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Rhenium-Catalyzed 1,3-Isomerization of Allylic Alcohols: Scope and Chirality Transfer

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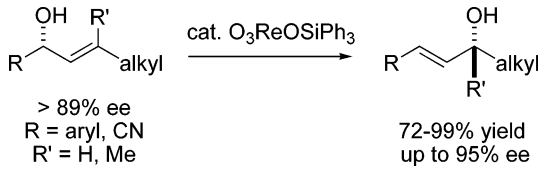

The scope of the triphenylsilyl perrhennate ($O_3ReOSiPh_3$, **1**) catalyzed 1,3-isomerization of allylic alcohols has been thoroughly explored. It was found to be effective for a wide variety of secondary and tertiary allylic alcohol substrates bearing aryl, alkyl, and cyano substituents. Two general reaction types were found which gave high levels of product selectivity: those driven by formation of an extended conjugated system and those driven by selective silylation of a particular isomer. The efficiency of chirality transfer with various substrates was investigated, and conditions were found in which secondary and tertiary allylic alcohols could be formed with high levels of enantioselectivity. Consideration of selectivity trends with respect to the nature of the substituents around the allylic system revealed that this is a reliable and predictable method for allylic alcohol synthesis.

1. Introduction

The scope and utility of [3,3]-rearrangements have expanded greatly since their initial discovery about 100 years ago.[1] A wide variety of methods for promoting Cope and Claisen rearrangements have been reported, including the use of Brønsted acids, Brønsted bases, Lewis acids, and transition metals. These developments led to the use of milder reaction conditions and, therefore, the examination of more complex and synthetically relevant substrates.[2] These methods also enabled new kinds of [3,3]-rearrangements, distinct from the well-known reactions of 1,5-dienes (Cope) and allyl vinyl ethers (Claisen). Polyhetero-Cope rearrangements, such as the [1,3]-dioxa-Cope rearrangement[3] of allylic acetates, did not receive considerable attention until reports appeared of a mild, catalytic version (Scheme 1, eq 1).[4] Although extensive studies have been conducted on these metal-catalyzed rearrangements, the related isomerization of allylic alcohols has received much less attention. In this paper, an extensive investigation of the scope of allylic alcohol isomerizations promoted by triphenylsilyl perrhennate ($O_3ReOSiPh_3$, **1**), a highly active catalyst originally disclosed by Osborn and co-workers, is reported (Scheme 1, eq 2).[5] Ongoing studies in our laboratory have revealed that this rhenium(VII) complex is effective for the isomerization of a wide variety of secondary and tertiary allylic alcohols.[6] In the case of enantioenriched substrates, a high degree of chirality transfer is observed, generating secondary and tertiary allylic alcohols with

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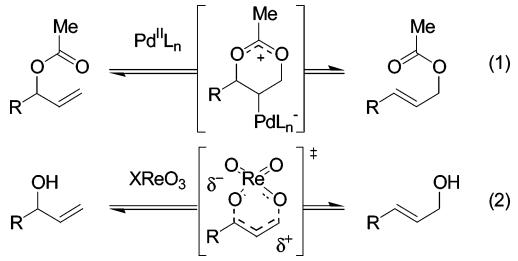
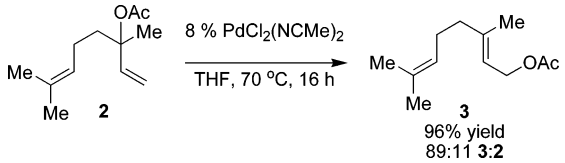
SCHEME 1. Polyhetero-Cope Rearrangements



SCHEME 2. Late Transition-Metal-Catalyzed Rearrangement



high levels of enantioselectivity. Consideration of the trends that correlate substrate structure and selectivity reveals this to be a reliable and predictable method.

2. Background

The rearrangement of allylic esters, or the [1,3]-dioxa-Cope rearrangement, was originally observed in the gas phase by Lewis and co-workers in the late 1960s.[7] The reaction was proposed to be a sigmatropic rearrangement, proceeding through a cyclic transition structure. Unlike the closely related Claisen rearrangement, this reaction was an equilibrium process, in which the product distribution was governed by the relative thermodynamic stabilities of the two allylic isomers. Therefore, for the [1,3]-dioxa-Cope rearrangement to become synthetically useful, strategies for obtaining high product selectivity were required. Brønsted acid catalysts could selectively isomerize tertiary allylic alcohols into the corresponding primary allylic acetates through an ionization−recombination mechanism, but mild reaction conditions were lacking.[8]

Early studies on a catalytic version of these rearrangements showed promising results. Overman and co-workers found that both allylic acetates and carbamates rearranged in the presence of either mercury(II)[9] or palladium(II)[10] catalysts with moderate to high levels of product selectivity (Scheme 2). Under catalysis by $PdCl_2(NCCH_3)_2$, high levels of chirality transfer were observed for enantioenriched allylic acetates. This method has proven useful in the synthesis of several natural products, including steroids,[11] amino acids,[12] and prostaglandins.[13] Overman has classified these transition-metal-catalyzed reactions as "cyclization-induced" rearrangements, proposing a unique mechanism for this class of rearrangements. The key feature of this mechanism was that the metal acted as an electrophilic catalyst, binding to the alkene and activating it toward nucleophilic attack by the pendant carbonyl oxygen to generate a cyclic, organometallic intermediate **i** (Figure 1).[14]

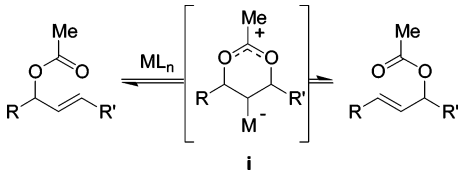


FIGURE 1. Mechanism of "cyclization-induced" rearrangements.

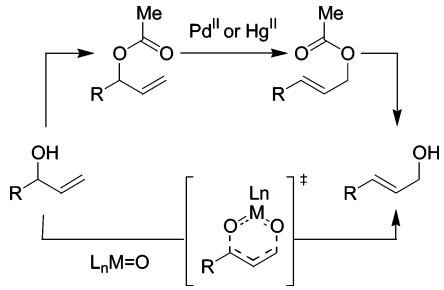


FIGURE 2. Metal oxo- vs late metal-catalyzed isomerizations.

Although late transition metal catalysis is highly effective for promoting the [1,3]-dioxa-Cope rearrangements of allylic esters, the direct isomerization of allylic alcohols cannot be performed with these catalysts. Such a direct transformation of allylic alcohols would be similar to that described for allylic acetates, but it would hold the advantage of occurring in one synthetic step rather than three (Figure 2). In the late 1960s, several high oxidation state, early transition metal−oxo catalysts were reported to directly isomerize allylic alcohols *without* prior esterification.[15] Binding of a metal−oxo complex to the alcohol formed the substrate for the [3,3]-rearrangement catalytically. This novel form of catalysis was originally reported in the patent literature. Extremely low catalyst loadings of vanadium− or tungsten−oxo complexes promoted the equilibration of allylic alcohols at high temperatures.[16] These reactions were generally effective for the isomerization of tertiary alcohols to form primary alcohols, such as the isomerization of linalool (**4**) to form a mixture of geraniol ((*E*)-**5**) and nerol ((*Z*)-**5**) (Table 1, entries 1−4). Chabardes and co-workers proposed that these

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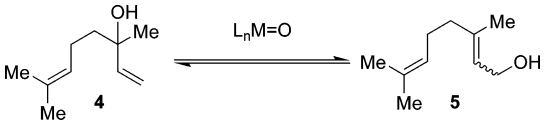
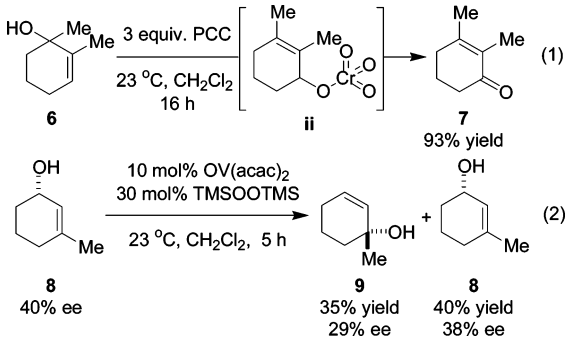
TABLE 1. Isomerizations with Early Metal−Oxo Complexes



entry	catalyst (mol %)	solvent	temp (°C)	time (h)	ratio (**4**/**5**)
1[15b]	$OW(OSiPh_3)_4$ (0.003)	neat	200	3	70:30
2[15b]	$OV(OSiPh_3)_4$ (0.007)	neat	160	1.5	69:31
3[16]	$OW(OMe)_4$−pyridine (0.01)	neat	200	3	61:39
4[16]	$OV(O^tBu)_4$ (0.054)	neat	200	2.5	62:38
5[19]	$OV(acac)_2$−$(TMSO)_2$ (10)	CH_2Cl_2	23	12	82:18
6	$O_3ReOSiPh_3$ (2)	Et_2O	23	0.5	62:38
7	$O_3ReOSiPh_3$/BSA/TMSA (2)	Et_2O	23	0.5	11:89

SCHEME 3. Isomerizations with Early Metal−Oxo Complexes



reactions occurred through a cyclic transition structure similar to that proposed for the related, thermal [1,3]-dioxa-Cope rearrangement.

Subsequent investigations with metal−oxo complexes containing molybdenum,[17] chromium,[18] and vanadium[19] revealed that these reactions could be promoted at ambient temperature. For example, pyridinium chlorochromate (PCC) isomerized tertiary allylic alcohols, presumably through the intermediate **ii**, with subsequent oxidation to form the isomeric α,β-unsaturated ketones (Scheme 3, eq 1).[18] The use of vanadyl bisacetoacetate (O═V(acac)$_2$) in combination with a catalytic amount of bistrimethylsilyl peroxide (TMSOOTMS) also allowed isomerizations to occur at ambient temperature (Table 1, entry 5).[19] The first example of chirality transfer with metal−oxo catalysis was demonstrated in this work with the isomerization of the enantioenriched alcohol **8** (Scheme 3, eq 2).

Further studies revealed that rhenium−oxo complexes also promoted these isomerizations under mild reaction conditions. Narasaka and co-workers demonstrated that under acidic conditions tetra-*n*-butylammonium perrhennate ($O_3ReONBu_4$) isomerized a variety of allylic alcohols (Scheme 4, eq 1).[20] The use of methyl trioxorhenium further demonstrated the utility of rhenium

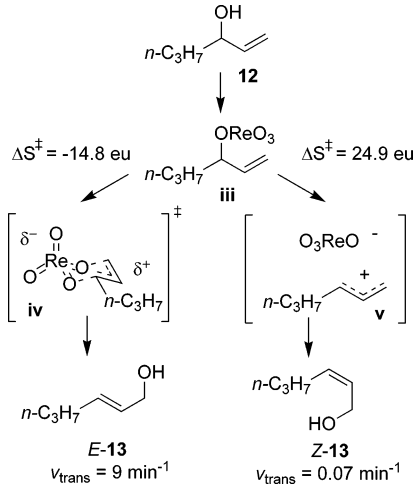
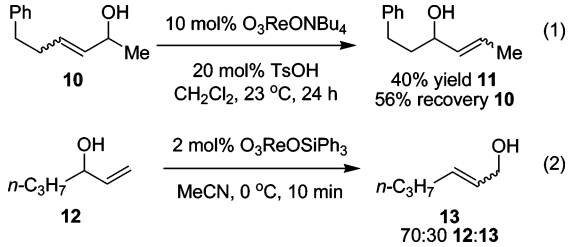


FIGURE 3. Proposed mechanism for $O_3ReOSiPh_3$-catalyzed isomerizations.

SCHEME 4. Rhenium Oxo-Catalyzed Allylic Alcohol Isomerizations



catalysis.[21] However, Osborn and co-workers' study of the reactions involving $O_3ReOSiPh_3$ (**1**) was the major breakthrough in this area (Scheme 4, eq 2).[5,22] Compared to other metal−oxo catalysts, **1** rapidly equilibrates an allylic alcohol and its isomer under neutral conditions with a low catalyst loading (Table 1, entry 6). The allylic alcohol product is usually obtained with high levels of *E*-selectivity. This catalyst has led to some interest in the synthetic community, as demonstrated by several recent publications.[23]

Mechanistic studies performed by Osborn on the isomerization of allylic alcohol **12**, promoted by rhenium complex **1**, supported a cyclic transition structure similar to that originally proposed by Chabardes and co-workers. Kinetic analysis demonstrated that the reaction was first order in both the catalyst and allylic alcohol. The thermodynamics of the reaction revealed a large, negative activation entropy for the formation of the major product, *E*-**13**, suggesting a [3,3]-rearrangement through a highly ordered, polarized, chairlike transition structure **iv** (Figure 3). Osborn proposed that the high oxidation state of the rhenium center generated the polarization in **iv**. In this chairlike transition structure, the observed selectivity for *E*-**13** could result from the minimization of diaxial interactions. Interestingly, this highly ordered transition structure was only

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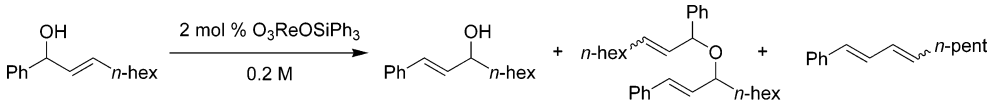
TABLE 2. Solvent Effects on the $O_3ReOSiPh_3$-Catalyzed Isomerization of 14



14 15 16 17

entry	solvent	temp (°C)	time (min)	**14** (%)[a]	**15** (%)[a]	**16** (%)[a]	**17** (%)[a]
1	CH_2Cl_2	23	2	0	15	55	30
2	CH_3CN	23	35	0	19	73	8
3	toluene	23	35	0	51	49	0
4	THF	23	35	0	38	38	24
5	Et_2O	23	35	0	37	51	12
6	CH_2Cl_2	−50	40	4	57	39	0
7	toluene	−50	40	28	72	0	0
8	THF	−50	40	0	100	0	0
9	Et_2O	−50	40	0	100	0	0

[a] Determined by ^{1}H NMR.

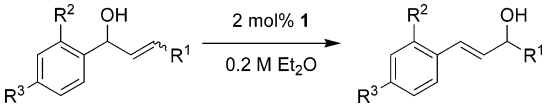
evident in the formation of the major product, *E*-**13**. The minor product, *Z*-**13**, appeared to form through a more disordered process, possibly an ionization−recombination pathway involving intermediate **v**, as evidenced by its positive activation entropy. The formation of only minor amounts of *Z*-**13** indicated that this less-ordered pathway was kinetically less competent when compared to the [3,3]-rearrangement pathway.

Despite these studies, allylic alcohol isomerizations catalyzed by $O_3ReOSiPh_3$ still possessed several shortcomings. The scope of the reaction with respect to substrate structure, general methods for obtaining high product selectivity, as well as the degree of chirality transfer inherent to the reactions of $O_3ReOSiPh_3$ remained unexplored. Therefore, we undertook studies to delineate the scope and limitations of this method with respect to allylic alcohol structure as well as to examine the potential for chirality transfer with $O_3ReOSiPh_3$. The first part of these studies, communicated in 2005,[6] described two methods for obtaining high product selectivity (Table 1, entry 7). The second part of these studies focused primarily on the chirality transfer and has revealed that this method is useful for the formation of enantioenriched secondary and tertiary allylic alcohols. In addition, the activity and selectivity patterns of related rhenium(VII) imido catalysts were investigated. Consideration of the observed trends with respect to both product selectivity and chirality transfer supports the mechanism proposed by Osborn and shows this reaction to be a mechanistically distinct alternative to the related [1,3]-dioxa-Cope rearrangements previously described in the literature. Understanding how the mechanism of this reaction fits into the continuum of mechanisms that exist between ionization−recombination and cyclization-induced rearrangements helps to make predictions about the performance of this $O_3ReOSiPh_3$ catalyst system with novel substrates.

3. Results

3.1. Isomerization of Allylic Alcohols Bearing Conjugating Substituents. The first strategy identified for obtaining high levels of product selectivity involved using substrates that would form an extended conjugated system upon isomerization. We proposed that the isomerization of 1-aryl-2-alkenol substrates such as **14** would result in high product selectivity due to the greater thermodynamic stability of conjugated isomer **15** (Table 2). Initial experiments performed with *E*-**14** at 23 °C in dichloromethane showed rapid consumption of the starting material. Unfortunately, the desired product **15** was accompanied by the formation of two other compounds: a mixture of diastereo- and regioisomeric bisallyl ethers (**16**, formed by condensation reactions) and an *E*/*Z*-mixture of dienes (**17**, formed by elimination reactions). The use of other solvents led to little improvement in the product distribution (entries 2−5), but we observed solvent-dependent rate differences among the competing reaction pathways. Reactions run in dichloromethane at 23 °C were clearly more rapid than those run in toluene or in an ethereal solvent at 23 °C. However, we found that only a combination of low temperatures and ethereal solvents led to good conversions and selective formation of the desired allylic alcohol **15** in short reaction times (entries 8 and 9).

TABLE 3. Isomerization of Aryl Secondary Allylic Alcohols

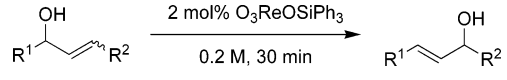


entry	SM (*E*/*Z*)[a]	R^1	R^2	R^3	temp (°C)	time (min)	yield (%)[b]
1	**14** (10:1)	*n*-hex	H	H	−50	30	98 (**15**)
2	**18a** (10:1)	*n*-hex	NO_2	H	23	30	98 (**19a**)
3	**18b** (<1:20)	*n*-hex	H	NO_2	0	30	94 (**19b**)
4[c]	**20** (>20:1)	*n*-hex	H	CF_3	−50	60	98 (**21**)
5[d]	**22a** (10:1)	*n*-hex	OMe	H	−78	120	68 (**23a**)
6[d]	**22b** (>20:1)	*n*-hex	H	OMe	−78	120	79 (**23b**)
7	**24** (12:1)[e]	*c*-C_6H_{11}	H	H	−50	30	95 (**25**)
8	**24** (1:12)[e]	*c*-C_6H_{11}	H	H	−50	30	93 (**25**)
9	**26**	H	H	H	0	30	98 (**27**)
10[f]	**28**	H	NO_2	H	23	30	98 (**29**)
11	**30**	H	OMe	H	−50	30	65 (**31**)

[a] Determined by ^{1}H NMR. [b] *E*/*Z* > 20:1 as determined by ^{1}H NMR. [c] 3 mol % of **1**. [d] 4 mol % of **1**. [e] Determined by GC. [f] Reaction performed in CH_2Cl_2.

Using these optimized conditions as a starting point, we examined the isomerizations of a number of allylic alcohols (Table 3). In all cases, high *E*-selectivity was exhibited. Using only 2−4 mol % of $O_3ReOSiPh_3$, we obtained good yields for substrates bearing either electron-donating or electron-withdrawing substituents on the aryl ring. Substrates bearing electron-withdrawing substituents exhibited significantly lower reaction rates. Higher reaction temperatures were required to reach high conversion in a time comparable to that of the parent compound

TABLE 4. Isomerization of Heteroaryl Secondary Alcohols



entry	SM[a]	R^1	R^2	solvent	temp (°C)	yield (%)[a]
1	**32a**	2-furyl	H	THF	−20	ND (**33a**)
2	**32b**	2-furyl	*n*-hex	Et_2O	−50	ND (**33b**)
3	**34a**	2-benzofuryl	H	THF	−50	98 (**35a**)
4	**34b**	2-benzofuryl	*n*-hex	THF	−50	98 (**35b**)
5	**36a**	2-thiophenyl	H	THF	−50	70 (**37a**)
6[b]	**36b**	2-thiophenyl	*n*-hex	Et_2O	−50	92 (**37b**)
7[b]	**38a**	2-(*N*-tosyl-indoyl)	H	THF	−50	56 (**39a**)
8	**38b**	2-(*N*-tosyl-indoyl)	*n*-hex	Et_2O	−50	66 (**39b**)

[a] *E*/*Z* > 20:1 as determined by ^{1}H NMR. [b] Reaction run for 10−15 min.

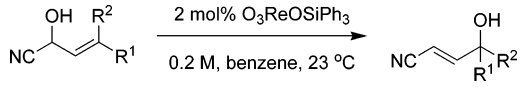
E-**14** (entries 2−4). Interestingly, the isomerization of *Z*-**18b** also showed high *E*-selectivity, despite the change in the initial alkene geometry (entry 3). Substrates bearing electron-donating substituents were more reactive. Lower temperatures were required to suppress the formation of undesired elimination and condensation products, and higher catalyst loadings were employed to maintain reasonable reaction rates at these temperatures (entries 5 and 6). Our observation that both the *E*- and *Z*-isomers of a given allylic alcohol isomerize to form the *E*-isomer of the product was again demonstrated in the isomerizations of *E*- and *Z*-**24** (entries 7 and 8). In both cases, *E*-**25** was selectively obtained in comparable yields.

A similar trend between the electronic nature of the arene and its reactivity was observed in the isomerization of the secondary allylic alcohols **26**, **28**, and **30** (Table 3, entries 9−11). When compared to the analogous compounds possessing disubstituted alkenes (entries 1, 2, and 5), these terminal alkene-containing substrates were noticeably less reactive (compare entries 1 and 9). Isomerization of electron-deficient substrate **28** only proceeded to high conversion in dichloromethane at 23 °C (compare entries 2 and 10), whereas that of electron-rich substrate **30** still required the use of an ethereal solvent and a low temperature (compare entries 5 and 11).

Allylic alcohols bearing heteroaromatic groups also exhibited similar electronic trends with respect to their reactivity (Table 4). Highly electron-rich, furyl-substituted substrates **32a**,**b** rapidly decomposed in the presence of catalyst **1**, and thus no product was obtained from their reactions (entries 1 and 2). The 2-benzofuryl substrates **34a**,**b** provided more promising results (entries 3 and 4). Thiophenyl substrates **36a**,**b** gave moderate to high yields under similar conditions (entries 5 and 6). Indoyl substrates **38a**,**b** which, like the furyl substrates, are relatively electron rich proved more problematic, again due to rapid decomposition in the presence of catalyst **1**. A strongly electron-withdrawing *N*-tosyl substituent was required to obtain reasonable yields of desired alcohols **39a**,**b** (entries 7 and 8). Other nitrogen protecting groups, such as an *N*-2-trimethylsilylethoxymethyl group, did not lead to formation of the desired allylic isomer.

To see if nonaryl groups could also serve as conjugating substituents, the isomerization of allylic cyanohydrins was investigated (Table 5). The analogous isomerization of cyanohydrin acetates and carbonates was precedented.[24] We hypothesized that these substrates would exhibit high product selectivity because the products contain extended conjugated systems in the form of α,β-unsaturated nitriles. Cyanohydrins **40a**,**b** proved to be remarkably unreactive substrates (entries 1 and 2). However, cyanohydrin **40c**, which possesses a trisubstituted alkene, showed a dramatic increase in reactivity (entry 3). The isomerization of **40c** was complete in 5 min at 23 °C, providing tertiary alcohol **41c** in high yield without significant side product formation. These results reflected the observed correlation between reaction rate and degree of alkene substitution that was described previously.

TABLE 5. Isomerization of Cyanohydrins



entry	SM	R^1	R^2	time	yield (%)
1	**40a**	H	H	6 h	ND (**41a**)
2	**40b**	Me	H	6 h	ND (**41b**)
3	**40c**	Me	Me	5 min	83 (**41c**)

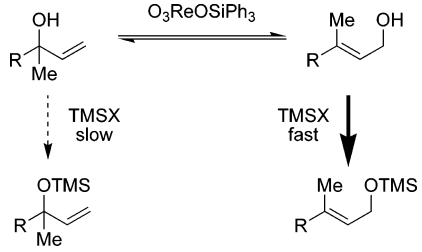


FIGURE 4. Using silylation to control product selectivity.

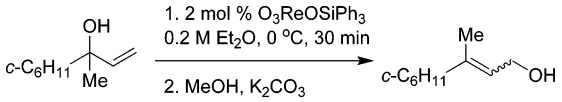
3.2. Isomerization of Allylic Alcohols without Conjugating Substituents. Although the results presented thus far established that conjugating substituents could lead to high product selectivity, many potential substrates could be envisioned that did not possess conjugating substituents. Could a method be developed to induce high product selectivity for this class of substrates as well? Studies by Osborn and co-workers suggested an interesting possibility. They observed that the isomerization of allyl silyl ethers was slow relative to that of allylic alcohols.[22a] Therefore, preferential silylation of one of the allylic alcohol isomers during the course of a reaction would remove it from the equilibrium (Figure 4). Because the preferential silylation of primary alcohols in the presence of secondary or tertiary alcohols is possible, we proposed that high product selectivity, favoring the primary alcohol isomer, could be obtained for substrates lacking conjugating substituents.

The choice of the silylating reagent presented a problem because it is well-known that most amine bases, which are often used to promote silylation reactions, form strong complexes with rhenium−oxo complexes.[25] In fact, it was found that tertiary amines such as diisopropylethylamine and even highly hindered

(24) (a) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021−2024. (b) Huenig, S.; Reichelt, H. *Chem. Ber.* **1986**, *119*, 1772−1800. (c) Mandai, T.; Hashio, S.; Goto, J.; Kawada, M. *Tetrahedron Lett.* **1981**, *22*, 2187−2190. (d) Holm, T. *Acta Chem. Scand.* **1965**, *19*, 242−245.

(25) (a) Herrmann, W. A.; Weichselbaumer, G.; Herdtweck, E. *J. Organomet. Chem.* **1989**, *372*, 371−389. (b) Edwards, P.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1984**, 2695−2702.

TABLE 6. Investigations into the Dependence of Isomerization on the Source of the BSA



42a **43a**

entry	equiv of BSA (source)	additive (equiv)	conv. (%)[a]	yield (%)[b]	*E*/*Z*[c]
1	–	–	–	30	4.7:1
2	1.2 (old Aldrich)	–	–	89	4.7:1
3	1.2 (new Aldrich)	–	9	ND	3.2:1
4	1.2 (distilled)	–	6	ND	ND
5	1.0 (distilled)	Ph_3SiOH (0.2)	6	ND	ND
6	1.0 (distilled)	TsOH−H_2O (0.2)	58	ND	4.6:1
7	1.0 (distilled)	TMSA (0.2)	91	84	4.6:1
8	–	TMSA (1.0)	53	42	4:1

[a] Determined by ^{1}H NMR of crude reaction mixtures. [b] >20:1 **43a**/**42a** as determined by GC. [c] Determined by GC.

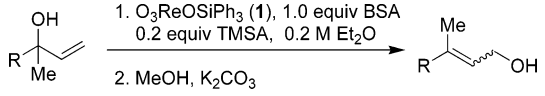
2,4,6-tri-*tert*-butylpyridine inhibited the isomerization reaction. The only method that was effective for this reaction employed *N*,*O*-bistrimethylsilyl-acetamide (BSA), a silylating reagent that does not require the use of an additional base. In the isomerization of tertiary alcohol **42a**, conversion to primary alcohol **43a** increased from 30% to 89% upon addition of 1.2 equiv of BSA (Table 6, entries 1 and 2). Under these conditions, a variety of tertiary alcohols were converted into the corresponding primary alcohols with high product selectivity.[6] However, since our initial communication, we have found that these results are dependent upon the source of the BSA. Although older bottles of BSA provided high product selectivity, freshly opened bottles did not (Table 6, entries 2 and 3). Our observation that freshly distilled BSA gave almost no conversion to primary alcohol **43a** led us to question the role of BSA as a promoter in these reactions (entry 4).

Because freshly distilled BSA did not promote high product selectivity, we suspected that a contaminant in the original bottle of BSA was vital to these isomerizations. The addition of 0.2 equiv of triphenylsilanol or *p*-toluenesulfonic acid, meant to mimic the roles of either trimethylsilanol or trace acid formed upon hydrolysis of BSA, to freshly distilled BSA did not induce high product selectivity (Table 6, entries 5 and 6). However, the addition of 0.2 equiv of *N*-trimethylsilyl acetamide (TMSA) did promote high product selectivity (entry 7). TMSA is the hydrolysis product of BSA, and therefore, it seems likely that it would be present in older bottles of BSA. Interestingly, the use of TMSA alone did not induce high product selectivity (entry 8). Only a combination of BSA and TMSA consistently reproduced the results that we had obtained with the original bottle of BSA.

Under these modified reaction conditions, all of the results reported in our original communication were reproduced with comparable yields and selectivities. A variety of primary alcohols were isolated in good yield after hydrolysis of the silyl ether (Table 7). In most cases, the balance of the material was unreacted starting material. Varying levels of geometrical selectivity were observed, again always favoring the *E*-allylic alcohol. As the size of the spectator group on the allylic alcohol substrate increased from *n*-butyl to cyclohexyl to *tert*-butyl, so did the degree of *E*-selectivity (entries 2−4).

This method also improved both the product selectivity and the geometrical selectivity in the isomerization of some tertiary alcohols bearing conjugating substituents (Table 8). In the case

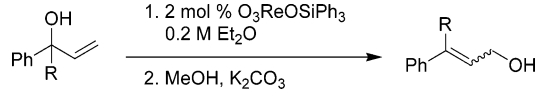
TABLE 7. Effect of BSA on the Isomerization of Alkyl Tertiary Allylic Alcohols



entry	SM	R	mol % of **1**	temp (°C)	time (min)	yield (%)	*E*/*Z*[a]
1[b]	**42a**	*c*-C_6H_{11}	2	0	30	30 (**43a**)	4.7:1
2	**42a**	*c*-C_6H_{11}	2	0	30	84 (**43a**)	4.6:1
3	**42b**	*n*-C_3H_7	2	0	30	93 (**43b**)	1.9:1
4	**42c**	*t*-Bu	4	0	60	82 (**43c**)	>99:1

[a] Determined by GC. [b] No BSA or TMSA was added.

TABLE 8. Effect of BSA on the Isomerization of Aryl Tertiary Allylic Alcohols



entry	SM	R	BSA/TMSA (equiv)	temp °C)	time	yield (%)	*E*/*Z*[a]
1	**44a**	Me	0/0	−10	30 min	67 (**45a**)	8.7:1
2[b]	**44a**	Me	0/0	−40	16 h	84 (**45a**)	18:1
3	**44a**	Me	1.0/0.2	−10	30 min	84 (**45a**)	19:1
4	**44b**	Et	0/0	−10	30 min	25 (**45b**)	1.2:1
5[b]	**44b**	Et	0/0	−30	29 h	83 (**45b**)	1.3:1
6	**44b**	Et	1.0/0.2	−10	30 min	78 (**45b**)	5.1:1

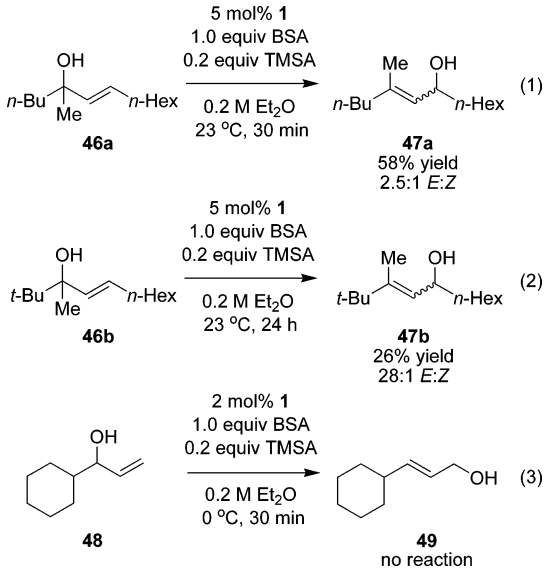
[a] Determined by GC. [b] 4 mol % of $O_3ReOSiPh_3$.

of tertiary alcohol **44a**, the yield improved from 67 to 84%, and the *E*/*Z* selectivity increased from 8.7:1 to 19:1, upon the addition of BSA and TMSA (entries 1 and 3). Similar results were observed in the case of alcohol **44b** (entries 4 and 6). Because of the presence of conjugating substituents on **44a**,**b**, improved yields and selectivities could also be obtained in the absence of BSA and TMSA, but only by employing a lower reaction temperature with a higher catalyst loading and significantly longer reaction times (entries 2 and 5).

The limitations of this method became clear upon further attempts to expand the scope of the reaction. The isomerization of tertiary alcohols **46a**,**b** to form secondary alcohols **47a**,**b** exhibited only moderate yields, again favoring the *E*-isomer (Scheme 5, eqs 1 and 2). The balance of the material existed in the form of various side products. These yields were still significant, however, because in the absence of BSA and TMSA no product could be isolated from these reactions due to rapid decomposition of **46a**,**b** in the presence of catalyst **1**. As we had observed previously, *E*-selectivity increased as the steric demands of the spectator group increased, going from 2.5:1 for **47a** to 28:1 for **47b**. Unfortunately, the beneficial effect of BSA and TMSA on product selectivity could not be extended to the isomerization of nonconjugated secondary allylic alcohols such as **48** (Scheme 5, eq 3). Although the reaction in the absence of BSA and TMSA led to an equilibrium mixture of alcohols (53:47 **48**/**49**), the addition of BSA and TMSA led to no reaction at all, likely due to competitive silylation of **48**.

3.3. Chirality Transfer with Enantioenriched Allylic Alcohols. Having found two different methods for obtaining high product selectivity, we next examined the efficiency of chirality transfer with $O_3ReOSiPh_3$. If the cyclic transition structure proposed by Chabardes and Osborn was operative in these isomerizations, then the enantiopurity of the product should

SCHEME 5. Problematic BSA/TMSA-Promoted Isomerizations



be equal to that of the starting material. Any decrease in enantiopurity upon isomerization could be attributed to either the geometrical purity of the starting material (vide infra) or the involvement of a competitive, acyclic ionized intermediate analogous to **v** (Figure 3). The predicted enantiopurity of each product, accounting for both the geometrical purity and the enantiopurity of the corresponding starting material, is included in subsequent tables.

Two classes of enantioenriched secondary benzylic alcohols were examined, generating secondary and tertiary allylic alcohols, respectively, upon isomerization. Both substrate types used the formation of an extended conjugated system to ensure high product selectivity. In each case, the isomerization can provide access to enantioenriched allylic alcohols which may be difficult to prepare in contrast to their allylic isomers. This is particularly true in the case of the tertiary allylic alcohols. Relatively few catalytic, asymmetric methods exist for tertiary allylic alcohol synthesis. At present, the most general method involves the use of a zinc reagent and a chiral bissulfonamide catalyst.[26] Therefore, a method that can translate the high enantioselectivity readily attained in secondary alcohol syntheses to that of tertiary alcohols would represent a novel synthetic approach.

3.3.1. Chirality Transfer to Prepare Enantioenriched Secondary Allylic Alcohols. Our initial experiments focused on substrates that generate secondary alcohols. Isomerization of (*R*,*E*)-**14** under the optimal conditions identified previously for its racemic analogue only showed a moderate level of chirality transfer. Further reducing the temperature to −78 °C slowed the reaction rate, but it allowed the product (*R*,*E*)-**15** to be obtained in good yield and enantiopurity (Table 9, entry 1). When (*R*,*Z*)-**14** was examined under similar conditions, the (*S*,*E*)-enantiomer of **15** was formed in good yield and enantiopurity (entry 2). The fact that the *E*- and *Z*-isomers of **14** led to the formation of enantiomeric products is consistent with the cyclic, chairlike transition structure **iv** proposed by Osborn and co-workers.

The influence of the electronic nature of the arene ring was also examined in the context of the chirality transfer. Substrate (*R*,*E*)-**22b**, possessing an electron-donating methoxy substituent, exhibited poor chirality transfer. Even at −78 °C, a temperature at which condensation and elimination pathways are almost completely suppressed, only racemic product was obtained (Table 9, entry 3). However, the isomerization of electron-deficient substrate (*R*,*E*)-**20** at −50 °C led to the isolation of highly enantioenriched alcohol (*R*,*E*)-**21** in good yield (entry 4). Therefore, the degree of chirality transfer increased in the series **20** > **14** ≫ **22b** and tracked well with the electronic nature of the substrates.

3.3.2. Chirality Transfer to Prepare Enantioenriched Tertiary Allylic Alcohols. We observed a similar trend in the isomerization of substrates that generated tertiary allylic alcohols (Table 10). However, an important difference existed between these substrates and those shown in Table 9. The additional methyl substituent in (*R*,*E*)-**50** dramatically decreased the efficiency of the chirality transfer compared to (*R*,*E*)-**14** (compare Table 10, entry 1, to Table 9, entry 1). Substrate (*R*,*E*)-**52**, bearing a trifluoromethyl substituent, exhibited improved chirality transfer relative to (*R*,*E*)-**50**, but it was still significantly less efficient than (*R*,*E*)-**20** (compare Table 10, entry 2, to Table 9, entry 4). In an effort to further improve the chirality transfer, we examined substrate (*R*,*Z*)-**54**, bearing two trifluoromethyl substituents, and found that it indeed exhibited a much higher degree of chirality transfer (Table 10, entry 3). We also investigated enantioenriched cyanohydrin (*R*,*E*)-**56**, which bears a nonaryl, conjugating substituent. Substrate (*R*,*E*)-**56** was readily prepared in high levels of enantiopurity by an enzyme-catalyzed cyanation using the oxynitrilase contained in raw, commercially available almonds.[27] In the isomerization of cyanohydrin (*R*,*E*)-**56**, high chirality transfer was observed *at ambient temperature*, and alcohol (*R*,*E*)-**57** was obtained in excellent yield and enantiopurity (Table 10, entry 4).

3.4. Effect of Catalyst Structure on Isomerization Selectivity. Having thoroughly examined the effect of allylic alcohol structure on product selectivity and chirality transfer, we then investigated the effect of catalyst structure by employing a rhenium(VII) imido catalyst. Imido groups are less electron withdrawing than oxo groups, partially due to contributions from the nitrogen lone pair. Rhenium−imido complexes were originally described by Nugent.[28] Early transition-metal−imido complexes have found only limited applications, including the stoichiometric isomerization of allylic alcohols to form allylic amines with tungsten and zirconium−imido complexes.[29] Therefore, we wished to ascertain whether rhenium(VII) imido catalysts would provide any advantages in these isomerizations.

Rhenium−imido complex **58** was synthesized by mixing 10 equiv of *N*-trimethylsilyl-*tert*-butylamine with either dirhenium heptaoxide or tetra-*n*-butylammonium perrhennate (Scheme 6). This reaction led to the rapid formation of complex **58**, which was isolated as a moisture-sensitive, yellow solid. As determined

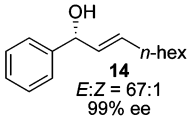
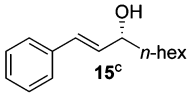
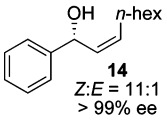
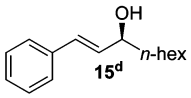
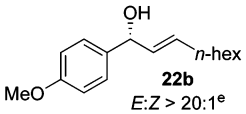
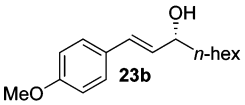
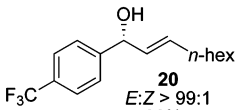
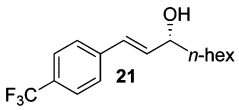
(26) (a) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355−8361. (b) Jeon, S. J.; Li, H.; Carcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448−455. (c) Li, H.; Garcia, C.; Walsh, P. J. *Proc. Natl. Acad. Sci.* **2003**, *101*, 5425−5427. (d) Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651−5666.

(27) Deardorff, D. R.; Taniguchi, C. M.; Nelson, A. C.; Pace, A. P.; Kim, A. J.; Jones, R. A.; Tafti, S. A.; Nguyen, C.; O'Connor, C.; Tang, J.; Chen, J. *Tetrahedron: Asymmetry* **2005**, *16*, 1655−1661.

(28) (a) Schoop, T.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H. G. *Organometallics* **1993**, *12*, 571−574. (b) Toreki, R.; Schrock, R. R.; Davis, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 3367−3380. (c) Danopolous, A. A.; Longley, C. J.; Wilkinson, G.; Hussain, B.; Hursthouse, M. B. *Polyhedron* **1989**, *8*, 2657−2670. (d) Nugent, W. A. *Inorg. Chem.* **1983**, *22*, 965−969.

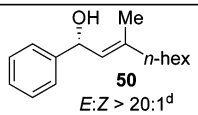
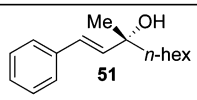
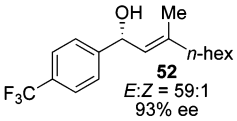
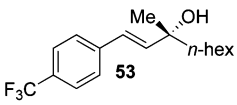
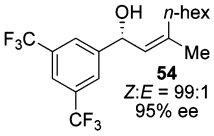
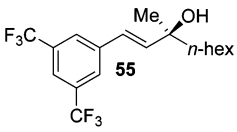
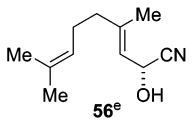
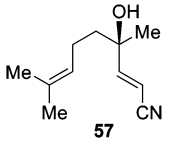
(29) (a) Lalic, G.; Blum, S. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 16790−16791. (b) Chan, D. M. T.; Nugent, W. A. *Inorg. Chem.* **1985**, *24*, 1422−1424.

TABLE 9. Chirality Transfer to Prepare Enantioenriched Secondary Allylic Alcohols[a]

entry	substrate	temp. (°C)	time (h)	product[b]	isolated yield (%)	ee (%)	predicted ee (%)
1	 **14** *E*:*Z* = 67:1 99% ee	−78	2	 **15**[c]	93	81	96
2	 **14** *Z*:*E* = 11:1 > 99% ee	−78	2	 **15**[d]	92	72	> 82
3	 **22b** *E*:*Z* > 20:1[e] 89% ee	−78	2	 **23b**	72	1	> 80
4	 **20** *E*:*Z* > 99:1 > 99% ee	−50	1	 **21**	99	95	> 97

[a] 0.2 M, ether, 3 mol % of **1**.Unless otherwise noted, *E*/*Z* was determined by GC, and ee was determined by chiral HPLC. [b] *E*/*Z* > 20:1 (^{1}H NMR). [c] Absolute configuration determined to be (*R*). [d] Absolute configuration determined to be (*S*). [e] Determined by ^{1}H NMR.

TABLE 10. Chirality Transfer to Prepare Enantioenriched Tertiary Allylic Alcohols[a]

entry	substrate	temp. (°C)	time (min)	product[b]	isolated yield (%)	ee (%)	predicted ee (%)
1[c]	 **50** *E*:*Z* > 20:1[d] 99% ee	−78	120	 **51**	81	9	> 89
2	 **52** *E*:*Z* = 59:1 93% ee	−50	30	 **53**	95	58	90
3	 **54** *Z*:*E* = 99:1 95% ee	-30	30	 **55**	85	90	93
4	 **56**[e] *E*:*Z* = 97:3 99% ee	23	10	 **57**	95	92	93

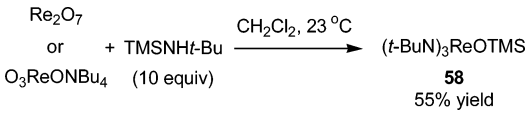
[a] 0.2 M, ether, 2 mol % of **1**.Unless otherwise noted, *E*/*Z* was determined by GC, and ee was determined by chiral HPLC. [b] *E*/*Z* > 20:1 as determined by ^{1}H NMR. [c] Reaction performed in THF with 4 mol % of **1**. [d] Determined by ^{1}H NMR. [e] Absolute configuration determined to be (*R*).

by ReactIR, this complex could also be generated in situ by a similar procedure.

Initial experiments conducted with in situ generated imido complex **58** and allylic alcohol **14** under the optimal reaction conditions determined previously with oxo complex **1** clearly demonstrated the lower reactivity of the imido complex. No conversion to alcohol **15** was observed at −50 °C. Performing the isomerization at 23 °C, however, led to complete conversion to **15** after 30 min (Table 11, entry 1). Because the analogous reaction with oxo complex **1** readily generated a complex product mixture (Table 2, entry 1), this result with catalyst **58** represents an improvement in terms of product selectivity. However, the chirality transfer with **58** at 23 °C was nearly identical to that observed with **1** at −78 °C (compare Table 11, entry 1, to Table 9, entry 1). The chirality transfer observed with **58** was unaffected by the stoichiometry of the amine (Table 11, compare entries 1 and 2).

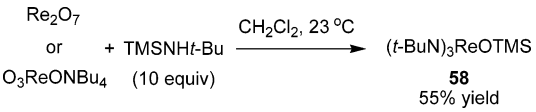
Interestingly, this reaction did not proceed in the presence of isolated imido complex **58** (Table 11, entry 3). The addition of triphenylsilanol to the reaction, a substitute for the trimeth-

SCHEME 6. Synthesis of Rhenium−Imido Complex 58



ylsilanol formed during the in situ imido group transfer, did not promote significant isomerization (entry 4). However, the addition of even small amounts of TMSNH^{t}Bu did allow reactivity to be recovered, generating allylic alcohol (*R*,*E*)-**15** in good yield and enantiopurity at 23 °C with only 2.5 mol % of **58** (entry 5).

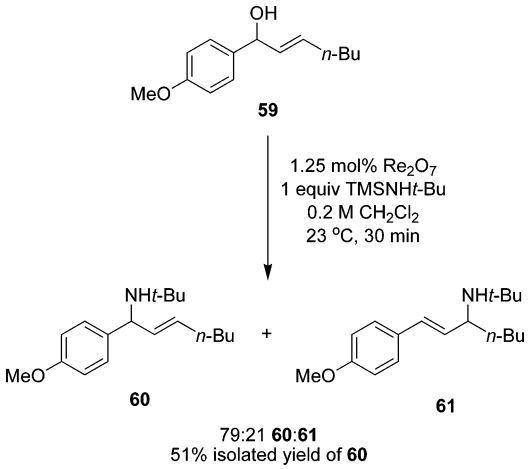
TABLE 11. Rhenium Imido-Catalyzed Isomerizations



entry	catalyst (mol %)	additive (mol %)	yield (%)[c]	ee
1	Re_2O_7 (1.25)	TMSNH^{t}Bu (100)	86	83
2	Re_2O_7 (1.25)	TMSNH^{t}Bu (15)	89	81
3	**58** (2.5)	−	−	−
4	**58** (2.5)	Ph_3SiOH (15)	−	−
5	**58** (2.5)	TMSNH^{t}Bu (15)	76	82

[a] Determined by GC. [b] Determined by chiral HPLC. [c] *E*/*Z* > 20:1 as determined by ^{1}H NMR.

SCHEME 7. Rhenium Imido-Catalyzed Isomerizations of 59



The decreased catalytic activity of imido complex **58** was confirmed by the fact that it did not react with electron-deficient allylic alcohol **20**. On the other hand, exposure of **58** to electron-rich allylic alcohol **59** promoted a rapid reaction but yielded none of the desired allylic alcohol isomer. Instead, it generated a mixture of allylic amines **60** and **61** (Scheme 7). Despite attempts at optimization, the ratio of these two isomeric amines could not be affected by changing the solvent or the amine structure.

4. Discussion

In this paper, the $O_3ReOSiPh_3$-catalyzed isomerization of allylic alcohols has been studied and the scope and limitations of the method have been examined. In this section, a more in-depth overview of the isomerization mechanism will be presented. Trends with respect to the electronic nature of the allylic alcohols and the degree of alkene substitution will be discussed in the context of both product selectivity and chirality transfer. The results obtained with imido and oxo catalysts will be compared, adding further support to the proposed catalytic cycle. This mechanistic understanding makes it relatively straightforward to predict the outcome of a given allylic alcohol isomerization by considering both the structure and the electronic nature of the substrate.

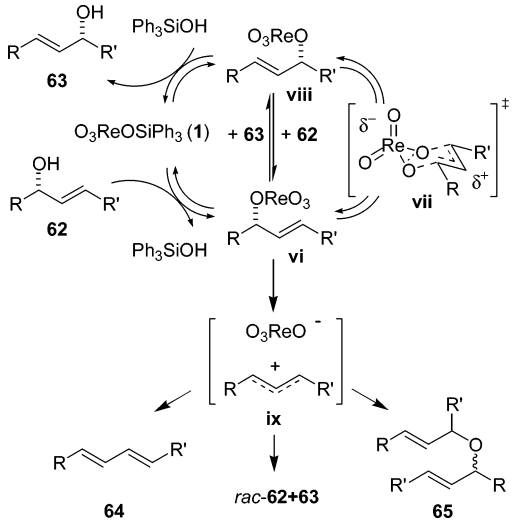


FIGURE 5. Proposed catalytic cycle for $O_3ReOSiPh_3$-catalyzed isomerizations.

4.1. Proposed Catalytic Cycle for $O_3ReOSiPh_3$-Catalyzed Isomerizations. On the basis of Osborn's proposed mechanism, a more detailed catalytic cycle can be drawn for the overall isomerization process (Figure 5).[5,22b] The first step forms the actual [3,3]-rearrangement substrate **vi** through displacement of triphenylsilanol from **1**. Isomerization then occurs through six-membered, chairlike transition structure **vii**, reminiscent of that involved in the Claisen rearrangement. This structure is supported by Osborn's measurement of a large, negative activation entropy for this reaction. After the isomerization occurs, rhennate ester **viii** is formed. Catalyst turnover then occurs by either direct displacement by allylic alcohol **62** or displacement by triphenylsilanol. Although the former seems more likely due to the high concentration of alcohol relative to that of silanol, triphenylsilanol may still be involved in the catalyst turnover step, acting as a proton donor ($pK_a = 16.57$ (DMSO)[30]).

Significant polarization exists in transition structure **vii** due to the high oxidation state of the rhenium atom and the presence of three strongly electron-withdrawing oxo ligands. Thus, carbon−oxygen bond cleavage likely precedes carbon−oxygen bond formation, leading to a partial positive charge on the allyl fragment and a partial negative charge on the rhennate fragment. The strong polarization of the carbon−oxygen bond in **vi** can also lead to competitive formation of ion pair intermediate **ix**. The involvement of this species is supported by Osborn's observation of a second reaction pathway, responsible for *Z*-allylic alcohol formation, with a positive activation entropy. Further support for the involvement of a cationic intermediate such as **ix** comes from the fact that trioxorhenium complexes,

(30) Bassindale, A. R.; Taylor, P. G. In *The Chemistry of Organosilicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons: New York, 1989; Chapter 12, Part 1, p 809−838.

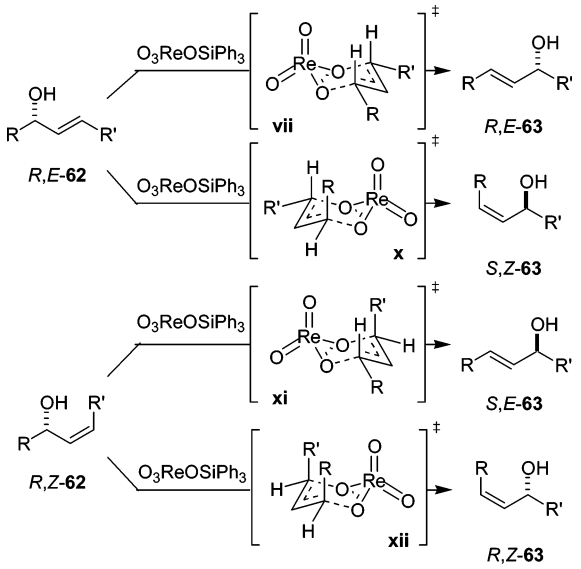
such as $O_3ReOSiPh_3$, are potent catalysts for Beckmann rearrangements and other dehydration reactions.[31] Therefore, we believe that an ionization−recombination pathway leads to the observed elimination, condensation, and racemization products (vide infra).

4.2. Structural Trends with Respect to Reactivity and Product Selectivity. If highly polarized transition structure **vii** is operative in these isomerizations, then electronic variations in the allylic alcohol should have a strong influence on the reaction rate. In our studies, a trend with respect to the electronic nature of the substrate is made clear by examining the reaction conditions required to suppress elimination and condensation reactions. In both the racemic and the enantioenriched series, substrates bearing electron-withdrawing substituents reacted more cleanly at higher temperatures when compared to their more electron-rich counterparts. This trend is exemplified in the reactions of **14**, **18a**, and **22a** (Table 3, entries 1, 2, and 5) as well as **26**, **28**, and **30** (Table 3, entries 9−11). We also observed that substrates bearing electron-donating substituents generally reacted more rapidly than those with electron-withdrawing substituents when performed under similar conditions. This trend is echoed in the reactions of the heterocycle-containing allylic alcohols. Particularly electron-rich substrates, such as furyl substrates **32a**,**b**, did not give any of the desired product when exposed to **1**, although all of the starting material was consumed (Table 4, entries 1 and 2). Presumably, these substrates were so reactive that competing reaction pathways simply could not be suppressed.

Our observation that electron-withdrawing groups seem to suppress undesired side processes, as well as decrease the overall reaction rate, supports the involvement of the two similar pathways for consumption of the allylic alcohol as suggested in section 4.1. The pathway leading to the desired products likely involves an asynchronous [3,3]-rearrangement through polarized transition structure **vii**. Electron-withdrawing groups will disfavor the buildup of positive charge on the allyl fragment of **vii** and thus slow the reaction. The pathway generating the elimination, condensation, and racemization products, on the other hand, likely involves an ionized intermediate such as **ix**. Electron-donating groups will stabilize this allyl cation, favoring its formation and therefore increasing the generation of undesired products. The partitioning of rhennate esters between these two pathways clearly depends on the electronic nature of the allylic alcohol.

A reactivity trend based on the degree of alkene substitution in the allyl system also exists. In the series **14**, **26**, and **50**, the reaction temperature required to maintain high product selectivity decreased as the degree of alkene substitution increased (Table 3, entries 1 and 9, and Table 10, entry 1). The reaction of **26** proceeded cleanly at 0 °C, whereas those of more substituted substrates **14** and **50** required temperatures of −50 °C or lower. The degree of alkene substitution also affected the reactivity of cyanohydrins **40a**−**c** (Table 5). Although the reaction of **40c** was complete in <5 min at 23 °C, less-substituted substrates **40a**,**b** did not react at 23 °C. This trend can be rationalized in a manner similar to that just presented. As the degree of alkene substitution increases, so does the ability to stabilize the buildup of positive charge in the asynchronous [3,3]-rearrangement transition structure **vii**.

SCHEME 8. Consequences of *E*/*Z* Isomerism on Selectivity



4.3. Structural Trends with Respect to Stereoselectivity. 4.3.1. Geometric Selectivity. Beyond the issue of product selectivity, two issues of stereoselectivity exist in these allylic alcohol isomerizations. The first is the geometrical selectivity observed in the formation of allylic alcohol products. In all cases, we observed moderate to high levels of *E*-selectivity. Minimization of $A_{1,3}$ interactions in the proposed chairlike transition structure can account for this observed *E*-selectivity, similar to results observed in the palladium(II)-catalyzed rearrangement of tertiary allylic acetates.[32] This explanation is supported by the results obtained from isomerizations that form trisubstituted alkenes. In the series **42a**−**c**, the level of *E*-selectivity increased with the steric demand of the substituents (Table 7). In addition, our observation that the *E*-selectivity in the isomerizations of **44a**,**b** increased upon either lowering the reaction temperature or adding BSA and TMSA suggests that the *E*-alkene is the kinetic product of these reactions (Table 8). Silylation would effectively remove the initial product from the reaction equilibrium, preventing further isomerization as well as possible erosion of *E*/*Z* selectivity.

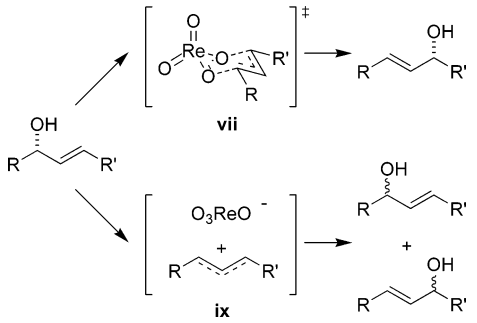
This analysis, which centers around the proposed chairlike transition structure **vii**, also serves to explain why both *E*- and *Z*-alkene-containing allylic alcohols yield the corresponding *E*-products after isomerization (Scheme 8). In the transition structures leading to *Z*-**63** vs *E*-**63**, a greater number of diaxial interactions must always be tolerated in the former. In the case of *E*-**62**, the transition structure leading to *E*-**63** (**vii**) has no diaxial interactions, whereas that leading to *Z*-**63** (**x**) has one. In the case of *Z*-**62**, the transition structure leading to *E*-**63** (**xi**) has a single diaxial interaction, whereas that leading to *Z*-**63** (**xii**) has two.

4.3.2. Chirality Transfer. The use of enantioenriched substrates in these isomerization reactions allows the efficiency of chirality transfer with $O_3ReOSiPh_3$ to be examined. This is the second issue of selectivity in these reactions and provides further insights into the mechanism of the process. In the

(31) (a) Ishihara, K.; Furuya, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 2983−2986. (b) Kusama, H.; Yamashita, Y.; Uchiyama, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 965−975. (c) Kusama, H.; Yamashita, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 373−377. (d) Klass, M. R.; Warwel, S. *Fett. Wissen. Technol.* **1995**, *97*, 250−252.

(32) Tamaru, Y.; Yamada, Y.; Ochiai, H.; Nakajo, E.; Yoshida, Z. *Tetrahedron* **1984**, *40*, 1791−1793.

SCHEME 9. Pathways for Chirality Transfer and Racemization



proposed chairlike transition structure, the *E*- and *Z*-isomers of a single enantiomer of an allylic alcohol will generate enantiomeric, *E*-alkene-containing products (Scheme 8). Competing transition structures leading to the *Z*-alkene-containing products would generate the epimeric alcohols, but *Z*-alkene-containing products are typically not observed in these isomerizations. We therefore took both the enantiopurity and the geometrical purity of the starting materials into account when predicting the enantiopurity of the products (Tables 9 and 10).

Gajewski has pointed out that transfer of chirality in a rearrangement, such as the Cope or Claisen rearrangement, is a hallmark of a concerted process.[33,34] If the major pathway for these isomerizations is a cyclic transition structure, then what is the source of the low level of chirality transfer that we have observed with some substrates? The formation of elimination and condensation side products seems to arise from a competitive ionization−recombination mechanism. Ionization and rapid rotation in the allyl cation prior to recombination could generate a racemic allylic alcohol (Scheme 9). Racemization through unselective attack of some oxygen-centered nucleophile, such as triphenylsilanol or water, on the achiral allylic cation might also be at play. Therefore, the degree of chirality transfer in the isomerization of enantioenriched allylic alcohols provides a unique window into the involvement of ionized intermediates in these isomerization reactions.

The relationship between the efficiency of chirality transfer and the electronic nature of the enantioenriched allylic alcohol reflects the same trend that we observed in the context of product selectivity. For example, in the series of isomerizations leading to the formation of the secondary allylic alcohols (Table 9), the degree of chirality transfer increases as the electron-withdrawing capacity of the aryl substituent increases. This observation supports the idea that a competing ionization−recombination pathway is responsible for racemization of the allylic alcohol. Unfortunately, it appears that lowering the reaction temperature cannot always completely exclude racemization, even though it can completely suppress the elimination and condensation pathways.

We observed the same electronic trend in reactions that generated enantioenriched tertiary allylic alcohols (Table 10). However, in these cases, the higher degree of alkene substitution counterbalanced the effect of electron-withdrawing groups. Comparing trifluoromethyl-substituted alcohols (*R*,*E*)-**20** and (*R*,*E*)-**52**, we found that significant loss of enantiopurity only occurred upon isomerization with (*R*,*E*)-**52** (compare Table 9, entry 4, and Table 10, entry 2). To obtain comparable levels of chirality transfer for tertiary and secondary alcohols, more strongly electron-withdrawing substituents are required on the former. For example, the addition of a second trifluoromethyl substituent led to efficient chirality transfer (Table 10, entry 3). This observation is consistent with the idea that electron-withdrawing substituents disfavor an ionization−recombination pathway, whereas increased alkene substitution has the opposite effect.

The direct attachment of an electron-withdrawing substituent to the allylic system promoted even more efficient chirality transfer (Table 10, entry 4). This observation is surprising because a single cyano group ($\sigma = 0.70$) is a less potent electron-withdrawing substituent when compared to two trifluoromethyl groups ($\sigma_{total} = 1.02$). However, the smaller conjugated system generated upon ionization of (*R*,*E*)-**56** compared to that of (*R*,*Z*)-**54** would be less effective for stabilizing a cationic intermediate. This result again supports the idea that factors which destabilize an allyl cation intermediate will positively affect the level of chirality transfer.

4.4. Effect of Catalyst Structure on Product Selectivity and Chirality Transfer. The partitioning of rhennate ester intermediates between an asynchronous [3,3]-rearrangement and an ionization−recombination pathway accounts for losses in either type of selectivity: product selectivity or chirality transfer. Although electron-withdrawing substituents can improve selectivity, a nonsubstrate-dependent method would be preferable. Because proposed transition structure **vii** is polarized toward the rhenium group, increasing the electron density at rhenium by varying its ligands should decrease this polarization and thus disfavor the competing ionization−recombination pathway responsible for the elimination, condensation, and racemization processes. Therefore, we exchanged less-electron-withdrawing imido groups for the oxo groups on $O_3ReOSiPh_3$ to form imido complex **58**.

Comparison of the isomerizations of **14** with $O_3ReOSiPh_3$ and with imido complex **58** confirms this analysis. Similar levels of product selectivity and chirality transfer could be obtained with both catalysts but at different temperatures. The reaction catalyzed by **58** proceeds cleanly at 23 °C with a good level of chirality transfer (Table 11, entry 1), and the $O_3ReOSiPh_3$-catalyzed reaction only gives comparable results at −78 °C (Table 9, entry 1). It is important to note that the reactions involving imido complex **58** must not proceed through a [3,3]-rearrangement similar to those involving oxo complex **1**. Instead, a less-favorable [1,3]-shift may be occurring, in analogy to that proposed to be operative in the methyl trioxorhenium (MTO)-catalyzed isomerization of allylic alcohols.[17a,21]

The formation of allylic amine products **60** and **61** also yields some interesting mechanistic insights (Scheme 7). The favored isomer is nonconjugated amine **60**, which indicates that these amines were likely not formed through an equilibrium process in which an imido group was exchanged for an oxo group. Studies by Osborn and co-workers on the isomerization of allylic alcohols with mixed oxo/imido−molybdenum complexes have shown that oxo−oxo transfer is favored over imido−oxo interchange.[17b] Therefore, the attack of a free amine on either the intermediate rhennate ester or an ionized intermediate seems more reasonable, especially because the nonconjugated isomer

(33) (a) Gajewski, J. J. *Acc. Chem. Res.* **1980**, *13*, 142−148. (b) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274−277.

(34) As pointed out in ref 33a, if the rate of collapse of the ion pair within a solvent cage is faster than the rate of bond rotation in the allylic cation, chirality transfer will be observed just as in the case of the cyclic transition structure. Therefore, a mechanism involving an extremely short-lived ion pair intermediate cannot be ruled out.

is favored. Overman has pointed out in his studies of the palladium(II)-catalyzed rearrangement of allylic acetates that the observation of such intermolecular trapping products supports the involvement of ionized intermediates.[9a]

The exact nature of the active intermediate in the isomerizations catalyzed by imido complex **58** remains unclear. The use of isolated imido complex **58** does not yield similar results when compared to the in situ generated complex. Consideration of the differences between the reaction conditions with an isolated vs an in situ generated imido complex reveals two differences: the presence of silanol and the presence of silylamine. The addition of triphenylsilanol to an isomerization catalyzed by the isolated imido complex **58** does not lead to a recovery of reactivity. However, the addition of TMSNH^{t}Bu does, suggesting an important role for this reaction component. Additional experiments will be required to fully elucidate the exact mechanism of the reaction with the rhenium−imido complex **58**.

4.5. Isomerizations of Nonconjugated Allylic Alcohols in the Presence of BSA/TMSA. Obtaining high product selectivity in these equilibrium reactions has been a major goal of this work from its inception. The formation of an extended conjugated system proved to be a valid method for obtaining this goal. Preferential silylation of the less-hindered allylic alcohol during the isomerization was a complementary method for substrates devoid of conjugating substituents. Even though it is established that BSA can silylate tertiary alcohols,[35] our results suggest that it silylates secondary and primary alcohols faster. These results also suggest that isomerization with O_3-ReOSiPh$_3$ is fast relative to silylation by BSA. Otherwise, we would have observed lower conversions because silylation would occur before equilibrium could be established in the isomerization reaction.

Our observation that BSA alone is not responsible for the high selectivities observed in these isomerizations does not change the rationale behind the source of this product selectivity. Instead, it raises some interesting questions about the nature of the reactive intermediates. BSA is a nitrogen-centered Lewis base, much like pyridine or diisopropylethylamine. Therefore, it seems reasonable that BSA could also bind to O_3ReOSiPh$_3$ and inhibit its isomerization activity. The role of TMSA may then be similar to that of TMSNH^{t}Bu in the reactions catalyzed by rhenium−imido complex **58**. The addition of TMSA could generate the imido complex (CH$_3$CON)$_3$ReOTMS (**66**). Isomerizations with this less Lewis acidic imido complex may not be inhibited by Lewis bases. Although this analysis seems reasonable, the inability to prepare **66** through a method analogous to **58**, and the fact that **58** in the presence of either BSA or TMSNH^{t}Bu could not give similar results in the isomerization of nonconjugated allylic alcohols, indicates that further studies are required to completely understand the role of BSA and TMSA in these isomerization reactions.

5. Conclusions

The [1,3]-dioxa-Cope rearrangement converts one allylic ester into its 1,3-isomer in a straightforward manner. The O_3-ReOSiPh$_3$-catalyzed process described in this work promotes the corresponding isomerization of allylic alcohols, making it a potentially more atom-economical route relative to the isomerization of allylic esters or carbamates catalyzed by palladium(II) or mercury(II). A thorough study of the scope and limitations of this process has been conducted. High levels of product selectivity, a significant challenge for these equilibrium reactions, can be achieved in the formation of conjugated primary, secondary, and tertiary allylic alcohols. The use of a BSA/TMSA combination as a silylating reagent promotes high product selectivity in the formation of nonconjugated primary and secondary allylic alcohols. Reactions of enantioenriched allylic alcohols have shown that chirality transfer can be quite efficient in the formation of conjugated secondary and tertiary allylic alcohols. Consideration of the trends observed throughout these studies leads to the conclusion that allylic alcohols bearing functional groups that are capable of stabilizing a positive charge (e.g., electron-donating groups, more substituted alkenes) will be more reactive, but less selective, in this isomerization reaction.

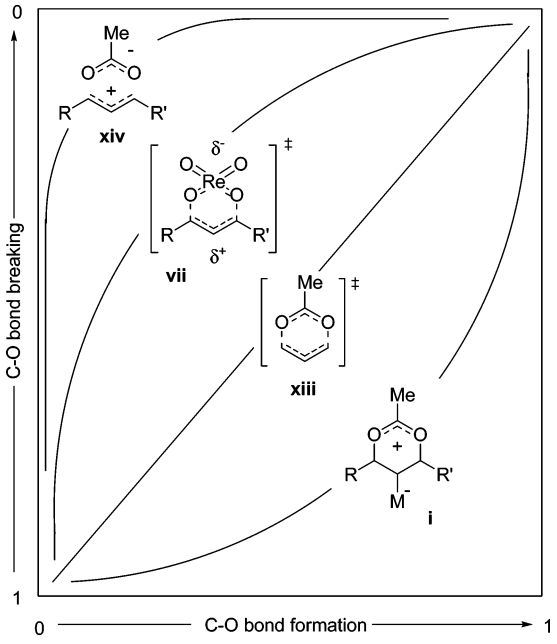


FIGURE 6. Comparison of mechanistically distinct [3,3]-rearrangements.

The relationship of this O_3ReOSiPh$_3$-catalyzed 1,3-isomerization of allylic alcohols to other reactions within the family of [1,3]-dioxa-Cope rearrangements becomes clear when they are considered in the broader context of a More O'Ferrall−Jencks Diagram (Figure 6).[33] Cyclization-induced rearrangements mediated by palladium(II) and mercury(II) show significant carbon−oxygen bond formation prior to carbon−oxygen bond cleavage and therefore lie in the lower right-hand quadrant (**i**). Thermal rearrangements are synchronous processes and lie in the middle of the diagram (**xiii**).[7b] Brønsted acid catalyzed rearrangements proceed through an ionization−recombination pathway and show significant carbon−oxygen bond cleavage prior to carbon−oxygen bond formation. They lie in the upper left-hand quadrant (**xiv**). The proposed cyclic transition structure in this O_3ReOSiPh$_3$-catalyzed 1,3-isomerization (**vii**) occupies a unique position within this scheme where carbon−oxygen bond cleavage precedes significant carbon−oxygen bond formation. However, unlike Brønsted acid catalyzed rearrangements, ionization is not required for these reactions to proceed. Therefore, the properties of a synchronous [3,3]-rearrangement

(35) Sasaki, T.; Nakanishi, A.; Ohno, M. *J. Org. Chem.* **1982**, *47*, 3219−3224.

process are manifest in this $O_3ReOSiPh_3$-catalyzed 1,3-isomerization of allylic alcohols despite its mechanistic differences.

Experimental Section

Experimental procedures and characterization data for novel compounds are provided in the Supporting Information. Experimental procedures and characterization data for compounds **14**, **15**, **18a**, **19a**, **22a**, **23a**, **24**−**31**, **36b**, **37b**, **42a**−**c**, and **44a** were given in a previous communication.[6]

Representative Procedure for Isomerization of Allylic Alcohols without Conjugating Substituents: (*E*)-3-Cyclohexylbut-2-en-1-ol (43a). In a glovebox, 6.6 mg of **1** (0.0125 mmol) was added to a two-necked, 25 mL round-bottom flask fitted with a septum and stopcock adapter. The flask was then removed from the glovebox, and 20 mg of *N*-trimethylsilyl-acetamide (0.125 mmol) and 4 mL of Et_2O were added to it. The solution was stirred for 10 min at 0 °C prior to addition of 140 μL of *N*,*O*-bis-(trimethylsilyl)-acetamide[36] (0.64 mmol) followed by 100 mg of **42a** (0.64 mmol)**.** The reaction quickly turned from yellow to deep purple, and it was allowed to stir at 0 °C for 30 min prior to addition of 40 μL of triethylamine. Removed the ice bath and allowed the solution to stir at room temperature for approximately 10 min before concentration. The residue was then dissolved in 5 mL of MeOH, and 220 mg of K_2CO_3 (0.8 mmol) was added. The suspension was stirred vigorously for 1 h prior to addition of 10 mL of aqueous NH_4Cl solution, extraction with CH_2Cl_2 (2 × 25 mL), and drying over Na_2SO_4. The residue was purified via silica gel chromatography (8:2 hexane/ether) to yield 84 mg of **43a** as a clear oil (84% yield). NMR spectral data agreed with that previously reported in the literature.[2] ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.38 (1H, t, J = 6.8 Hz), 4.15 (2H, d, J = 6.6 Hz), 1.7 (7H, m), 1.64 (3H, s), 1.2 (5H, m). ^{13}C NMR (300 MHz, $CDCl_3$, ppm): δ 144.9, 121.7, 59.6, 47.3, 31.9, 26.8, 26.5, 14.8. HRMS (EI) calcd. for $C_{10}H_{18}O$: 154.1358. Found: 154.1352.

Representative Procedure for Chirality Transfer to Prepare Enantioenriched Secondary Allylic Alcohols: (*E*)-1-(4-(Trifluoromethyl)phenyl)non-1-en-3-ol (21). In a glovebox, added **1** (6 mg, 0.012 mmol) to a 4 mL vial. The solution was removed from the glovebox. Ether was added (2 mL), and the solution was placed in a Cryotrol bath set to −50 °C and stirred for approximately 10 min. **20** (114.3 mg, 0.4 mmol) was added via syringe and stirred at −50 °C for 1 h. Removed from Cryotrol, immediately added 20 μL of triethylamine, and let it stir until it was warmed to room temperature. The solution was concentrated in vacuo and purified directly via silica gel chromatography (8:2 pentane/ether) to obtain 112.9 mg of **21** as an oil (99% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.57 (2H, d, J = 8.4 Hz), 7.47 (2H, d, J = 8.4 Hz), 6.62 (1H, d, J = 15.9 Hz), 6.33 (1H, dd, J = 15.9, 6.0 Hz), 4.32 (1H, dt, J = 6.2, 6.2 Hz), 1.79 (1H, br), 1.65 (2H, m), 1.35 (8H, m), 0.90 (3H, t, J = 7.1 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$, ppm): δ 140.5 (d, J = 5.4 Hz), 135.5, 129.6 (q, J = 129 Hz), 128.8, 126.8, 125.7 (q, J = 15.4 Hz), 124.4 (q, J = 108.1 Hz), 72.9, 37.6, 32.0, 29.4, 25.6, 22.8, 14.3. HRMS (EI) calcd for $C_{16}H_{21}F_3O$: 286.1544. Found: 286.1537. Enantiomeric excess determined to be 95% by chiral HPLC (OD-H column, 1% *i*-PrOH in hexanes, 1 mL/min). $[\alpha]_D$ = −7.7 (24 °C, $CHCl_3$, c = 1.0).

Representative Procedure for Chirality Transfer to Prepare Enantioenriched Tertiary Allylic Alcohols: (*E*,*R*)-4-Hydroxy-4,8-dimethyl-nona-2,7-diene Nitrile ((*R*,*E*)-57). In a glovebox was added **1** (7 mg, 0.014 mmol) to a 4 mL vial. The solution was removed from the glovebox, and 3 mL of toluene was added followed by (*R*,*E*)-**56** (100 mg, 0.56 mmol). The reaction was allowed to stir for 10 min at 23 °C prior to addition of 20 μL of triethylamine. It was concentrated in vacuo and purified directly via silica gel chromatography (6:4 hexane/ether) to obtain 95 mg of (*R*,*E*)-**56** as a clear oil (95% yield). ^{1}H NMR (300 MHz, C_6D_6, ppm): δ 5.97 (1H, d, J = 16.0 Hz), 5.17 (1H, d, J = 16.0 Hz), 4.99 (1H, m), 1.71 (2H, m), 1.46 (3H, s), 1.12 (2H, m), 0.83 (1H, s), 0.72 (3H, s). ^{13}C NMR (75.4 MHz, C_6D_6, ppm): δ 160.45, 132.56, 124.56, 118.04, 98.09, 73.35, 41.82, 27.80, 26.11, 23.04, 18.04. HRMS (EI) calcd for $C_{11}H_{17}NO$: 179.1307. Found: 179.1310. IR (thin film): 3468, 2970, 2927, 2225, 1632, 1451, 1376, 1251, 1195, 1124. Enantiomeric excess determined to be 91.8% by chiral HPLC (OB column, 5% *i*-PrOH in hexanes, 1 mL/min, 220 nm). $[\alpha]_D$ = 3.9 (20 °C, EtOH, c = 1.1).

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Supporting Information Available: Experimental procedures, compound characterization data, and ^{1}H and ^{13}C NMR spectra are provided for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) BSA was distilled by a short path at 70 °C/35 mmHg prior to use.