (t, J = 10.1 Hz, 1H), 1.98-2.10 (m, 3H), 1.73 (s, 3H), 1.22-1.68 (m, 5H), 1.03 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H) ppm; MS (EI, 70 V): 222 (M$^+$), 207, 204, 193, 189, 165, 139, 123, 109, 96, 81, 68; HRMS *m/z* calcd for C$_{15}$H$_{26}$O (M$^+$): 222.1984, found 222.1077.

(E)-3β- (But-1-enyl)-2α,3α-dimethyl-6β-(prop-1-en-2-yl)cyclohexanol

(97c2): The title compound is isolated 55 mg (25 %) as second major product with **97c1**. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.37 (d, J = 15.7 Hz, 1H), 5.29 (dt, J = 15.7, 5.3 Hz, 1H), 4.91 (s, 1H), 4.87 (s, 1H), 3.93 (dd, J = 10.8, 4.7 Hz, 1H), 2.15 (td, J = 10.7, 7.9 Hz, 1H), 2.05 (qd, J = 7.5, 5.5 Hz, 2H), 1.75 (s, 3H), 1.53-1.85 (m, 5H), 1.10 (s, 3H), 0.98 (t, J = 7.4 Hz, 3H), 0.85 (d, J = 7.1 Hz, 3H) ppm.

2α,2β,3β- Trimethyl-6β-(prop-1-en-2-yl)-3α-vinyl cyclohexanol (97d1) and **2α,2β,3α-Trimethyl-6β-(prop-1-en-2-yl)-3β-vinylcyclohexanol (97d2)**:

General Procedure **J** for cascade olefin isomerization/Claisen rearrangement/ene reaction was followed employing (*E*)-3,7-Dimethyl-1-(2-methylallyloxy)octa-2,6-diene (**93d** , 104 mg, 0.5 mmol) and 2 % catalyst (iridium dimer 4.5 mg, PCy$_3$ 8.4 mg and NaBPh$_4$ 3.4 mg) at 40 ^{o}C for 2 h. Then treated in Me$_2$AlCl (1.0 M in hexanes, 0.8 ml, 0.8 mmol). Purification by flash chromatograph on silica gel (3 % ethyl ether in hexanes) yields 83 mg (80 %) of the title compound as colorless oil. Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T$_r$ = 31.4 and 32.5 min] provided the diastereomer ratio: 33 (**97d2**): 67 (**97d1**). The major isomer (**97d1**) data: ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.95 (dd, J = 17.5, 11.0 Hz, 1H), 5.01(dd, J = 11.0, 1.5 Hz, 1H), 4.95 (dd, J = 17.5, 1.5 Hz, 1H), 4.90 (d, J = 1.5 Hz, 1H), 4.86 (d, J = 1.5 Hz, 1H), 3.57 (d, J = 10.8 Hz, 1H), 2.19 (td, J = 11.3, 5.6 Hz, 1H), 1.75 (s, 3H), 1.37-1.69 (m, 3H), 1.25 (t, J = 6.5 Hz, 1H), 1.06 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 147.3, 145.9, 113.2, 112.0, 73.5, 49.2, 42.7, 40.3, 32.5, 25.8, 21.9, 19.7, 18.9, 16.5 ppm; IR (liquid film): 3493, 2976, 1635, 1459, 1372, 1080, 910 cm^{-1}; MS (EI, 70 V): *m/z* 208 (M$^{+\cdot}$), 193, 190, 175, 165, 147, 135, 121, 109, 93, 81, 68, 55; HRMS *m/z* calcd for C$_{13}$H$_{22}$O (M$^{+\cdot}$): 208.1827; found 208.1835. The minor isomer (**97d2**) data: ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.25 (dd, J = 17.4, 1.1 Hz, 1H), 5.06 (dd, J = 11.1, 1.5 Hz, 1H), 5.03 (dd, J = 17.4, 1.5 Hz, 1H), 4.90 (d, J = 1.5 Hz, 1H), 4.86 (d, J = 1.5 Hz, 1H), 3.50 (d, J = 10.8 Hz, 1H), 1.83 (td, J = 12.7, 5.4 Hz, 1H), 1.72 (s, 3H), 1.37-1.69 (m, 3H), 1.21 (t, J = 6.4 Hz, 1H), 0.98 (s,

3H), 0.97 (s, 3H), 0.94 (s, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 147.3, 143.4, 113.2, 113.0, 73.7, 49.0, 43.0, 40.6, 33.9, 25.8, 22.4, 19.7, 18.8, 15.9 ppm.

### 5.3.2.2 Cascade isomerization-Claisen-Wittig-Cope reaction
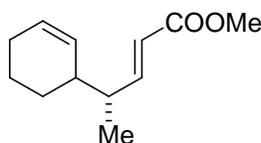
(4S,E)-methyl 4-(cyclohex-2-enyl)pent-2-enoate (99a): **General Procedure of cascade ICR-Wittig reaction**: General Procedure **D** was followed employing 3-(allyloxy)cyclohex-1-ene (**95a**, 72 mg, 0.5 mmol) and 1 % catalyst loading in DCE, after 30 min at ambient temperature, the solvent was removed in vacuum. The crude allyl vinyl ether (**96a**) and Ph$_3$PCHCOOMe (211 mg, 0.63 mmol) in 3 ml toluene was added in sealed tube and heated in microwave oven at 180 °C for 2 h (*anti: syn* = 90: 10). Remove the solvent and chromatography with silica gel (5 % ethyl acetate in hexanes) yields 72 mg (72 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.93 (dd, J = 15.7, 7.5 Hz, 1H), 5.78 (dd, J = 15.7, 1.3 Hz, 1H), 5.68-5.75 (m, 1H), 5.55 (d, J = 10.2 Hz, 1H), 3.71 (s, 3H), 2.30 (hex, J = 6.6 Hz, 1H), 2.08-2.20 (m, 1H), 1.90-1.99 (m, 2H), 1.64-1.78 (m, 2H), 1.40-1.56 (m, 1H), ,1.17-1.31 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (300 MHz, CDCl$_3$): δ 167.1, 153.4, 129.0, 128.8, 120.0, 51.3, 40.9, 26.2, 25.1, 21.6, 16.0 ppm; IR (liquid film): 2932, 1725, 1655, 1435, 1314, 1197, 1174, 722 cm^{-1}.
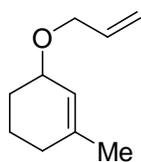
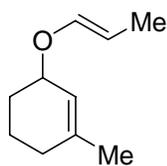**3-(Allyloxy)-1-methylcyclohex-1-ene (95b)**: General Procedure **A** was followed employing 1.12 g of 3-methylcyclohex-2-enol (10.0 mmol), 480 mg NaH (20.0 mmol) and 1.5 ml allyl bromide (20.0 mmol). Purification by flash chromatography (2 % EtOAc/hexanes) gave 1.37 g (90 %) of the title compound as colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.91 (ddt, J = 17.2, 10.3, 5.6 Hz, 1H), 5.47-5.52 (m, 1H), 5.25

(dq, J = 17.2, 1.7 Hz, 1H), 5.12 (dq, J = 10.3, 1.4 Hz, 1H), 4.03 (ddt, J = 12.7, 5.5, 1.4 Hz, 1H), 3.97 (ddt, J = 12.7, 5.7, 1.4 Hz, 1H), 3.81-3.89 (m, 1H), 1.48-2.00 (m, 6H), 1.66 (s, 3H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 138.7, 135.4, 122.0, 116.2, 72.5, 69.0, 30.1, 27.9, 23.6, 19.2 ppm; MS (EI, 70 V): m/z 111 (M$^{+\cdot}$-C$_3$H$_5$); HRMS m/z calcd for C$_7$H$_{11}$O (M$^{+\cdot}$-C$_3$H$_5$): 111.0810; found 111.0848.

(E)-1-Methyl-3-(prop-1-enyloxy)cyclohex-1-ene (96b): General Procedure **D** was followed employing 3-(allyloxy)-1-methylcyclohex-1-ene (**95b**, 304 mg, 2.0 mmol) and 1 mol% catal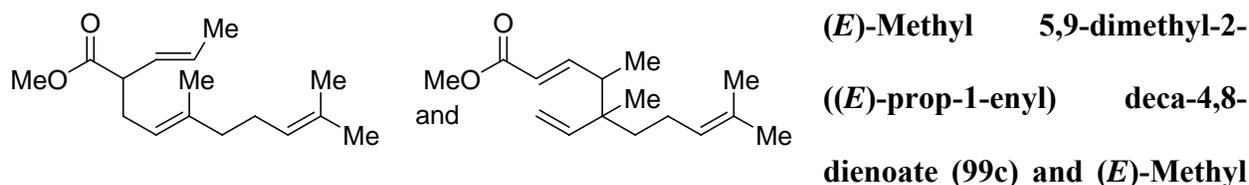yst (9.0 mg Ir-dimer, 16.8 mg PCy$_3$ and 6.8 mg NaBPh$_4$) in dichloromethane for 30 min. Add pentane 5 ml and pass the solution to a short Florisil plug to yield 270 mg (90 %) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.13 (dq, J = 12.3, 1.6 Hz, 1H), 5.49-5.53 (m, 1H), 4.90 (dq, J = 12.3, 6.7 Hz, 1H), 4.16-4.19 (m, 1H), 1.70 (s, 3H), 1.54 (dd, J = 6.7, 1.6 Hz, 3H), 1.20-1.90 (m, 6H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ 145.1, 140.0, 121.0, 100.5, 73.7, 30.0, 28.1, 23.7, 19.0, 12.5 ppm.
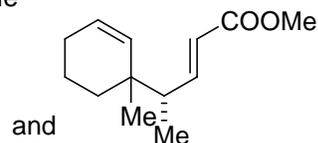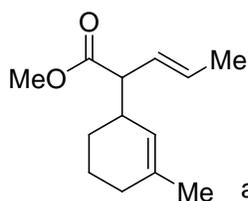
(E)-Methyl 2-(3-methylcyclohex-2-enyl)pent-3-enoate (99b) and (E)-Methyl 4-(1-methylcyclohex-2-enyl)pent-2-enoate (98b): Gen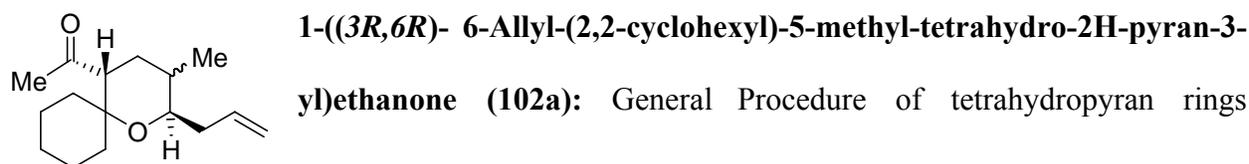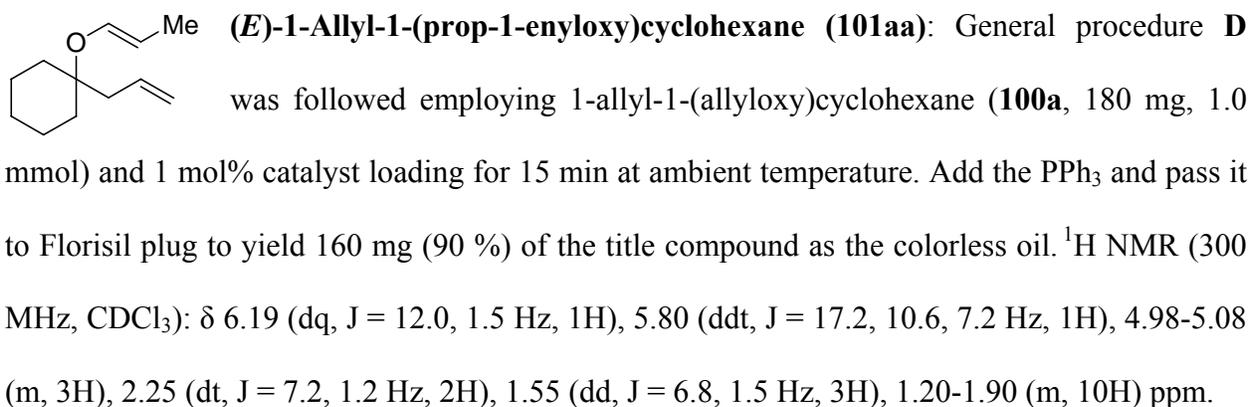eral Procedure of cascade ICR-Wittig reaction was followed employing 3-(allyloxy)-1-methylcyclohex-1-ene (**96b,** 152 mg, 1.0 mmol) and Ph$_3$PCHCOOMe (422 mg, 1.26 mmol) heated in microwave oven at 180 ^{o}C for 2 h, the ratio of **99b**: **98b** is 57: 43. Continuing heating at 200 ^{o}C for another 2 h, The ratio of **99b**: **98b** increased to 69: 31. Data for **99b:** ^{1}H NMR (300

MHz, CDCl$_3$): δ 5.20-5.50 (m, 2H), 5.12 (s, 1H), 3.69 (s, 3H), 1.60-1.90 (m, 6H), 1.68 (dd, J = 6.3, 1.4 Hz, 3H), 1.63 (s, 3H) ppm.

**(E)-Methyl 5,9-dimethyl-2-((E)-prop-1-enyl) deca-4,8-dienoate (99c) and (E)-Methyl 4,5,9-trimethyl-5-vinyldeca-2,8-dienoate (98c)**: General Procedure of cascade ICR-Wittig reaction was followed employing (E)-1-(allyloxy)-3,7-dimethylocta-2,6-diene (**94b**, 194 mg, 1 mmol) and Ph$_3$PCHCOOMe (422 mg, 1.26 mmol) at 160 °C for 2 h at microwave oven. The ratio of **99c** : **98c** = 80: 20. Data for **99c**: ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.35-5.65 (m, 2H), 5.03-5.10 (m, 2H), 3.67 (s, 3H), 2.99 (q, J = 7.5 Hz, 1H), 2.35-2.50 (m, 1H), 2.15-2.30 (m, 1H), 1.91-2.07 (m, 4H), 1.58-1.70 (m, 12 H) ppm.

5.3.2.3 Cascade tetrahydropyran formation

(E)-1-Allyl-1-(prop-1-enyloxy)cyclohexane (101aa): General procedure **D** was followed employing 1-allyl-1-(allyloxy)cyclohexane (**100a**, 180 mg, 1.0 mmol) and 1 mol% catalyst loading for 15 min at ambient temperature. Add the PPh$_3$ and pass it to Florisil plug to yield 160 mg (90 %) of the title compound as the colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.19 (dq, J = 12.0, 1.5 Hz, 1H), 5.80 (ddt, J = 17.2, 10.6, 7.2 Hz, 1H), 4.98-5.08 (m, 3H), 2.25 (dt, J = 7.2, 1.2 Hz, 2H), 1.55 (dd, J = 6.8, 1.5 Hz, 3H), 1.20-1.90 (m, 10H) ppm.

1-((3R,6R)- 6-Allyl-(2,2-cyclohexyl)-5-methyl-tetrahydro-2H-pyran-3-yl)ethanone (102a): General Procedure of tetrahydropyran rings

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formation: A solution of methyl vinyl ketone (mg, 2.0 mmol, 2.2 equiv), homoallyl vinyl ether (**101a,** 160 mg, 0.9 mmol) and 2,6-*di-tert*-butyl-4-methylpyridine (DTBMP, 310 mg, 1.5 mmol, 1.6 equiv) in CH_2Cl_2 (0.1 M) was cooled to -78 $^{\circ}$C, A solution of $TiBr_4$ (0.4 M in CH_2Cl_2, 736 mg, 2.0 mmol, 2.2 equiv) was added dropwise via syringe. The reaction mixture was then stirred at -78 $^{\circ}$C for 1 h. Then saturated sodium bicarbonate solution was added at -78 $^{\circ}$C and the mixture was allowed to warm to ambient temperature. Purification by flash chromatograph on silica gel (5-20 % ethyl acetate in hexanes) yields 155 mg (70 %) of the title compound as colorless oil (4: 1 mixture). Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T_r = 43.3 and 46.6 min] provided the diastereomer ratio: 19 (**102a1**): 81 (**102a2**). Major isomer: ^{1}H NMR (300 MHz, CDCl$_3$): δ 5.75-6.00 (m, 1H), 5.08 (d, J = 17.2 Hz, 1H), 5.02 (d, J = 10.2 Hz, 1H), 3.60 (ddd, J = 8.5, 5.4, 2.7 Hz, 1H), 2.78 (dd, J = 13.5, 3.4 Hz, 1H), 2.17 (s, 3H), 1.20-2.20 (m, 15H), 0.96 (d, J = 7.0 Hz, 3H) ppm; MS (EI, 70 V): *m/z* 250 (M$^{+\cdot}$), 190, 152, 109, 94, 84; HRMS *m/z* calcd for $C_{16}H_{26}O_2$ (M$^{+\cdot}$): 250.1933; found 250.1939.
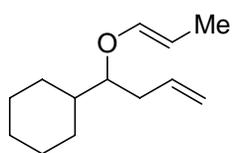
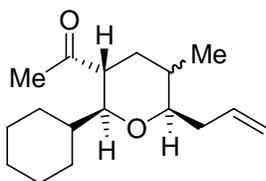**(*E*)-(1-(Prop-1-enyloxy)but-3-enyl)cyclohexane (101b):** General procedure **D** was followed employing (1-(allyloxy)but-3-enyl)cyclohexane [138] (**100b,** 388 mg, 2.0 mmol) and 1 mol% catalyst loading for 12 min at ambient temperature, the crude proton NMR show the ratio of **101b: 100b:** allyl vinyl ether = 84: 12: 4. Quenched catalyst in 20 min, the ratio is 74: 26: 0. Add the PPh$_3$ and pass it to Florisil plug to yield 240 mg (60 %) of the title compound as the colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 6.06 (d, J = 12.2 Hz, 1H), 5.83 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.24 (d, J = 10.2 Hz, 1H), 5.23

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[138] Schmit, B. *J. Chem. Soc. Perkin Trans 1*, **1999**, 18, 2627-2638.

(d, J = 17.2 Hz, 1H), 4.87 (dq, J = 12.2, 6.7 Hz, 1H), 3.53 (q, J = 5.8 Hz, 1H), 2.40-2.50 (m, 2H), 1.54 (d, J = 6.7 Hz, 3H), 1.00-1.90 (m, 11H) ppm.


1-((2S,3R,6R)-6- Allyl-2-cyclohexyl-5-methyl-tetrahydro-2H-pyran-3-yl)ethanone (102b): General Procedure of tetrahydropyran rings formation was followed employing (E)-(1-(prop-1-enyloxy)but-3-enyl)cyclohexane (**101b**, 240 mg, 1.2 mmol, 1.0 equiv). Purification by flash chromatograph on silica gel (5-20 % ethyl acetate in hexanes) yields 200 mg (63 %) of the title compound as colorless oil (1: 1 mixture). Separating the stereoisomers by GLC [Varian CP Wax 52CB column (30 m x 0.25 mm), flow rate 0.6 mL/min, method: 80 °C for 2.00 min, ramp @ 5.00 °C/min to 250 °C, hold for 20.00 min, T_r = 45.9 and 46.7 min] provided the diastereomer ratio: 42 (**102b1**): 58 (**102b2**). MS (EI, 70 V): m/z 264 (M$^{+\cdot}$), 223,205, 181, 152, 111, 94; HRMS m/z calcd for $C_{17}H_{28}O_2$ (M$^{+\cdot}$): 264.2089; found 264.2092.

APPENDIX A

X-RAY STRUCTURE OF SEMICARBAZIDE DERIVED 64A′ FROM ANTI-2-((*E*)-1,3-DIPHENYLALLYL)-2-METHYLHEXANAL
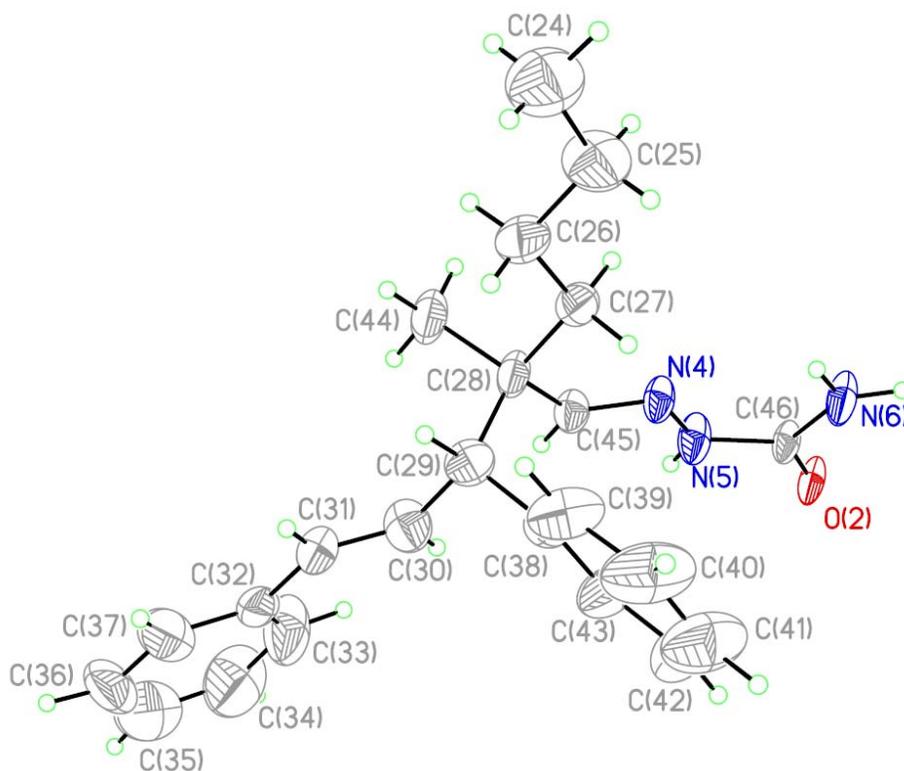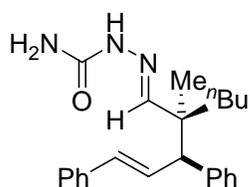
| Empirical formula | $C_{23}H_{29}N_3O$ |
| Formula weight | 363.49 |

Temperature   295(2) K

Wavelength   0.71073 Å

Crystal system   Triclinic

Space group   P-1

Unit cell dimensions   a = 10.440(2) Å α= 114.083(4)°.

   b = 14.165(3) Å β= 105.058(4)°.

   c = 16.869(4) Å γ = 92.317(4)°.

Volume   2168.6(8) Å^3

Z   4

Density (calculated)   1.113 Mg/m^3

Absorption coefficient   0.069 mm^{-1}

F(000) 784

Crystal size   0.15 x 0.08 x 0.08 mm^3

Theta range for data collection   1.60 to 25.00°.

Index ranges   -12<=h<=12, -16<=k<=16, -20<=l<=20

Reflections collected   15885

Independent reflections   7644 [R(int) = 0.0905]

Completeness to theta = 25.00°   99.8 %

Absorption correction None

Max. and min. transmission   0.9945 and 0.9897

Refinement method   Full-matrix least-squares on F^2

Data / restraints / parameters 7644 / 0 / 511

Goodness-of-fit on F^2 1.111

Final R indices [I>2sigma(I)] R1 = 0.1411, wR2 = 0.2873

R indices (all data)   R1 = 0.2571, wR2 = 0.3305

Largest diff. peak and hole   0.272 and -0.229 e.Å^{-3}

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3. "Stereoselective Quaternary Carbon Construction Enabled by Olefin Isomerization-Claisen Rearrangement Reactions" **Wang, K.**; Bungard, C. J.; Nelson, S. G. *Org. Lett.*. **2007**, *9*, 2325-2328.

4. "Catalytic Asymmetric Mannich Reactions Based on Ketene-Imine [4+2] Cycloadditions" Xu, X., **Wang, K.**, Nelson, S. G., *J. Am. Chem. Soc*. **2007**, *129,* 11690-11691

5. "Stereoselective Quaternary Carbon Construction Enabled by Olefin Isomerization-Claisen Rearrangement Reactions" **Wang, K**.; Bungard, C. J.; Nelson, S. G. 231st ACS national meeting, Atlanta, GA, **2006**.