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Conversion of Allylic Alcohols to Stereodefined Trisubstituted Alkenes: A Complimentary Process to the Claisen Rearrangement

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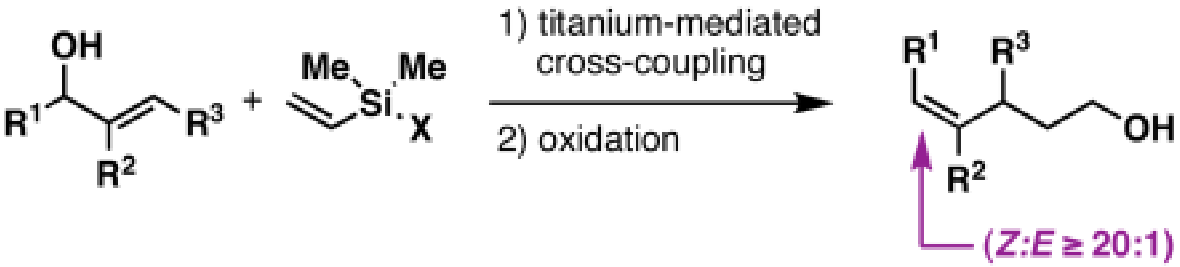
Abstract



A stereoselective method for the conversion of allylic alcohols to (*Z*)-trisubstituted alkenes is presented. Overall, the reaction sequence described is stereochemically complimentary to related Claisen rearrangement reactions – processes that typically deliver the stereoisomeric trisubstituted alkene containing products.

Methods for the synthesis of geometrically defined trisubstituted olefins define a pillar of modern synthetic organic chemistry. From a target-based perspective, these stereodefined structural motifs are ubiquitous in natural products and molecules of biomedical and physical relevance (Figure 1). From a reactivity-based perspective, geometrically defined olefins serve as a foundation for stereoselective synthesis. These factors have driven the invention of a large variety of chemical methods for the convergent synthesis of stereodefined olefins. While many of these methods proceed from carbonyl addition chemistry or alkyne functionalization, the use of allylic alcohol derivatives in sigmatropic processes defines a powerful means to access a subset of stereodefined polysubstituted olefins.[1] Of these, Claisen-based methods have been particularly effective at establishing stereodefined (*E*)-trisubstituted olefins. Here, we describe a metal-mediated reductive cross-coupling reaction that defines a stereochemically complimentary means of converting allylic alcohols to products related to those derived from Claisen rearrangement (Figure 2). While describing a unique stereoselective transformation for complex molecule synthesis, this study also defines a novel reductive cross-coupling reaction between alkenes and allylic alcohols.[2, 3]

Recently, we demonstrated that allylic alcohols are useful substrates in titanium-mediated reductive cross-coupling reactions with internal alkynes.[4] In these reactions, 1,4-dienes result from C–C bond formation between preformed titanium–alkyne complexes and allylic alkoxides. While quite useful for the stereoselective synthesis of substituted 1,4-dienes, we wondered whether a related reductive cross-coupling process could define a stereoselective convergent pathway to isolated di- and trisubstituted olefins. To accomplish such a

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transformation, we targeted a reductive cross-coupling reaction between allylic alcohols and vinylsilanes.[5]

Our initial studies, depicted in Figure 3, provided some hope that the desired stereoselective transformation would be possible. In general, the preformed lithium alkoxide of an allylic alcohol was combined with vinyltrimethylsilane in Et_2O, cooled and treated with the combination of $ClTi(Oi\text{-}Pr)_3$ and C_5H_9MgCl (−78 to 0 °C).[6] While cross-coupling of allylic alkoxides **1** and **4** with vinyltrimethylsilane (**2**) provided cross-coupled products **3** and **5** in 58–66% yield, these reactions proceeded without stereoselection (*E:Z* = 1:1). In contrast, reductive cross-coupling of the (*Z*)-disubstituted alkene **6** with **2** provided the (*E*)-alkene **7** in 64% (*E:Z* = 9:1). Highest levels of (*E*)-selectivity were observed in the reaction of **8** with **2**. This process provided **9** in 69% yield with ≥20:1 selectivity; defining a stereoselective transformation that also establishes a quaternary center.[7]

While the cross-coupling reaction of terminally substituted allylic alcohols (i.e. **6** and **8**) delivers stereodefined (*E*)-disubstituted alkenes, the reaction of allylic alcohols bearing a 1,1-disubstituted olefins proceedes in a stereochemically unique manner. Reductive cross-coupling of **10** with **2** delivers **11** in 50% yield, with ≥ 20:1 selectivity, favoring the formation of the central stereodefined (*Z*)-trisubstituted alkene. Similarly, the coupling of the trisubstituted allylic alcohol **12** with **2** provides **13** in 65% yield (*Z:E* ≥ 20:1).

While preliminary studies investigating the coupling of simple acyclic- and cyclic alkenes with vinyltrimethylsilane indicate that this reaction is flexible and stereoselective (Scheme 2 and Table 1, entries 1–3), we searched to identify a coupling partner that would allow for facile oxidation of the C–Si bond resident in the products. The combination of these two reactions, cross-coupling and oxidation, would then define a means to access stereodefined products related to those derived from Claisen rearrangment.[1]

As illustrated in Figure 4, reductive cross-coupling of allylic alcohols **6** and **12** with vinyldimethylchlorosilane[5] (**20**) proceeds in a stereoselective manner, and delivers the corresponding silylethers **21** and **22** in 53% and 75% yield (*E:Z* =10:1 to ≥ 20:1). Oxidation of the C–Si bond under standard conditions[8] then delivers the stereodefined unsaturated primary carbinol (i.e. **22** → **23**). While products like **23** could be derived from **12** by the application of well-known Claisen rearrangement-based procedures, the cross-coupling reaction described here has the potential to deliver stereodefined products not readily accessible with these robust [3,3]-sigmatropic rearrangement processes. For example, Claisen rearrangement of **10**, followed by carbonyl reduction, provides the (*E*)-trisubstituted olefin **24** with high levels of stereoselection (*E:Z* = 20:1).[9] In this complimentary process, reductive cross-coupling of **10** with vinyldimethyl-chlorosilane (**20**), followed by oxidation, provides the isomeric (*Z*)-trisubstituted olefin **25** in 58% yield (*Z:E* ≥ 20:1).[10]

As illustrated in Table 2, this (*Z*)-selective reductive cross-coupling reaction is useful for the stereoselective functionalization of a variety of allylic alcohols (entries 1–5) Additionally, stereochemically defined products can be prepared from the coupling of mixtures of isomeric allylic alcohols (i.e. entries 6 and 7). Interestingly, coupling of **36** with **20** does not proceed in a similarly stereoconvergent manner, indicating a potential role of the PMB ether in the stereochemical course of this reaction (entry 8).[12]

The regio- and stereochemical control observed in this allylic alcohol functionalization process is consistent with the empirical model depicted in Figure 6. In short, pre-association of the allylic alkoxide with a preformed titanacyclopropane (derived from the vinylsilane) produces an intermediate mixed titanate ester capable of rearrangement via formal metallo-[3,3]-rearrangement.[4] While the C–C bond formation proceeds with allylic transposition, stereochemical control is thought to derive from minimization of non-bonded steric interactions in a boat-like conformation (i.e. **A′** and **B′**) where the σ_{C-Ti} bond is aligned with the $\pi_{C=C}$ bond.[13]

In sum, we have described a new regio- and stereoselective reductive cross-coupling reaction between allylic alcohols and vinylsilanes. This reaction proceeds with allylic transposition, delivers products with stereodefined di- and trisubstituted olefins, and provides a means to establish allylic tertiary and quaternary carbon centers. In addition to defining a novel olefin functionalization reaction and metal-mediated reductive cross-coupling process,[14] this reaction provides a stereochemically unique pathway to functionalized acyclic products not readily accessible with modern [3,3]-sigmatropic rearrangement reactions.[1] Future study will explore both the utility of this process in target-oriented synthesis and the interplay between allylic alcohol substitution and selectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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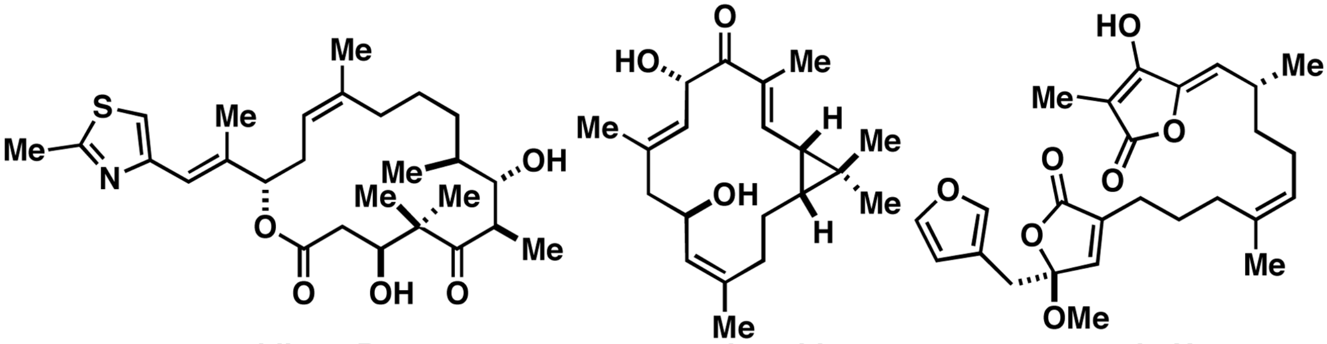
9. Abouabdellah A, Bonnet-Delpon D. Tetrahedron 1994;50:11921–11932.
10. Titanium-mediated reductive cross-coupling reactions of allylic alcohols with internal alkynes proceed with a similar sense of stereoselection. See ref 4a for details.
11. Derived from addition of 2-propenylmagnesium bromide to the corresponding chiral aldehyde. See Supporting Information for details.
12. The stereochemistry of the major/minor isomer was not determined. Future studies will examine the relationship of the relative stereochemistry of 36 on the stereochemical course of the reductive cross-coupling reaction.
13. This empirical model does not yet address the number of ligands present on the metal center in the transition state. Others have suggested –ate complexes as reactive intermediates in the Kulinkovich reaction: a)Kulinkovich OG, Kanonovich DG. Eur J Org Chem 2007:2121–2132.2132b)Kananovich DG, Kulinkovich OG. Tetrahedron 2008;64:1536–1547.1547 For the proposal of related intermediates in the reductive ethylation of allylic ethers, see: c)Matyushenkov EA, Churikov DG, Sokolov NA, Kulinkovich OG. Russ J Org Chem 2003;39:478–485.485
14. While this reaction has not yet been rendered catalytic in the metal (Ti), the process provides a stereochemically unique transformation of great potential utility in organic synthesis. Like the Claisen rearrangement, these reactions proceed by substrate control, thereby eliminating the necessity to control stereochemistry by reagent- or catalyst-based methods. Finally, due to the low cost of the metal-containing reagents, and benign nature of the byproducts (TiO_2 and magnesium (II) salts), the reaction in its current form should be of great utility in organic chemistry.



epothilone D **agrostistachin** **sarcotin H**

Figure 1.

Natural products possessing stereodefined (*Z)*-trisubstituted alkenes.

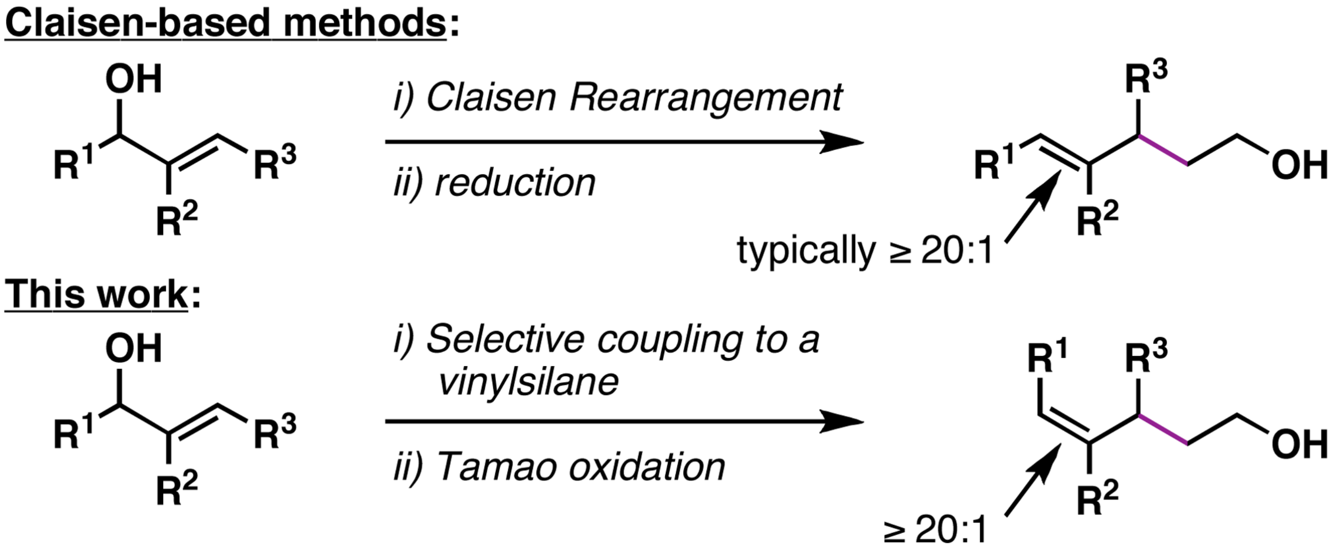


Figure 2.

A stereochemically unique method for the synthesis of stereodefined trisubstituted alkenes from allylic alcohols.

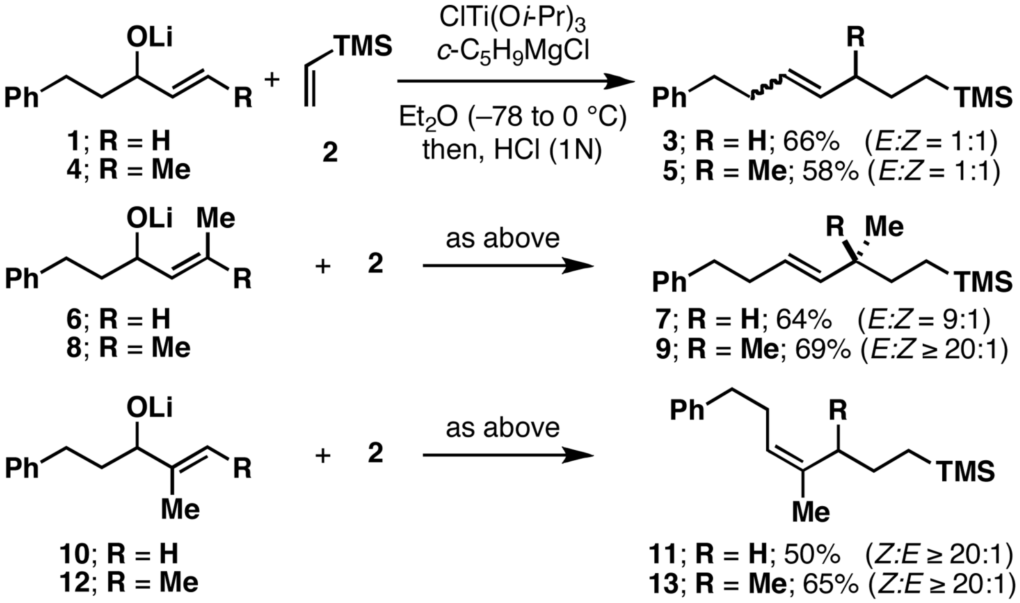
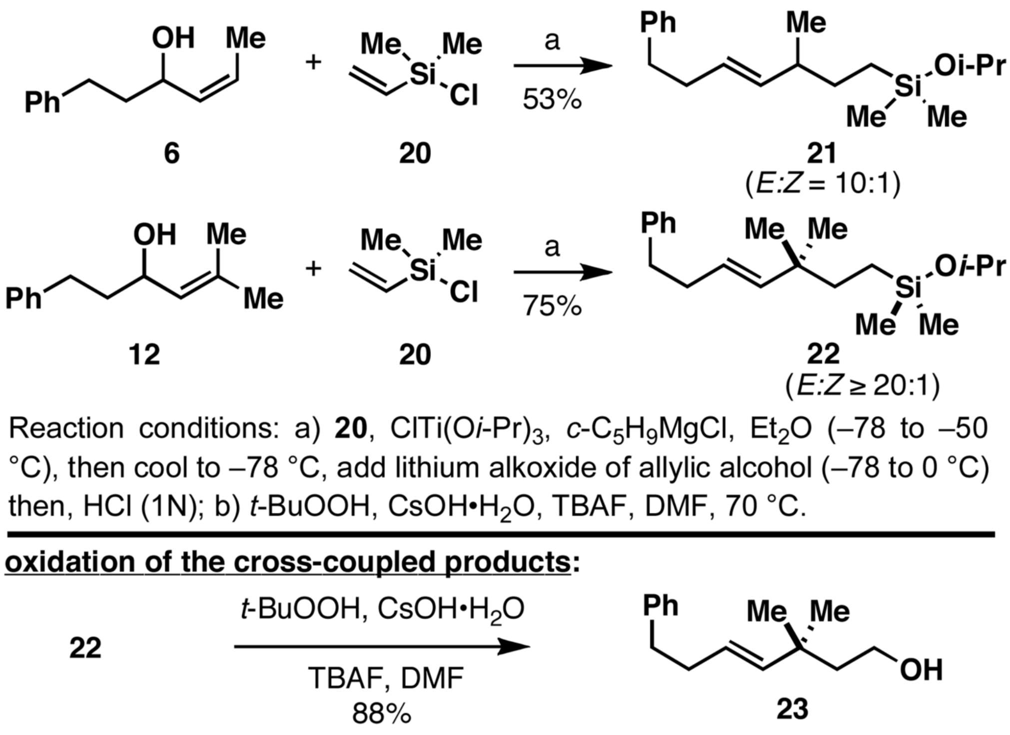


Figure 3.

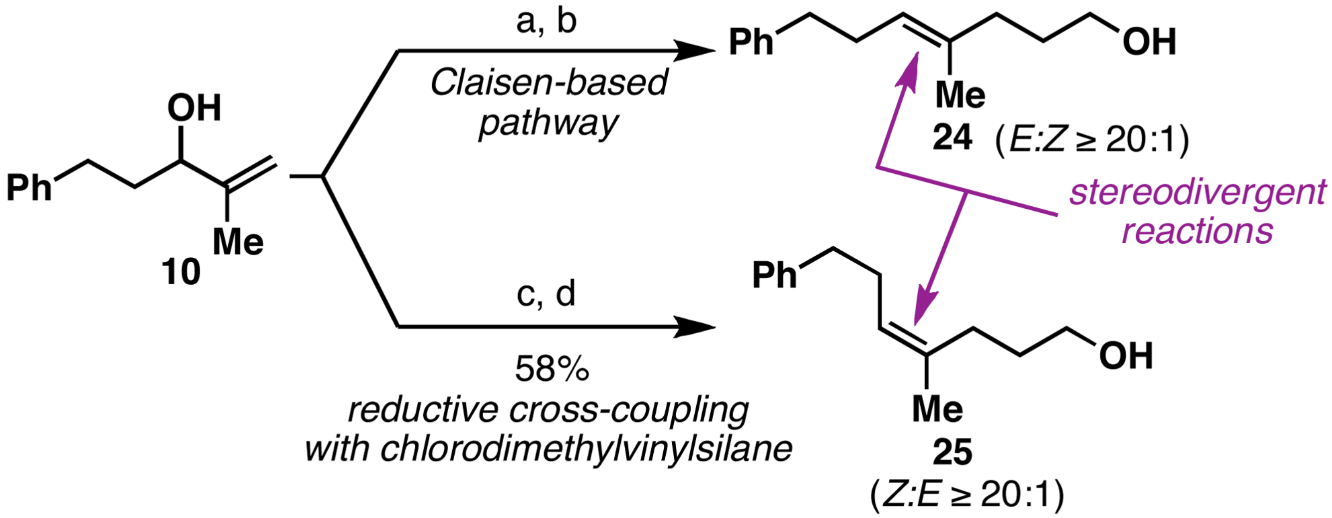
Preliminary study of stereoselection in reductive cross-coupling of allylic alcohols with vinylsilanes.



Reaction conditions: a) **20**, $ClTi(O\textit{i}\text{-}Pr)_3$, $c\text{-}C_5H_9MgCl$, Et_2O (–78 to –50 °C), then cool to –78 °C, add lithium alkoxide of allylic alcohol (–78 to 0 °C) then, HCl (1N); b) *t*-BuOOH, $CsOH{\bullet}H_2O$, TBAF, DMF, 70 °C.

Figure 4.

Cross-coupling reactions with vinyldimethylchlorosilane.



Reaction conditions: a) Johnson ortho-ester Claisen rearrangement; b) reduction;[9] c) **20**, ClTi(O*i*-Pr)$_3$, *c*-C_5H_9MgCl, Et_2O (–78 to –50 °C), then cool to –78 °C and add lithium alkoxide of **10** (–78 to 0 °C) then, HCl (1N) (75%, *Z*:*E* ≥ 20:1); d) *t*-BuOOH, CsOH•H_2O, TBAF, DMF, 70 °C.

Figure 5.

A stereochemically complimentary process with respect to the Claisen rearrangement.

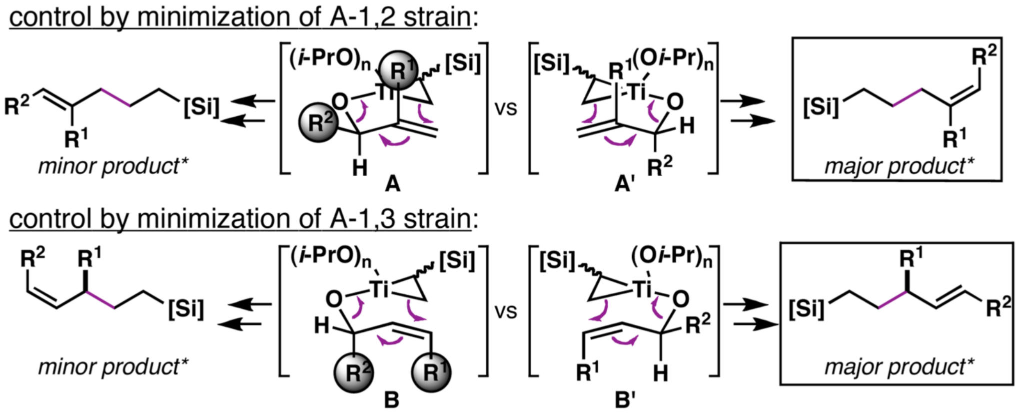
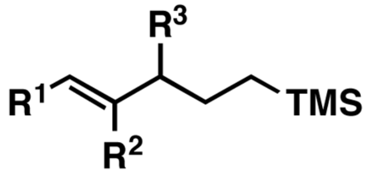
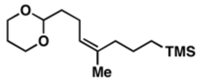
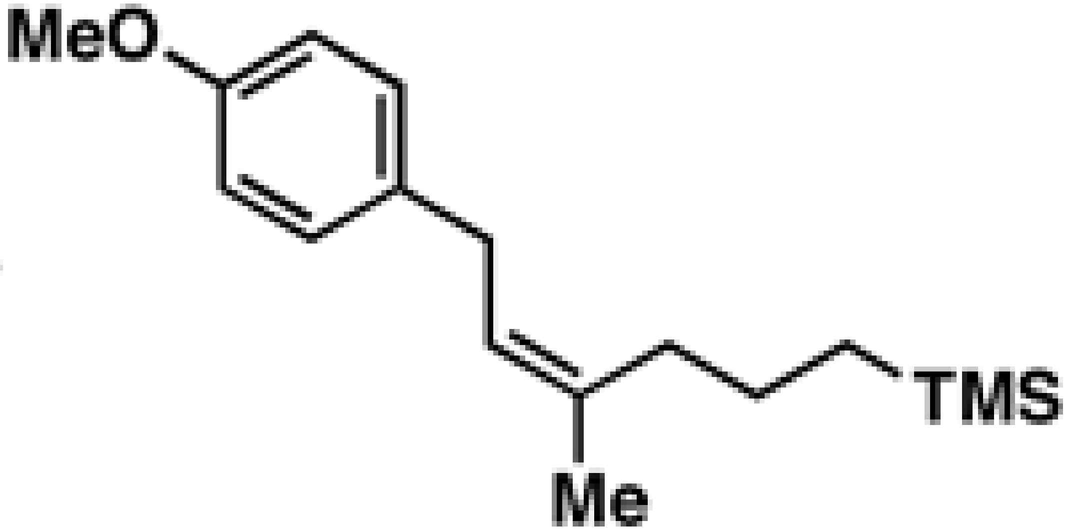
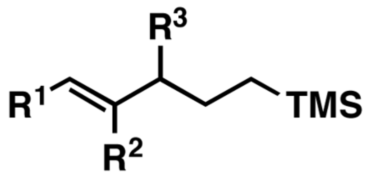


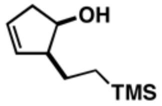
Figure 6.

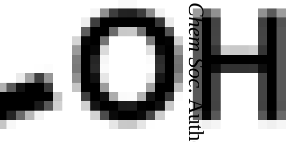
Model of stereoselection.



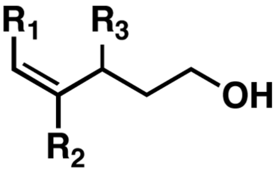
vinylsilane	yield (%)	(Z:E)	dr	product
2	62	≥ 20:1	—	 **15**
2	71	≥ 20:1	—	 **17**

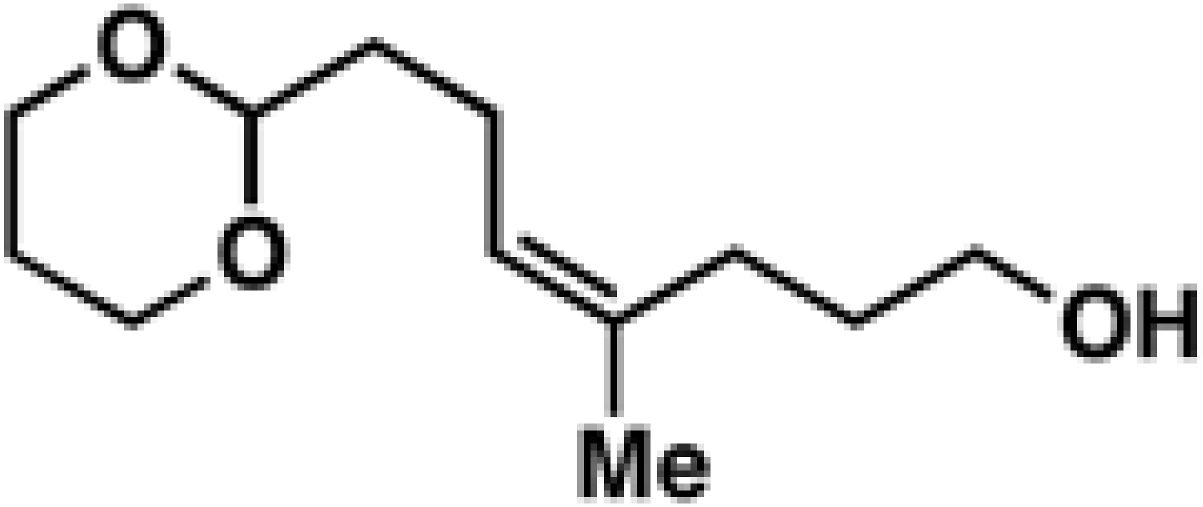


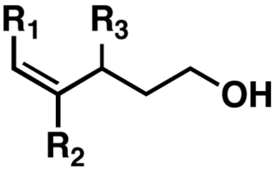
vinylsilane	yield (%)	(Z:E)	dr	product
2	64	—	5:1	 **19**

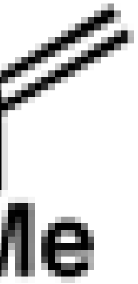
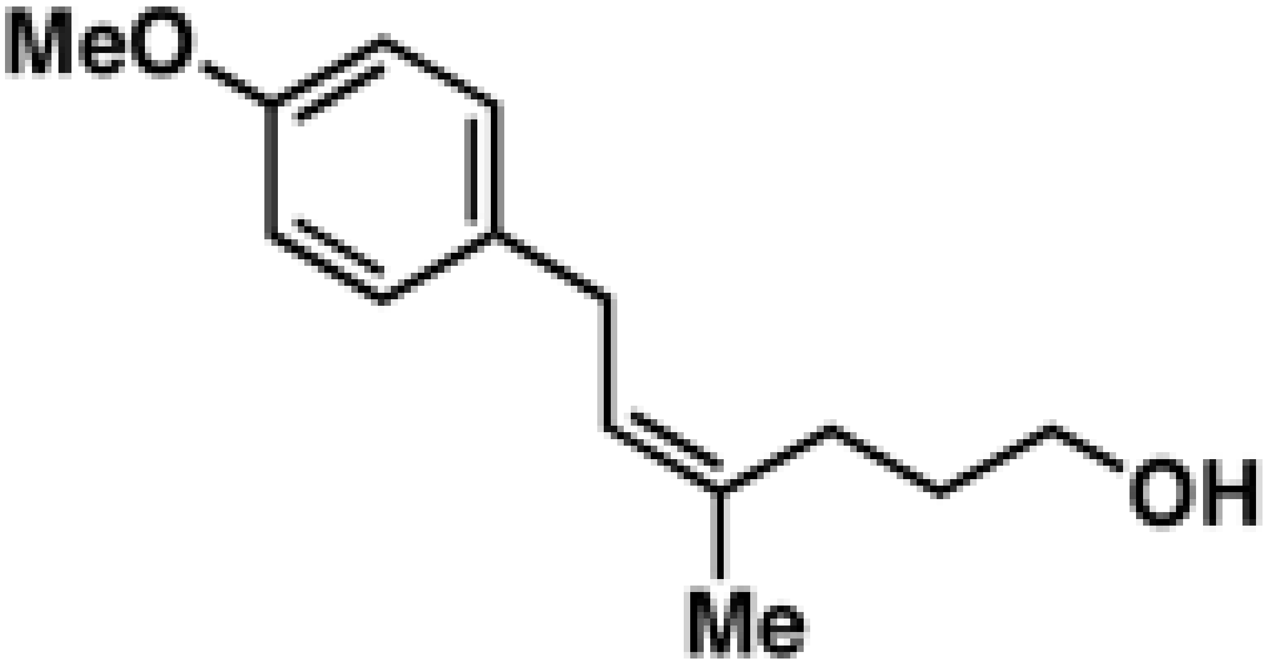


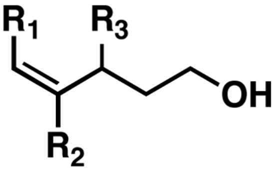
HCl (1N).

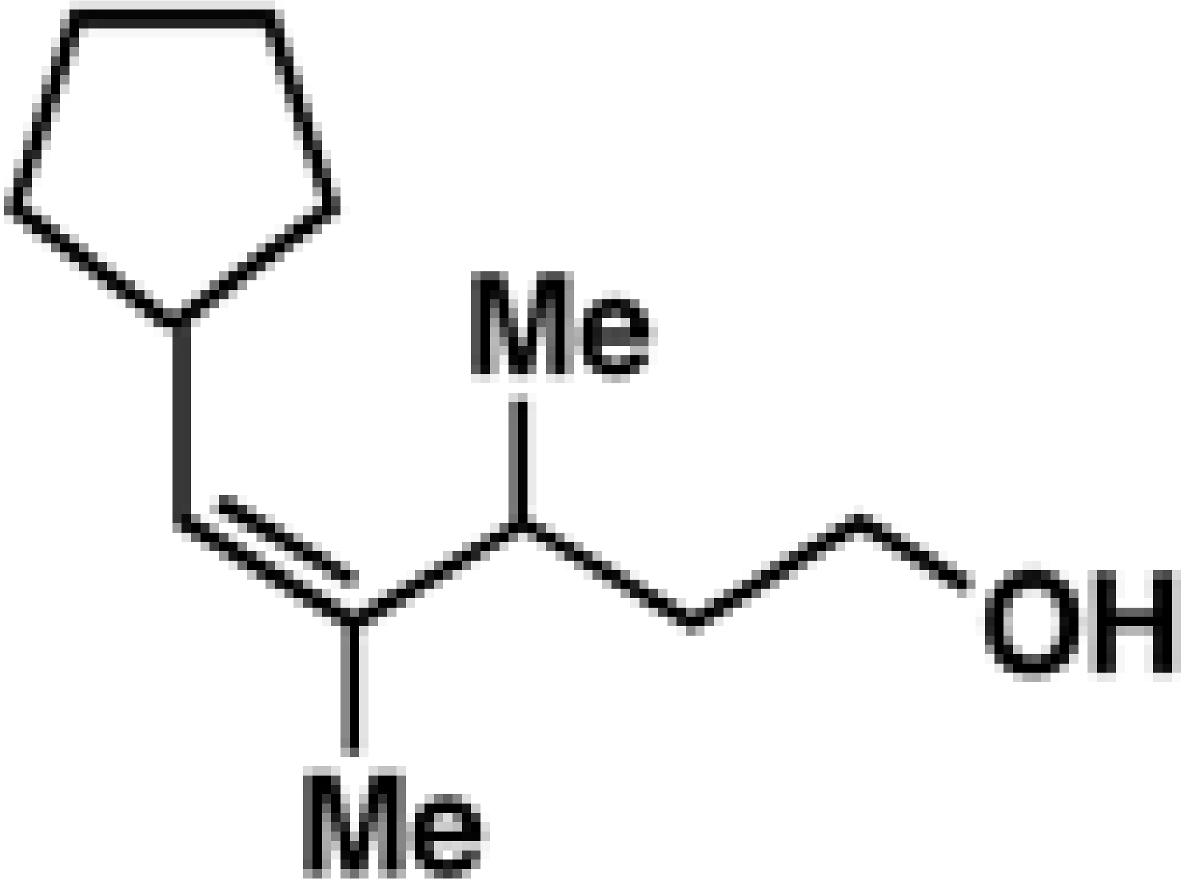


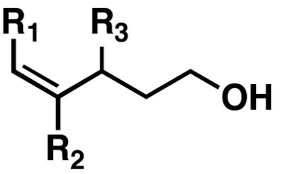
vinylsilane	yield (%)[a]	(Z:E)	product
20	51	≥ 20:1	 **26**

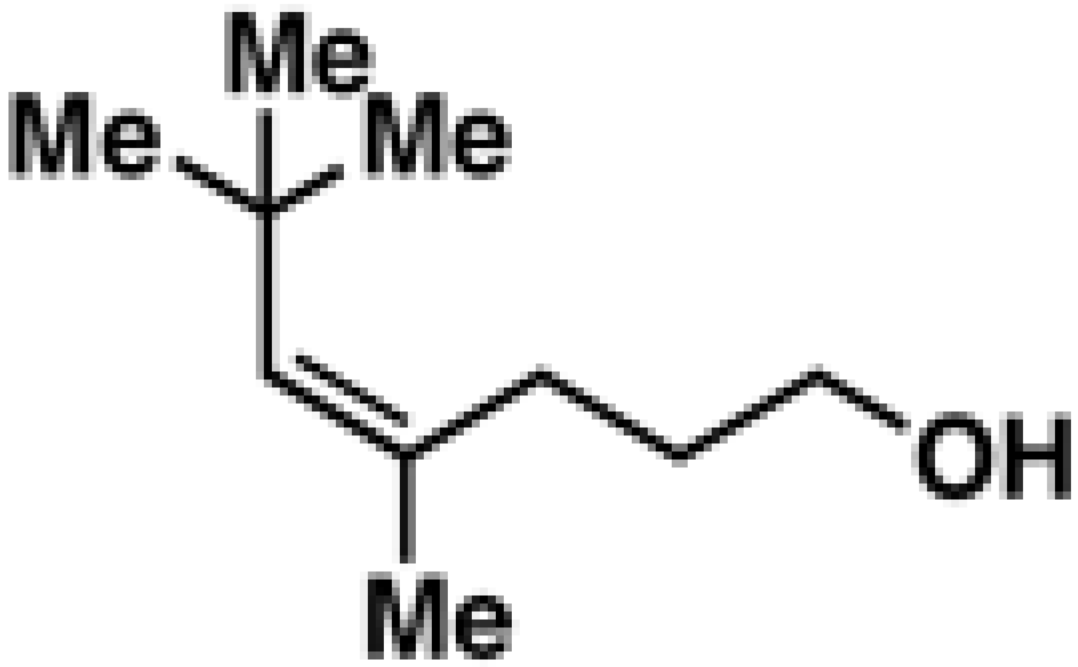


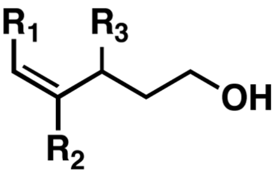
	vinylsilane	yield (%)[a]	(Z:E)	product
	**20**	58	≥ 20:1	 **27**

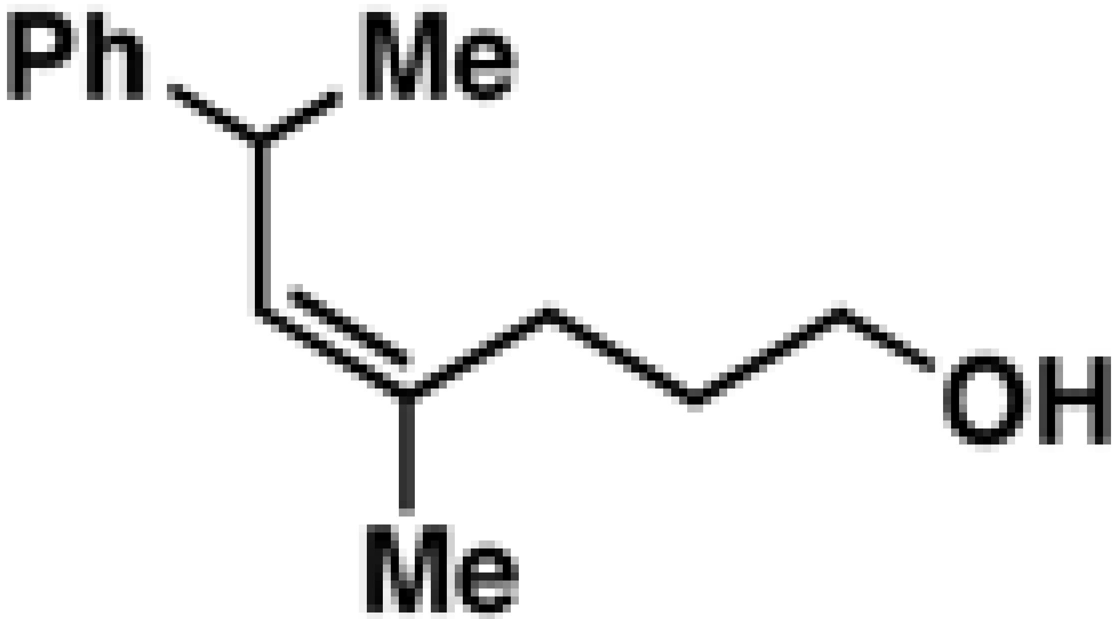


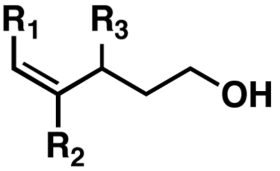
vinylsilane	yield (%)^a	(Z:E)	product
20	69	≥ 20:1	 **29**

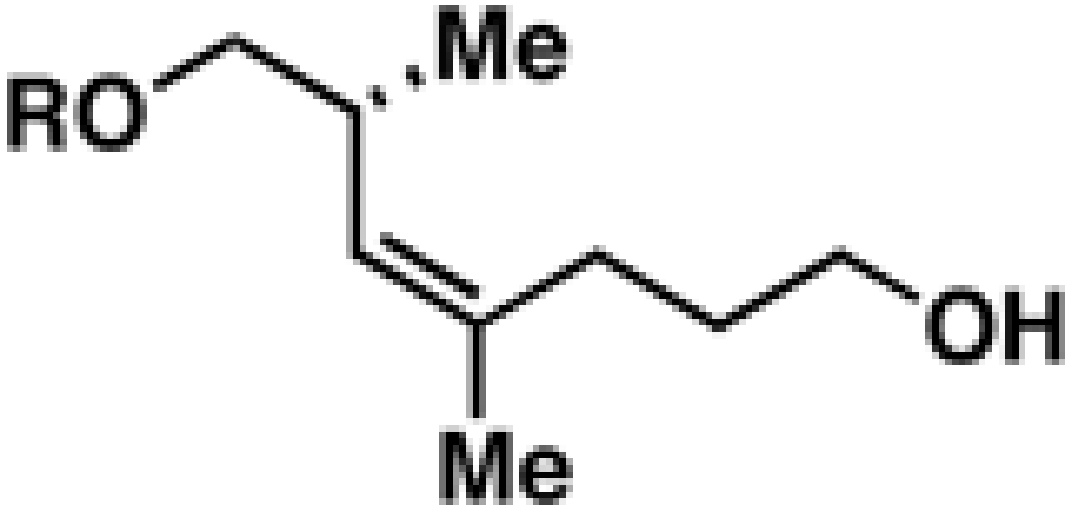


vinylsilane	yield (%)[a]	(Z:E)	product
20	56	≥ 20:1	 **31**



vinylsilane	yield (%)^{a}	(Z:E)	product
20	64	≥ 20:1	 **33**



vinylsilane	yield (%)[a]	(Z:E)	product
			
20	66	≥ 20:1	**37; R = H**
20	61	≥ 20:1	**37; R = H**
20	61	1.2:1[12]	**38; R = PMB**

[a] Yield reported is over the two-step process: 1) Reductive cross-coupling (**20**, ClTi(O*i*-Pr)$_3$, *c*-C_5H_9MgCl, Et_2O (−78 to −50 °C), then cool to −78 °C and add lithium alkoxide of the allylic alcohol (−78 to 0 °C) then, HCl (1N)), 2) oxidation (*t*-BuOOH, $CsOH{\cdot}H_2O$, TBAF, DMF, 70 °C).