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Conformationally Biased Ketones React Diastereoselectively with Allylmagnesium Halides

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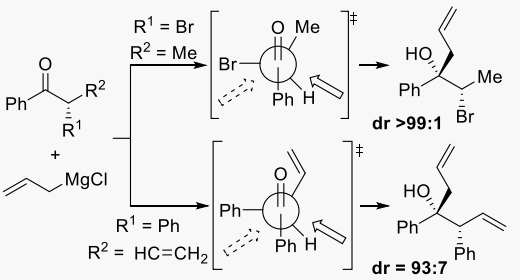
ABSTRACT: The addition of the highly reactive reagent allylmagnesium halide to α-substituted acyclic chiral ketones proceeded with high stereoselectivity. The stereoselectivity cannot be analyzed by conventional stereochemical models because these reactions do not conform to the requirements of those models. Instead, the stereoselectivity arises from the approach of the nucleophile to the most accessible diastereofaces of the lowest-energy conformations of the ketones. High stereoselectivity is expected, and the stereochemical outcome can be predicted, with conformationally biased ketones that have sterically distinguishable diastereofaces wherein only one face is accessible for nucleophilic addition. The conformations of the ketones can be determined by a combination of computational modeling and, in some cases, structure determination by X-ray crystallography.



INTRODUCTION

The stereochemical outcomes of nucleophilic additions to carbonyl compounds are typically analyzed using stereochemical models such as the Felkin–Anh[1,2] and chelation-control models.[3,4] These models require that the widest range of competing transition states are accessible, leading to product distributions that reflect the relative energies of different transition states.[4] In the reactions of ketones with highly reactive nucleophiles, such as allylmagnesium halides, the chelation-control and Felkin–Anh models fail to explain the observed stereoselectivities, however.[4,5] This inability to follow the models occurs because the rate of carbon–carbon bond formation is so fast that each encounter complex between the electrophile and the nucleophile proceeds to the product before it can dissociate and form a new complex that might lead to a lower-energy transition state.[3,5,6] Considering that the complexation step is itself not likely to be stereoselective, low diastereoselectivity is observed in many cases.[3−5] Nevertheless, stereoselectivity is observed for some reactions, usually for transformations involving particularly sterically hindered ketones.[7−16] When a sterically hindered ketone is energetically restricted to a conformation in which one diastereoface of the carbonyl compound is inaccessible to the nucleophile, high diastereoselectivity can be achieved.[4]

Herein, we provide evidence that reactions of highly reactive nucleophiles with relatively unhindered acyclic chiral ketones can be stereoselective even if they do not conform to accepted models for stereoselection. Reactions with highly reactive nucleophiles, exemplified by allylmagnesium chloride, cannot be analyzed by considering all the possible competing low-energy transition states. Instead, few reaction pathways are available. The stereoselectivity is high if the ketone substrate is generally biased to one particular conformation (or closely related conformers), resulting in preferential addition to only one diastereoface of the carbonyl group. Considering how rapidly the carbon–carbon bond-forming reaction occurs, interconversion between stereoisomeric encounter complexes must be slower than irreversible bond formation. It is only the destabilizing steric interactions that develop upon the approach of the reagent to one diastereoface of the carbonyl group (that is, steric-approach control)[17−19] that prevent attack from that face, resulting in a stereoselective reaction.[20]

RESULTS AND DISCUSSION

In contrast to many examples of poorly selective additions of highly reactive Grignard reagents to chiral acyclic ketones,[21−28] the addition reactions to some acyclic α-substituted ketones proceeded with high stereoselectivity (Scheme 1). The addition of allylmagnesium chloride[3,5,29] to racemic[30] α-halogenated propiophenones **1** and **3** produced alcohols **2** and **4**, respectively, with high stereoselectivity. The reaction of α-bromoketone **3** also formed the 1,2-*cis* epoxide **5**, which would be formed by cyclization of the intermediate magnesium alkoxide.[31] The cyclization was slower than the addition, however, as the amount of **5** increased when the reaction

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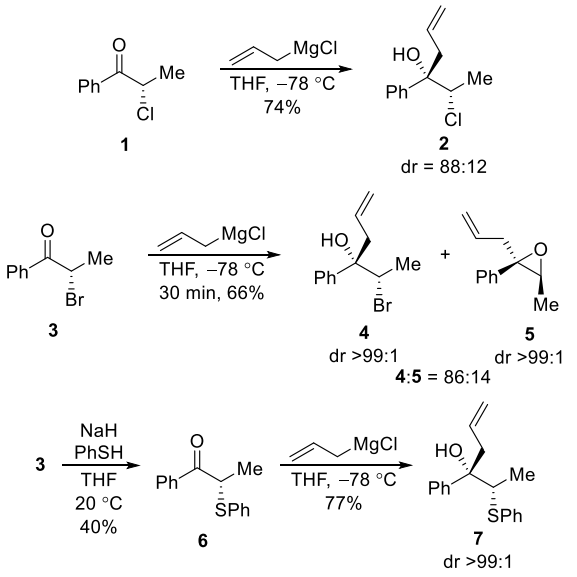
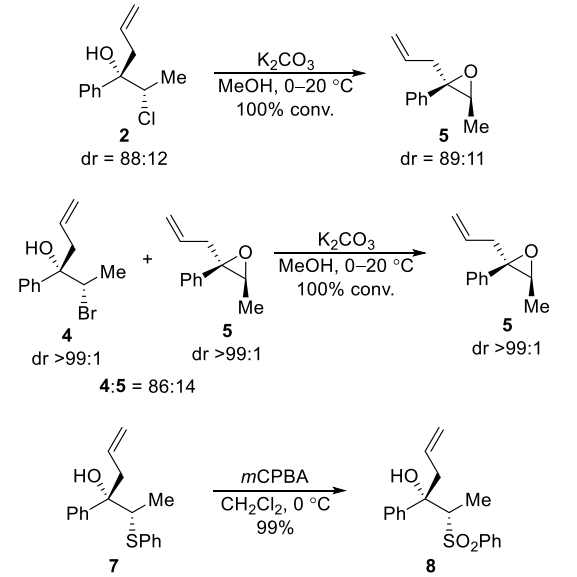
Scheme 1. Selective Additions of Allylmagnesium Chloride to α-Substituted Propiophenones



mixture was stirred for a longer time prior to the addition of methanol to quench any unreacted reagent. Adding methanol only five seconds after the addition of the reagent resulted in a small amount (∼5%) of epoxide **5** along with a 95% conversion to the addition product, suggesting that cyclization was still rapid. Epoxide **5** was not observed in the reaction with the α-chloroketone **1**, however, likely because the magnesium alkoxide was not sufficiently nucleophilic to displace the weaker leaving group, namely the chloride ion.[32] Allylation of the related α-thiophenyl ketone **6** also occurred with high diastereoselectivity, forming alcohol **7** as a single diastereomer (dr >99:1).

The reactions of all three ketones proceeded with the same 1,2-*anti* stereochemistry. The configurations of alcohols **2** and **4** were determined by chemical correlation of the halohydrins and epoxide **5** (Scheme 2).[33,34] X-ray crystallographic analysis

Scheme 2. Stereochemical Proofs of Additions to α-Substituted Propiophenones



of sulfone **8**, formed from the oxidation of thioether **7**, established the relative stereochemistry of this product. The stereochemical courses of these reactions are consistent with nucleophilic addition to the same face of each ketone (i.e., addition *anti* to the α-substituent), as might be expected from addition through the favored transition state of the polar Felkin−Anh model (Figure 1, transition state **9**). This

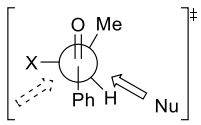
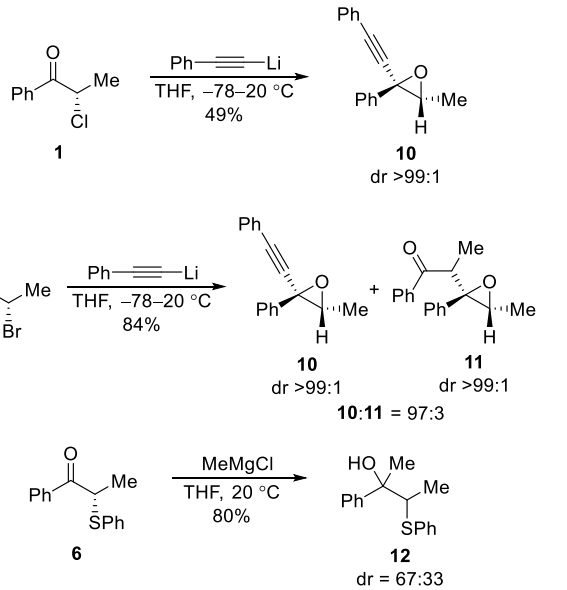


Figure 1. Polar Felkin−Anh transition state of α-halopropiophenones and α-thiopropiophenones.

explanation for the stereocontrol for the reactions of α-halopropiophenones **1** and **3** is unsatisfying, however, considering that many additions of nucleophiles to acyclic[35] and cyclic[7] α-halogenated ketones occur with low stereoselectivity.

The conventional explanation to explain stereoselectivity by invoking reaction through transition state **9** also is unlikely considering the stereoselectivities observed with other nucleophiles. It was not possible to compare the stereoselectivities of the additions to α-halogenated ketones **1** and **3** with allylmagnesium chloride to the stereoselectivities observed with other Grignard reagents such as MeMgCl and *n*-PrMgCl because the dehalogenation of the ketones occurred faster than the addition with those reagents.[7,36,37] The additions of an alkynyllithium reagent to α-haloketones **1** and **3**, however, were highly diastereoselective (Scheme 3).[38] Unlike the reactions of organomagnesium reagents illustrated in Scheme 1, these reactions formed epoxide **10** directly, likely because lithium alkoxides are more nucleophilic than magnesium alkoxides.[39,40] The stereochemical outcomes of these reactions were assigned by comparing the spectra of epoxide **10** with the spectra of the known epoxide.[38] In the

Scheme 3. Additions of Organometallic Reagents to α-Substituted Propiophenones



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case of α-bromoketone **3**, small quantities of an additional epoxide, **11**, were formed. This product likely forms by lithium−halogen exchange to form the enolate, which then adds to ketone **3** and then cyclizes. The configuration of epoxide **11** was not proven but was assigned by analogy to the configuration of epoxide **10**.

Finding a comparison between the reactions of allylmagnesium reagents and other Grignard reagents was more straightforward for α-thiophenyl ketone **6** than it was for the halogenated ketones. The addition of methylmagnesium chloride to ketone **6** occurred cleanly but with low stereoselectivity (dr = 67:33). This low selectivity was also observed for the addition of MeLi to this ketone.[41]

The configurations of the products formed by the addition of the alkynyllithium reagent to ketones **1** and **3** are opposite to those observed for the reactions involving the allylmagnesium reagent. Justifying these results would require applying the Felkin−Anh model (Figure 2), where the methyl group

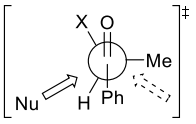

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Figure 2. Felkin−Anh transition state of α-halopropiophenones and α-thiopropiophenones.

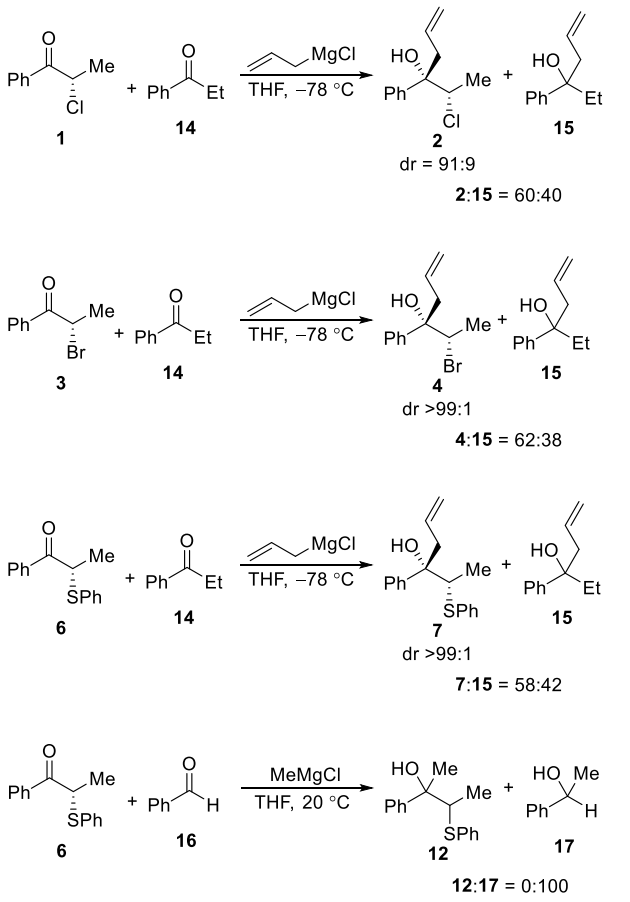
serves as the large substituent, and not the polar Felkin−Anh model, where the heteroatom serves as the large substituent (that is, transition state **13**, not transition state **9**).

Collectively, the results in Schemes 1 and 3 suggest that caution should be exercised when using the Felkin−Anh stereochemical model, in either of its forms, to predict stereoselectivities. The reactions of the allylmagnesium reagent usually do not occur with high diastereoselectivity. In this case, however, the major products are consistent with the polar Felkin−Anh model wherein the heteroatom occupies a position nearly perpendicular to the π-system of the carbonyl group. On the other hand, the additions of the alkynyllithium reagent to α-haloketones **1** and **3** suggest that the Felkin−Anh model, not its polar variant, would be consistent with these results. Finally, the low stereoselectivity in the case of the addition of MeMgCl to the α-thiophenyl ketone **6** illustrates the difficulty of predicting the outcomes of reactions.

Competition experiments revealed that applying the polar Felkin−Anh model to understand the diastereoselectivities of additions of allylmagnesium chloride (Scheme 1) would be difficult. This model requires that the additions occur under a Curtin−Hammett kinetic scenario,[42] but experiments show that complexation between the two reagents is likely not reversible. The competition experiments performed under optimized conditions[5] provided reproducible, although likely approximate, values for the relative rates considering how rapid the reactions are.[29] Additions of the allylmagnesium reagent to the α-substituted ketones and propiophenone (**14**) occurred at comparable rates (Scheme 4). These competition experiments reveal that the rate of carbon−carbon bond formation from an encounter complex or a Lewis acid−base complex is faster than the rate of dissociation of that complex; thus, the overall rate of addition occurs at rates approaching diffusion.[5,29]

Competition experiments between ketone **6** and benzaldehyde (**16**) with MeMgCl, however, demonstrate that additions

Scheme 4. Competition Experiments[a] between α-Substituted Ketones and Propiophenone or Benzaldehyde with Organometallic Reagents[b]



[a]Competition experiments involved the dropwise addition (one drop every minute) of the diluted nucleophile (≤0.2 M) to a rapidly stirring mixture of 4 equiv of each electrophile at a low concentration (≤1.0 M). [b]Ratios for all competition experiments were determined by $^{13}C\{^{1}H\}$ NMR spectroscopy.[43]

of this Grignard reagent can be analyzed by models such as the Felkin−Anh or chelation-control models because the prerequisites of these models are met. The rates of complexation and decomplexation are faster than that of addition, so the full range of possible transition states can be accessed. Therefore, it is possible for addition to occur to any low-energy conformation. In this case, however, the reaction was not stereoselective.

Given that neither the Felkin−Anh model nor its polar variant can be used to predict stereoselectivities, other possible origins of the stereoselectivity for the addition of nucleophiles, particularly for allylmagnesium halides, should be considered. In the case of highly hindered cyclic ketones, understanding the inherent conformations of the ketone led to explanations of the stereochemical outcome of the reaction through an attack on the more exposed diastereoface of the carbonyl group.[3,7,8,44] Although the energy of a conformer of a substrate contributes to the transition-state energies of its reactions,[45] it is not obvious that conformational preferences could be the decisive factor in more conformationally flexible and relatively unhindered acyclic ketones.

Elucidating the conformational preferences of the ketones provided insight into the origin of the stereoselectivities

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observed for the addition of allylmagnesium reagents to α-substituted propiophenones. Calculations using density functional methods both in the gas phase and in THF as the solvent[46] revealed that the α-substituted ketones exhibited strong conformational biases. These ketones adopt a conformation in the ground state that resembles the conformer invoked in the transition state of the polar Felkin–Anh model (Figure 1, transition state **9**). This conformer was the lowest-energy conformer, and the conformers resembling transition state **13** were >1 kcal/mol (X = Cl) and >2 kcal/mol (X = Br or SPh) higher in energy when calculated at the B3LYP/aug-cc-pVDZ level of theory[47] using the polarized continuum model to simulate THF as the solvent. This combination of functional and basis set has been used to determine the conformational preferences of other halogenated ketones.[47] This orientation of the substituents in the lowest-energy conformer, which promotes hyperconjugative interactions of $\sigma_{C-X} \rightarrow \pi^*_{C-O}$, is often observed in computational studies,[48] solution-phase experiments,[49] and solid-phase structures of α-chloroketones,[50−54] α-bromoketones,[55−59] and α-thiophenyl ketones.[60−64] The greater preference for conformation **9** when X = Br and X = SPh compared to that when X = Cl can be attributed to the carbon–bromine bond and the carbon–sulfur bond being better electron donors than the carbon–chlorine bond.[65−67]

The calculated low-energy conformation of 2-chloropropiophenone (ketone **1**) was nearly identical to that observed by single-crystal X-ray diffraction. Determining the molecular structure and analyzing the conformation of ketone **1** itself by X-ray diffraction was not feasible because the compound exists as an oil at room temperature. Using a single-step crystallization protocol,[68,69] ketone **1** was captured within a host framework generated from guanidinium (G) and organosulfonate (S) ions to produce a crystalline inclusion compound. The framework was selected from a family of hydrogen-bonded host frameworks that form persistent hydrogen-bonded sheets, which are connected by organosulfonate "pillars" that create cavities between the sheets.[70] This protocol is particularly useful for determining the molecular structure, as well as the relative stereochemistry and absolute configuration, of compounds that cannot be crystallized directly.[69] The slow evaporation of a methanol–ethanol solution containing a minute amount (<1 mg) of racemic ketone **1** and the guest-free apohost (guanidinium)$_2$biphenyl disulfonate (G_2BPDS, **18**) afforded a colorless plate of an inclusion compound with the formula G_2BPDS⊃(2-chloropropiophenone).

Single-crystal X-ray diffraction revealed that the host framework adopted a bilayer architecture wherein BPDS pillars spanned the hydrogen-bonded GS sheets, creating cavities flanked by pillars that encapsulated two molecules of the ketone guest molecule (Figure 3). Water molecules incorporated into the GS sheets bridged the bilayers. The structure was refined in the space group *Cc*, with each cavity containing a pair of the enantiomers related by the *c*-glide operation. The conformation of the ketone guest (Figure 3B), as measured by the Cl–C–C–O dihedral angle of 98.5°, was nearly identical to that from the calculated structure, which had a dihedral angle of 103.7°. This conformation, which closely resembles the structure of the carbonyl compound in the polar Felkin–Anh transition state (conformer **9**), positions the carbon–chlorine bond in an orientation that maximizes hyperconjugative interactions and suggests that the nucleophile

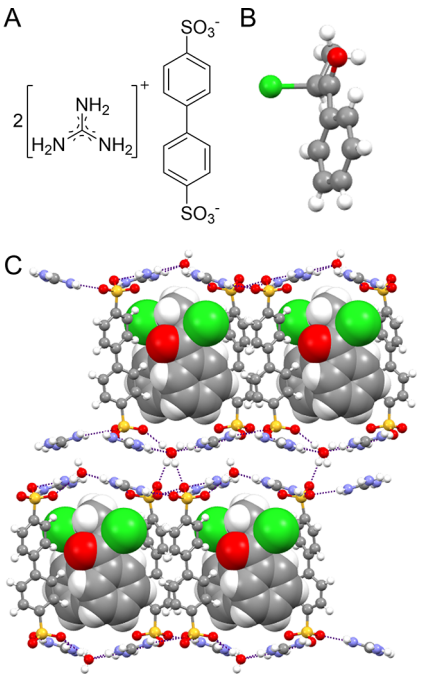

Figure 3. (A) Guanidinium and biphenyldisulfonate ions comprising the G_2BPDS apohost **18**. (B) Ball-and-stick representation of one of the ketone **1** enantiomers confined within the G_2BPDS framework cavities, revealing the polar Felkin–Anh conformation. (C) Crystal structure of G_2BPDS⊃(2-chloropropiophenone). The host cavities contain racemic pairs of ketone **1**. Guest molecules are rendered as space-filled models, and frameworks are rendered as ball-and-stick.

would need to attack from the diastereoface opposite that atom. Although the influence of the host framework on the conformation of the guest cannot be ignored, the agreement between the solid-state and calculated structures, combined with the stereochemical outcomes of the addition reactions, supports the argument that the conformational preference of the ketone plays a significant role in the observed stereoselectivity.

The calculated conformational preferences correlate with the observed diastereoselectivities. The higher selectivities observed in the reactions of α-bromo and α-thiophenyl ketones **3** and **6** with allylmagnesium chloride can be rationalized by considering the approach of the nucleophile to the sterically distinct diastereofaces of these more conformationally biased ketones (Figure 1). Mechanistically, the additions of allylmagnesium reagents to ketones should occur though a concerted transition state with allylic transposition.[6] Addition through a six-membered-ring transition state[6,71] likely occurs more rapidly to the sterically accessible diastereoface of the ketone (the right side of the carbonyl group of structure **9**) after complexation than to the face blocked by the α-substituent (the left side of structure **9**).

Given the high diastereoselectivities of additions of allylmagnesium halides to ketones with Cl, Br, and S atoms at the α-position, subsequent experiments addressed the selectivities of additions to ketones with an O atom at the α-position. This possibility seemed likely to lead to a low diastereoselectivity considering that the presence of an α-alkoxy group in a ketone does not lead to stereoselective additions of allylmagnesium reagents.[21−23] By contrast, the addition of allylmagnesium chloride to α-silyloxy acyclic ketones, which were prepared according to Scheme 5, occurred

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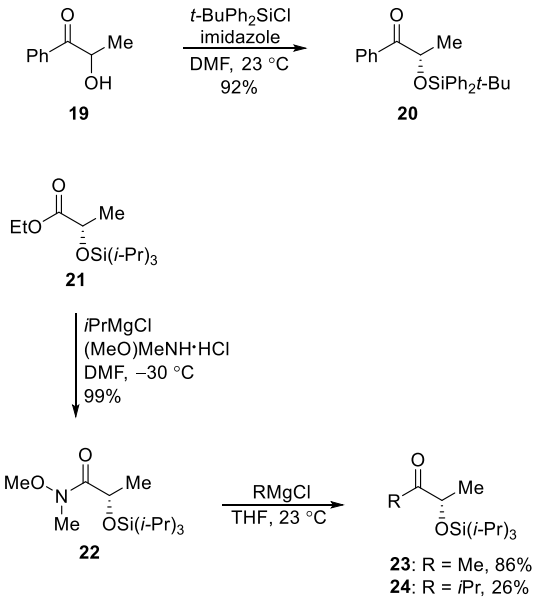
Scheme 5. Preparation of α-Silyloxy-Substituted Ketones



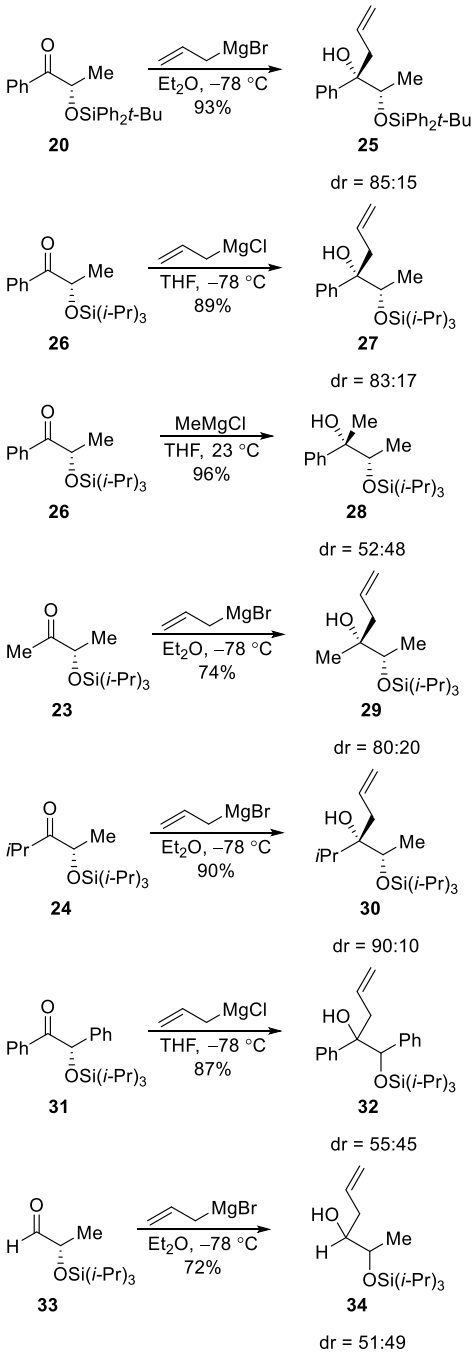
rapidly and, in many cases, stereoselectively at −78 °C (Scheme 6).[3] The only cases where reactions were not stereoselective were for ketones where the stereogenic center had two larger groups (ketone **31**, which had a silyloxy group and a phenyl group) and an aldehyde (**33**). The reactions of a silyloxy ketone, **26**, with a less reactive Grignard reagent, MeMgCl, did not occur at −78 °C. The addition of this reagent required warming the reaction mixture to room temperature, but this reaction was not stereoselective (dr = 52:48).

The configurations of the products of these reactions were established by a combination of crystallography and chemical correlation (Scheme 7). The relative configuration of alcohol **25** was determined through chemical correlation. Silyloxy-protected alcohol **27**, whose stereochemistry was previously reported,[3] and OTBDPS-protected alcohol **25** were both deprotected to yield alcohol **35**. Crystalline carbamate **40**, prepared from silyloxy-protected alcohol **30**, was analyzed by X-ray crystallography. The relative stereochemistry of alcohol **29** was not established but was tentatively assigned by analogy to alcohols **27** and **30**.

Competition experiments using α-silyloxy ketones **26** and **31** indicated that the allylmagnesium reagents reacted rapidly with the ketones after complexation, precluding the equilibration of the complexes (Scheme 8). Considering that propiophenone (**14**) and deoxybenzoin (**41**) react at rates that approach the diffusion limit, additions to ketones **26** and **31** also must occur upon the encounter of the reagent and the ketone. Consequently, these reactions do not occur in a Curtin−Hammett kinetic scenario; thus, the selectivity cannot be rationalized by the Felkin−Anh model.

Just as with the α-halogenated and α-thiophenyl ketones, the conformation of the ketone and the steric hindrance provided by the silyloxy group could be responsible for the stereoselectivity. Unlike the halogenated ketones, however, hyperconjugative interactions would not determine the low-energy ground-state conformations of ketones **20** and **26** because the carbon−oxygen bond is not a strong electron donor.[66,72] The selectivity also does not arise from chelation-control because the large silyloxy protecting groups prevent the oxygen atom

Scheme 6. Additions of Grignard Reagents to α-Silyloxy-Substituted Ketones and an α-Silyloxy-Substituted Aldehyde



from engaging in chelation.[73−76] Moreover, no kinetic acceleration[77] was noted in the competition experiments shown in Scheme 8.

Computational studies provide some insight into the origin of the stereoselectivity. Although α-silyloxy ketones can exhibit a range of conformers in the solid state,[78−82] calculations for ketone **20** in THF (B3LYP/6-31G* with the polarized continuum model[83] to account for the influence of solvent)[84] suggest that the conformer with the dipoles aligned, as illustrated by conformer **43** (Figure 4), represents the lowest-energy family of conformers (by more than 1 kcal/mol). These conformers position the silyloxy group on one face of the carbonyl group and the alkyl group on the other face, differing

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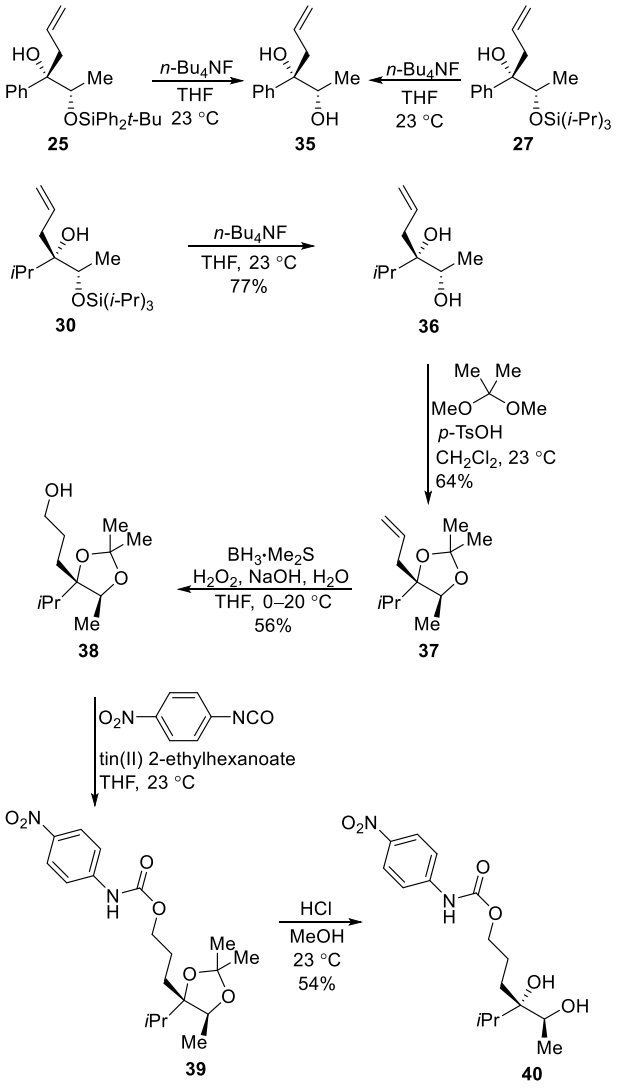
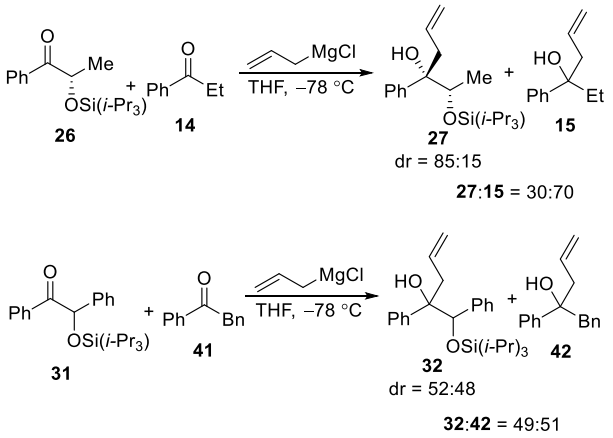
Scheme 7. Derivatizations and Chemical Correlations of α-Silyloxy-Substituted Propiophenone Addition Products



Scheme 8. Competition Experiments[a] between α-Silyloxy Ketones and Unhindered Ketones with Allylmagnesium Chloride[b]



[a]Competition experiments involved the dropwise addition (one drop every minute) of the diluted nucleophile (≤0.2 M) to a rapidly stirring mixture of 4 equiv of each electrophile at a low concentration (≤1.0 M). [b]Ratios for all competition experiments were determined by $^{13}C\{^{1}H\}$ NMR spectroscopy.[43]

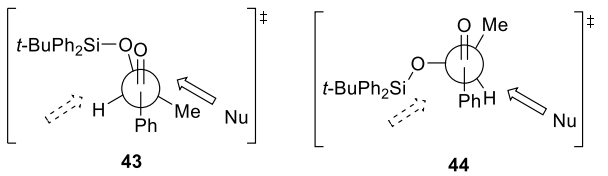


Figure 4. Conformational preferences of α-silyloxy-substituted propiophenones.

only in the orientation of the groups on silicon. In the case of ketone **20**, addition would be expected to occur from the more exposed face (Figure 4). This mode of attack is indistinguishable from addition through a Felkin–Anh transition state (**44**), although the energies of conformers resembling **44** are >2 kcal/mol higher than those of the lower-energy structures resembling **43**. Attack through transition state **43** is consistent with the major products observed with ketones **23**, **24**, and **26**.

This analysis also explains the lack of stereoselectivity for the addition of allylmagnesium chloride to ketone **31** (Scheme 6). In that case, the approach of the nucleophile from either face would be sterically disfavored due to unfavorable steric interactions with large substituents, such as Ph and OSi(*i*-Pr)$_3$, from either face. As a result, allylmagnesium chloride would add to ketone **31** from either diastereoface of a conformer resembling **43** with comparable difficulty.

The presence of a heteroatom at the α-carbon atom of a ketone is not required for stereoselective reactions of allylmagnesium reagents to be observed. Ketone **46**, bearing a phenyl group and a vinyl group at the stereogenic center, reacted with allylmagnesium chloride with high diastereoselectivity to form alcohol **47** (Scheme 9, dr = 93:7).[44] The relative stereochemistry of the addition product was determined by X-ray crystallographic analysis of epoxide **49**, which was synthesized from alcohol **47** (Scheme 10). Competition experiments revealed that, just as for the ketones with a heteroatom at the α-carbon atom, the addition cannot be explained by the Felkin–Anh model because the rates of addition of allylmagnesium chloride were the same for ketone **46** and propiophenone.

The stereoselectivity observed with allylmagnesium reagents was also observed with an alkyl Grignard reagent. The addition of *n*-propylmagnesium chloride to ketone **46** yielded both the addition product, alcohol **50**, and the reduction product,[85] alcohol **45**, with high diastereoselectivity (Scheme 11). Chemical correlation of the addition product **50** with allylated alcohol **47**, whose structure was established by X-ray crystallography (Scheme 10), confirmed that the configurations of the two products were consistent with nucleophilic addition from the same face (Scheme 12). Unlike the reaction with allylmagnesium chloride, the reaction with *n*-propylmagnesium chloride does conform to the conditions of the Felkin–Anh model. A competition experiment between ketone **46** and propiophenone (**14**) indicated that the addition of *n*-propylmagnesium chloride to ketone **46** was considerably slower than the addition to propiophenone, suggesting that this reaction occurred under a Curtin–Hammett kinetic regime. As a result, this addition may proceed through a broad range of possible complexes en route to the lowest-energy transition state.

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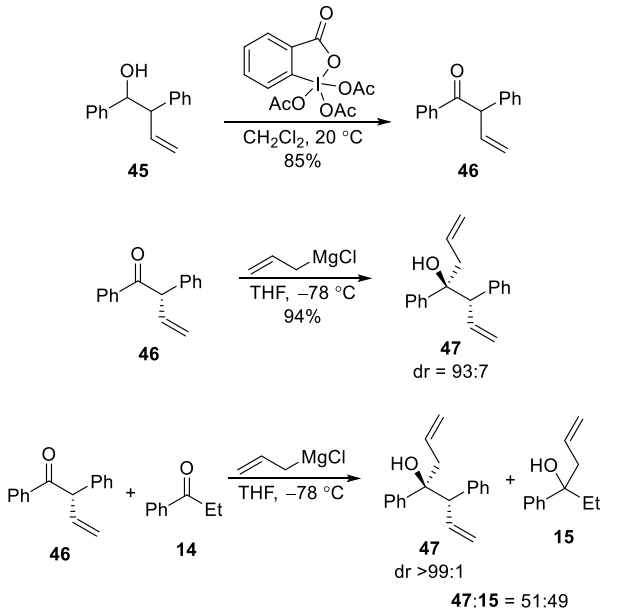
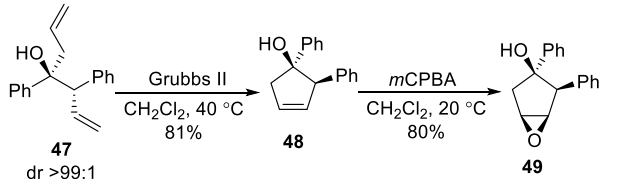
Scheme 9. Selective Addition of Allylmagnesium Chloride to α-Vinyl-Substituted Ketone 46 and Competition Experiment[a] between Ketone 46 and Propiophenone with Allylmagnesium Chloride[b]



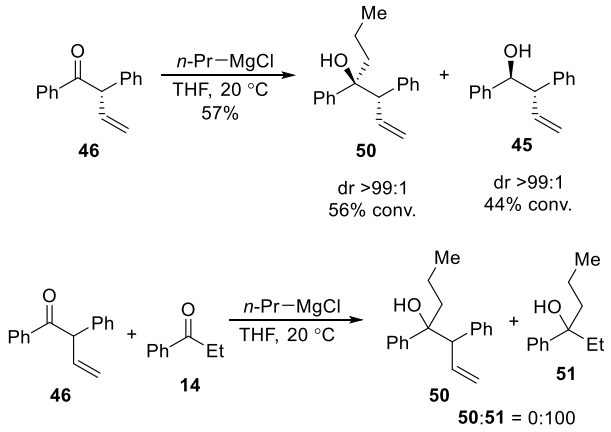
[a]Competition experiments involved the dropwise addition (one drop every minute) of the diluted nucleophile (≤0.2 M) to a rapidly stirring mixture of 4 equiv of each electrophile at a low concentration (≤1.0 M). [b]Ratios for all competition experiments were determined by $^{13}C\{^{1}H\}$ NMR spectroscopy.[43]

Scheme 10. Stereochemical Proof of Alcohol 47



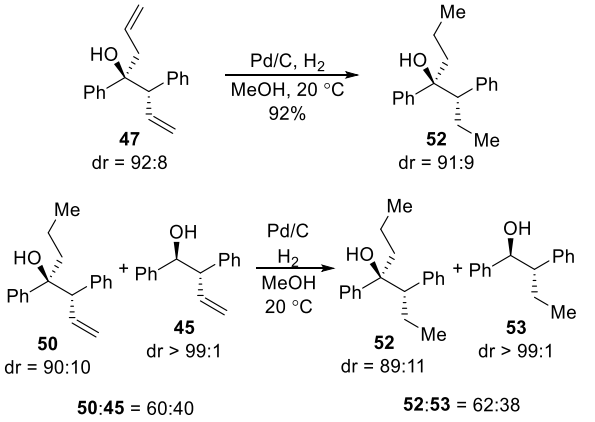
The stereoselectivity of additions of allylmagnesium reagents to α-phenyl-substituted ketone **46** can be explained by examining the preferred conformation of the carbonyl compound, just as it explained reactions with the heteroatom-substituted ketones. Computational analysis (B3LYP/6-31G* in THF)[84] of ketone **46** suggests that it favors conformer **54** by >1 kcal/mol over any conformer that places the phenyl group in another position (Figure 5).[46] This orientation of an aromatic ketone is exhibited in X-ray crystal structures for many α-phenyl-substituted ketones.[86−90] Considering that ketone **46** likely exists predominantly in this conformation, complexation and a subsequent attack from the more accessible face would form the major product. Although this result can be interpreted using the Felkin−Anh model, the stereochemical outcome is not because this transition state is favored over all other possible ones. Instead, the ketone adopts the structure resembling the Felkin−Anh transition state, and rapid addition occurs only to the more accessible face. In the case of *n*-propylmagnesium chloride, however, this transition state could be the lowest-energy one considering that this reaction occurs in a Curtin−Hammett kinetic regime. Despite the difference in the reactivities of these nucleophiles, the additions of allylmagnesium chloride and alkylmagnesium chloride to ketone **46** both proceed with high diastereoselectivities for the same diastereomer but for different reasons.

Scheme 11. Addition of *n*-Propylmagnesium Chloride to α-Vinyl-Substituted Ketone 46 and Competition Experiment[a] between Ketone 46 and Propiophenone with *n*-Propylmagnesium Chloride[b]



[a]Competition experiments involved the dropwise addition of the nucleophile to a rapidly stirring mixture of 4 equiv of each electrophile at a low concentration (≤1.0 M). [b]Ratios for all competition experiments were determined by $^{13}C\{^{1}H\}$ NMR spectroscopy.[43]

Scheme 12. Stereochemical Correlation of Alcohols 47 and 50 to Alcohol 52



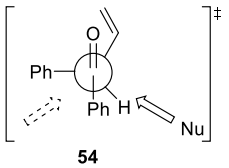


Figure 5. Conformational preferences of α-vinyl-substituted deoxybenzoin.

The above analyses of the reactions of acyclic ketones with allylmagnesium halides rely on the assumption that the highly reactive nucleophile can attack only from the more accessible face of a low-energy conformer. Nevertheless, these ketones are conformational flexible, and it is possible that the stereochemistry could result from other modes of attack. Consequently, the assumption that a sterically large group could hinder the attack of the highly reactive reagent was tested.

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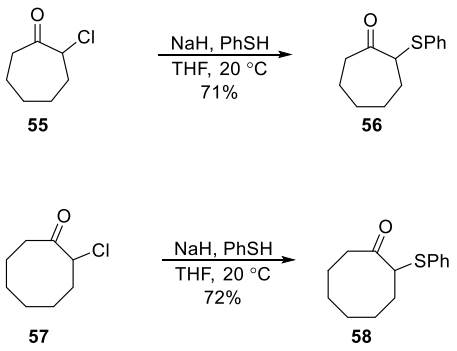
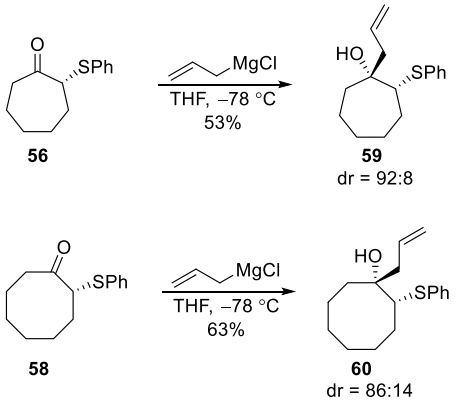
Reactions of cyclic ketones provide insight into the approach of nucleophiles that would not be evident with acyclic systems. The reactions of sulfur-containing substrates were chosen because these substrates were not subject to the reductions observed for the α-halogenated substrates.[7] Initially, it was important to determine whether α-thiophenyl ketones could function as models for the halogenated ketones. This hypothesis was tested with reactions of medium-ring ketones, which were synthesized according to Scheme 13. Much like the

Scheme 13. Preparation of α-Thiophenyl Cyclic Ketones



reactions of α-halogenated cycloheptanone and α-halogenated cyclooctanone,[7] the allylations of α-thiophenyl cyclic ketones **56** and **58** were stereoselective (Scheme 14).[41] The formation

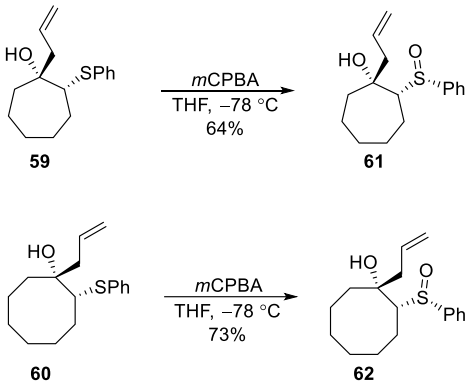
Scheme 14. Additions of Allylmagnesium Chloride to α-Thiophenyl Cyclic Ketones



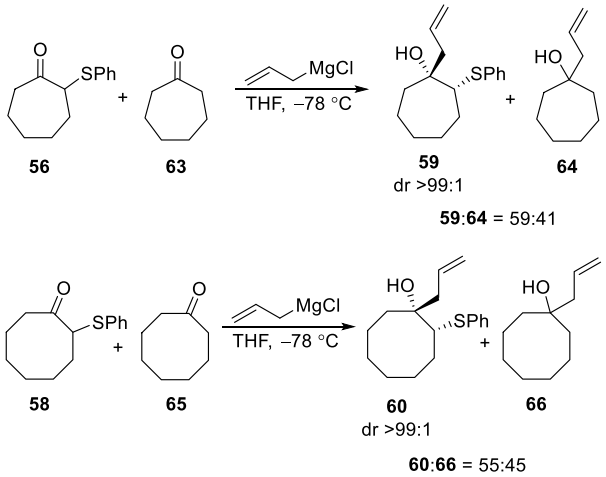
of the 1,2-*anti* product as the major diastereomer was determined by X-ray crystallographic analysis of sulfoxides **61** and **62**, which were formed by the oxidation of sulfides **59** and **60**, respectively (Scheme 15).

Competition experiments involving hindered ketones **56** and **58** and cyclic ketones **63** and **65** illustrate that the additions of allylmagnesium chloride do not conform to a Curtin−Hammett kinetic scenario. The additions to substituted and unsubstituted ketones occurred at similar rates (Scheme 16), indicating that bond formation occurred rapidly once the two reactants approached each other. These cyclic substrates further exemplify an inability to apply the Felkin−Anh model because the constraints of the cyclized system preclude a Felkin−Anh transition state.[7] Regardless of the α-substituent, the nucleophilic approach to the carbonyl group is governed by the ring itself, which blocks the nucleophile's approach to the internal face of the ketone and forces addition to occur from

Scheme 15. Stereochemical Proofs of Additions to α-Thiophenyl Cyclic Ketones



Scheme 16. Competition Experiments[a] between Ketones 56 and 58 and Cyclic Ketones with Allylmagnesium Chloride[b]



[a]Competition experiments involved the dropwise addition (one drop every minute) of the diluted nucleophile (≤0.2 M) to a rapidly stirring mixture of 4 equiv of each electrophile at a low concentration (≤1.0 M). [b]Ratios for all competition experiments were determined by $^{13}C\{^{1}H\}$ NMR spectroscopy.[43]

the external face. Selectivity in these larger ring systems arises from faster addition to the sterically uncongested face of the ketone (Figure 6).[7]

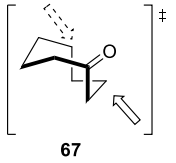


Figure 6. Nucleophilic approach to cyclooctanone.

In contrast to reactions of medium-ring cyclic ketones, reactions of α-thiophenyl cyclohexanone (**68**) with allylmagnesium chloride proceeded with low diastereoselectivity. The two diastereomers of the product could be formed by axial or equatorial attack on either the axial conformer, which should be favored in solution;[48,49] an attack on the equatorial conformer; or an attack on both. A competition experiment between ketone **68** and unhindered ketone **70** indicated that these two ketones reacted at the same rate (Scheme 17); thus,

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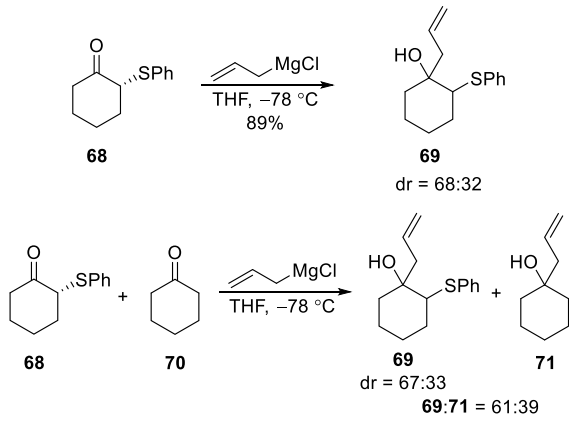
Scheme 17. Addition of Allylmagnesium Chloride to α-Thiophenyl Ketone 68 and Competition Experiment[a] between Ketone 68 and Cyclohexanone (70) with Allylmagnesium Chloride[b]



[a]Competition experiments involved the dropwise addition (one drop every minute) of the diluted nucleophile (≤0.2 M) to a rapidly stirring mixture of 4 equiv of each electrophile at a low concentration (≤1.0 M). [b]Ratios for all competition experiments were determined by $^{13}C\{^{1}H\}$ NMR spectroscopy.[43]

like the results with the acyclic ketones, these reactions do not conform to a Curtin−Hammett kinetic scenario. Attempts to compare these results with the reactions of other Grignard reagents, such as MeMgBr and *n*-PrMgCl, were unsuccessful because reactions with those reagents proceeded with low conversions under comparable conditions. The addition of MeLi, however, is known to proceed with high stereoselectivity (dr = 88:12).[41]

Reactions of substituted cyclohexanones address the issue of which face is attacked. A nucleophile can approach an unhindered cyclohexanone from either the equatorial face or the axial face, but a suitably positioned axial substituent at C3 or C5 in cyclohexanone blocks the axial addition of the nucleophile, requiring addition to occur to the equatorial face (Figure 7).[9] We therefore prepared α-substituted ketones **74**

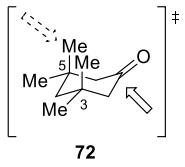
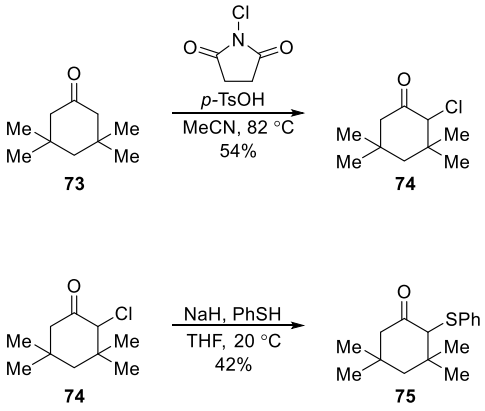


Figure 7. Sterically inaccessible addition due to axial substituents at C3 and C5 on cyclohexanone.

and **75** with axial substituents at C3 and C5 to determine if the orientation of a substituent at C2 had an impact on the preference for equatorial addition (Scheme 18).

Both the axial and equatorial conformers of ketones **74** and **75** are likely to be present in solution. Computations using the method used for the calculations of other α-halogenated carbonyl compounds (B3LYP/aug-cc-pVDZ in THF)[47] indicated that ketone **74** had a small preference (<0.3 kcal/mol) for the equatorial conformer, which was also favored in the solid state, as determined by X-ray crystallography (**76**, Figure 8). The bromine-substituted variant of this ketone also adopted the equatorial conformation in the solid state.[91] By contrast, the corresponding thiophenyl-substituted ketone **75**

Scheme 18. Synthesis of α-Substituted Tetramethylcyclohexanones



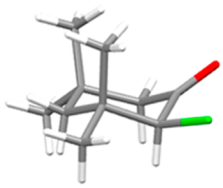
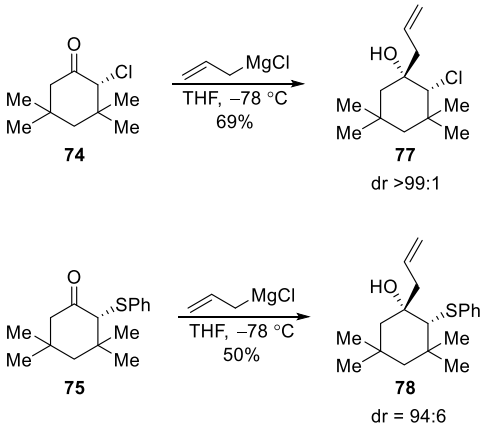


Figure 8. X-ray crystal structure of ketone **74**.

was an oil. Calculations (B3LYP/6-31G* in THF)[84] showed that it had a small (0.6 kcal/mol) preference for the equatorial conformer. Taken together, these calculations indicated that analysis of the reactivity of these cyclic ketones would need to consider both the axial and the equatorial conformers.

Additions of the highly reactive nucleophile allylmagnesium chloride to the sterically hindered α-substituted cyclohexanones **74** and **75** proceeded with high diastereoselectivity in both cases (Scheme 19). The major diastereomers of both

Scheme 19. Additions of Allylmagnesium Chloride to α-Substituted Tetramethylcyclohexanones



allylated products **77** and **78** were the 1,2-*anti* isomers. Chlorohydrin **77** could not be cyclized to the epoxide, suggesting that it had the illustrated stereochemistry. X-ray crystallographic analysis of sulfoxide **80** established the configuration of alcohol **78** (Scheme 20). The additions of less-reactive Grignard reagents (MeMgBr and PhMgBr) to ketone **75** proceeded with the same relative stereochemistry and with high stereoselectivity (dr ≥ 97:3).[92]

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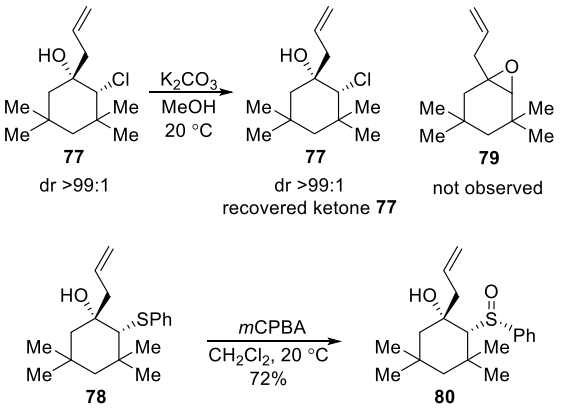
Scheme 20. Stereochemical Proofs of Alcohols 77 and 78



The stereoselectivities of the reactions shown in Scheme 19 are consistent with either axial addition to the axial conformer or equatorial addition to the equatorial conformer. Axial addition to the axial conformer corresponds to a polar Felkin–Anh transition state. Such an addition, however, is unlikely because it would require the nucleophile to approach the carbonyl group over the two axial methyl groups (**81** and **82**, Figure 9), which is disfavored.[7] Furthermore, the polar Felkin–

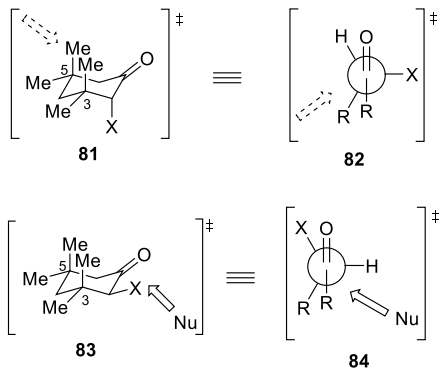


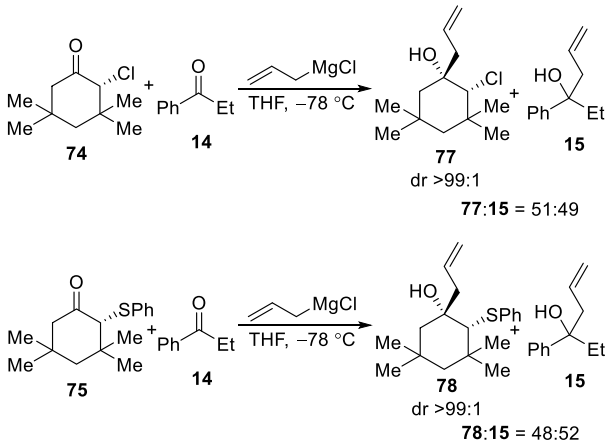
Figure 9. Possible modes for nucleophilic approach to ketones **74** and **75**.

Anh model cannot be evoked for these substrates because the reaction does not occur in a Curtin–Hammett kinetic regime, as indicated by competition experiments that demonstrate a similar rate of addition to sterically encumbered ketones **74** and **75** and propiophenone (Scheme 21).

Because axial attack is sterically inaccessible due to the axially substituted methyl groups at C3 and C5, equatorial addition is more likely. The configurations of the products **77** and **78** indicate that addition occurs to the equatorial conformer of the ketones **74** and **75**, as illustrated in **83** and **84** (Figure 9). These results suggest that any electronic stabilization of the transition state that might occur upon nucleophilic addition *anti* to the heteroatom, which would be expected by the Felkin–Anh model, is not as important as steric effects.[45] As a result, the avoidance of the axially substituted methyl groups defines which face of the ketone is attacked.

These results allow for the analysis of the reactions of the unhindered ketone, 2-thiophenylcyclohexanone (**68**), to be refined. The product *syn*-**69**, where the allyl group is positioned *syn* to the thiophenyl group, cannot be formed by equatorial

Scheme 21. Competition Experiment[a] between Ketones 74 and 75 and Propiophenone with Allylmagnesium Chloride[b]



[a]Competition experiments involved the dropwise addition (one drop every minute) of the diluted nucleophile (≤0.2 M) to a rapidly stirring mixture of 4 equiv of each electrophile at a low concentration (≤1.0 M). [b]Ratios for all competition experiments were determined by $^{13}C\{^{1}H\}$ NMR spectroscopy.[43]

attack on the axial conformer (the nucleophilic approach represented by the dotted arrow on conformer **85**, Figure 10).

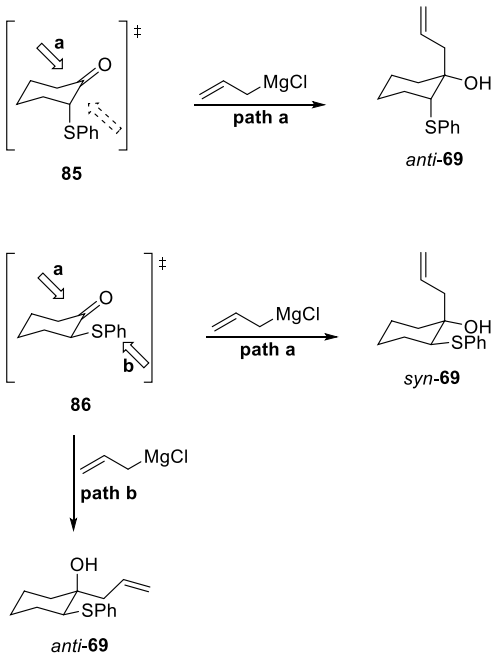


Figure 10. Nucleophilic approach on possible conformations of ketone **68**.

That mode of attack was available in the case of ketone **75**, but the product from that transition state was not observed. Rather, the *syn*-addition product must be formed by axial attack on the equatorial conformer, a mode of attack possible for the unhindered ketone **68** but not for the hindered ketone **75**. The formation of the 1,2-*anti* alcohol *anti*-**69**, however, can arise from either axial attack on the axial conformer or equatorial attack on the equatorial conformer of this unhindered ketone (Figure 10).

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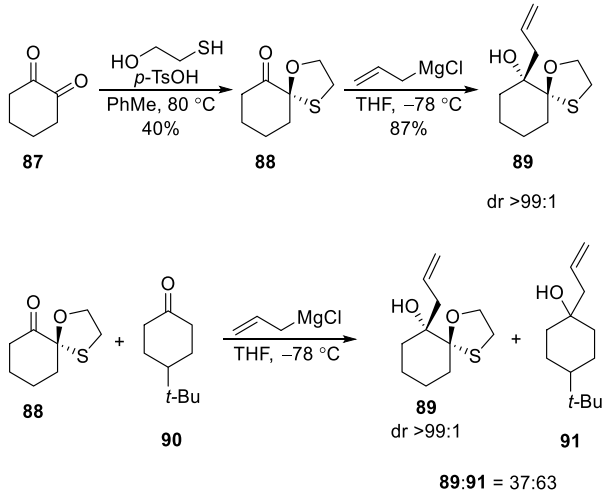
Just as the placement of the axial methyl substituents at C3 and C5 blocked one face of the carbonyl group, a geminal substitution at C2 also blocked the attack from one face. The addition of allylmagnesium chloride to sterically congested ketone **88**[93] was highly diastereoselective for the 1,2-*anti* product **89** (Scheme 22). The configuration of alcohol **89** was

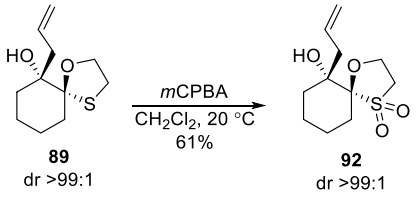
Scheme 22. Addition of Allylmagnesium Chloride to Cyclic Ketone 88 and Competition Experiment[a] between Ketone 88 and 4-*tert*-Butyl Cyclohexanone with Allylmagnesium Chloride[b]



[a]Competition experiments involved the dropwise addition (one drop every minute) of the diluted nucleophile (≤0.2 M) to a rapidly stirring mixture of 4 equiv of each electrophile at a low concentration (≤1.0 M). [b]Ratios for all competition experiments were determined by $^{13}C\{^1H\}$ NMR spectroscopy.[43]

determined by X-ray crystallographic analysis of sulfone **92** (Scheme 23). This crystal structure provided the only example

Scheme 23. Stereochemical Proof of Alcohol 89



in this study where the allyl group was placed in an axial orientation on a six-membered ring. The same high preference for *anti*-addition was also observed for the reaction of MeMgCl with ketone **88**.[93] Competition experiments suggest that, just as for the other ketones, carbon−carbon bond formation is faster than decomplexation once allylmagnesium chloride and the ketone encounter each other (Scheme 22).

The stereochemical course of the reaction that forms alcohol **89** can be explained by considering the possible steric hindrance between the nucleophile and the α-oxathiolane group on ketone **88**. This approach should be particularly sterically hindered from the equatorial position, resulting in axial approach of the nucleophile through a six-membered-ring transition state[6] (Figure 11). Calculations using optimized parameters that accounted for significant noncovalent interactions (ωB97X-D/cc-pVDZ in THF)[94] supported this

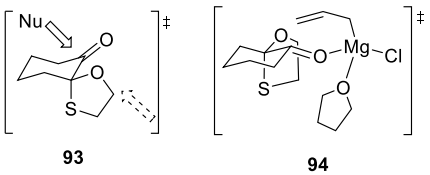


Figure 11. Sterically inaccessible equatorial addition due to the α-oxathiolane group on cyclohexanone.

prediction. The conformer with the sulfur atom of the oxathiolane ring positioned axially (as illustrated in transition state **94**) was calculated to be favored by 1.3 kcal/mol.[49,93] Computational studies using this functional and basis set combination[7] showed that the attack on **93** from both faces of the carbonyl group involved relatively low-energy six-membered-ring transition states ($\Delta G^{\ddagger}$ < 8 kcal/mol), indicating that the bond-forming step was competitive with dissociation of a complex between the reagent and the ketone.[95] Nevertheless, the transition state for attack from the axial face (through a transition state resembling **94**) was lower in free energy by 3 kcal/mol.[46]

Collectively, these experiments with hindered cyclic ketones provide useful information regarding the reactions of acyclic ketones with highly reactive allylmagnesium reagents. When a large group is positioned on one face, as expected for acyclic ketones, that group is sufficient to block nucleophilic attack to that face.

■ CONCLUSION

Reactions of acyclic ketones with allylmagnesium chloride that do not conform to a Curtin−Hammett kinetic scenario can still proceed with high diastereoselectivity, provided that they meet some conditions. The ketone should favor a conformer or related conformers where one diastereoface of the carbonyl group is sufficiently hindered and inaccessible to nucleophilic attack, resulting in selective additions with reagents that form carbon−carbon bonds immediately upon complexation. When these conditions are met, the nucleophilic additions to ketones are likely to be stereoselective, even with highly reactive nucleophiles that react at rates approaching the diffusion rate limit.[4]

■ EXPERIMENTAL SECTION

General Experimental. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were obtained at room temperature using Bruker AVIII-400 (400 and 100 MHz, respectively), AVIIIHD-400 (400 and 100 MHz, respectively), and AV-600 (600 and 150 MHz, respectively) spectrometers. Spectroscopic data are reported as follows: chemical shifts reported in parts per million (ppm) on the δ scale, ^1H and $^{13}C\{^1H\}$ NMR spectra internally referenced to tetramethylsilane (^1H NMR, $CDCl_3$ δ 0.00; $^{13}C\{^1H\}$ NMR, $CDCl_3$ δ 0.00), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Ratios of products were obtained from ^1H NMR or $^{13}C\{^1H\}$ NMR integrations using diagnostic peaks in the unpurified reaction mixture.[43] One-pulse ^1H NMR spectra were taken when determining product ratios. Multiplicities of carbon peaks were determined using HSQC experiments. Infrared (IR) spectra were recorded using a Thermo Nicolet AVATAR Fourier Transform IR spectrometer using attenuated total reflectance (ATR). High-resolution mass spectra were acquired on an Agilent 6224 Accurate-Mass time-of-flight spectrometer and were obtained using peak matching. The ionization sources used were either atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI), as indicated. Liquid

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chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on silica gel (SiO_2) 60 (230−400 mesh). Tetrahydrofuran, diethyl ether, dichloromethane, and methanol were dried and degassed using a solvent purification system before use. All dry reactions were run under a nitrogen atmosphere in glassware that had been flame-dried under reduced pressure. Unless otherwise noted, all reagents and substrates were commercially available. Ketones **1**,[96] **26**,[3] **31**,[97] **55**,[7] and **57**[7] were prepared using known methods. Ester **21**,[98] aldehyde **33**,[98] and alcohol **45**[99] were prepared using known methods. Compounds **15**,[3] **17**,[3] **42**,[100] **51**,[3] **64**,[7] **66**,[7] **71**,[101] and **91**[102] are known in the literature. Spectroscopic data (^{1}H NMR or ^{13}C{^{1}H} NMR) for the formation of these products in the course of competition experiments are consistent with the data reported.

Representative Procedure for the Addition of Grignard Reagents to Ketones: (2*R,3*R**)-2-Chloro-3-phenylhex-5-en-3-ol (2) and (2*R**,3*S**)-2-Chloro-3-phenylhex-5-en-3-ol (2′).** To a cooled (−78 °C) solution of ketone **1** (0.084 g, 0.50 mmol) in THF (5 mL) was added allylmagnesium chloride (300 μL, 2.0 M solution in THF, 0.60 mmol). After 30 min, MeOH (2 mL) was added to the mixture, followed by concentration in vacuo. To the mixture were then added H_2O (10 mL) and HCl (5 mL, 1.0 M in H_2O), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohols **2** were formed as an 88:12 mixture of diastereomers. Purification by flash chromatography (3:97 EtOAc−hexanes) afforded the alcohols **2** and **2′** as a colorless oil (0.078 g, 74%) with a diastereomeric ratio of 88:12. This mixture was used for characterization. The relative stereochemical configurations of alcohols **2** were assigned by the derivatization of alcohol **2** to epoxide **5**: IR (ATR) 3546, 2983, 1447, 998, 919, 767 cm^{-1}; HRMS (APCI) *m*/*z* calcd for $C_{12}H_{15}O$ [(M + H) − HCl]$^+$ 175.1117, found 175.1116.

Major Diastereomer ***2***. ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.38−7.34 (m, 2H), 7.30−7.27 (m, 1H), 5.62−5.52 (m, 1H), 5.16−5.08 (m, 2H), 4.36 (q, *J* = 6.6, 1H), 2.87−2.82 (m, 1H), 2.74−2.68 (m, 1H), 2.50 (s, 1H), 1.48 (d, *J* = 6.8, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.2 (C), 132.7 (CH), 128.0 (CH), 127.4 (CH), 126.4 (CH), 119.8 (CH_2), 77.7 (C), 65.8 (CH), 42.1 (CH_2), 19.5 (CH_3).

Minor Diastereomer ***2′***. ^{1}H NMR (100 MHz, $CDCl_3$, diagnostic peaks) δ 2.30 (s, 1H), 1.25 (d, *J* = 6.7, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.7 (C), 132.9 (CH), 128.3 (CH), 127.2 (CH), 125.7 (CH), 119.3 (CH_2), 77.6 (C), 66.7 (CH), 45.5 (CH_2), 19.6 (CH_3).

(2R,3R*)-2-Bromo-3-phenylhex-5-en-3-ol (**4**) and (2R*,3S*)-2-Allyl-3-methyl-2-phenyloxirane (**5**).* Alcohol **4** and epoxide **5** were prepared using the representative procedure for the addition of Grignard reagents to ketones using 2-bromopropiophenone (300 μL, 1.97 mmol) and allylmagnesium chloride (1.47 mL, 2.0 M solution in THF, 3.0 mmol) in THF (19 mL) at −78 °C for 30 min. ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **4** and epoxide **5** were formed as an 86:14 mixture of products (**4**:**5**). Alcohol **4** and epoxide **5** were formed as a single diastereomer (dr >99:1). Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohol **4** as a colorless oil (0.285 g, 57%) and epoxide **5** as a light yellow oil (0.032 g, 9%). The relative stereochemical configuration of alcohol **4** was assigned by the derivatization of alcohol **4** to epoxide **5**. The spectroscopic data (^{1}H NMR, ^{13}C{^{1}H} NMR, IR, and HRMS) for epoxide **5** are consistent with the data reported in the literature:[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m 5H), 5.79−5.68 (m, 1H), 5.08−5.03 (m, 2H), 3.21 (q, *J* = 5.5, 1H), 2.83 (dd, *J* = 14.7, 6.6, 1H), 2.50 (dd, *J* = 14.7, 7.4, 1H), 0.98 (d, *J* = 5.4, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.3, 132.8, 128.0, 127.2, 127.0, 118.2, 65.0, 59.3, 42.0, 14.5; HRMS (APCI) *m*/*z* calcd for $C_{12}H_{15}O$ [M + H]$^+$ 175.1117, found 175.1114.

Alcohol ***4***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2H), 7.38−7.34 (m, 2H), 7.31−7.26 (m, 1H), 5.61−5.50 (m, 1H), 5.15−5.06 (m, 2H), 4.52 (q, *J* = 6.8, 1H), 2.87−2.81 (m, 1H), 2.77−2.72 (m, 1H), 2.51 (s, 1H), 1.72 (d, *J* = 6.8, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.7 (C), 132.8 (CH), 128.0 (CH), 127.4 (CH), 126.2 (CH), 119.6 (CH_2), 77.5 (C), 60.8 (CH), 42.1 (CH_2), 20.7 (CH_3); IR (ATR) 3521, 1447, 1178, 994, 918, 765 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{14}Br$ [(M + H) − H_2O]$^+$ 237.0273, found 237.0271.

*1-Phenyl-2-(phenylthio)propan-1-one (**6**).* A reported procedure[103] was adapted to prepare ketone **6**. To a solution of sodium hydride (0.480 g, 60% in mineral oil, 12.0 mmol) in THF (12 mL) was added thiophenol (1.2 mL, 12.0 mmol) dropwise over 5 min. After 30 min, a solution of 2-bromopropiophenone (1.5 mL, 10.0 mmol) in THF (5 mL) was added by cannula to the reaction mixture. After 3 h, HCl (30 mL, 1.0 M in H_2O) was added to the mixture. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **6** as a yellow oil (0.962 g, 40%). The spectroscopic data (^{1}H NMR, ^{13}C{^{1}H} NMR, and HRMS) are consistent with the data reported in the literature:[104] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.94 (m, 2H), 7.58−7.54 (m, 1H), 7.46−7.43 (m, 2H), 7.36−7.34 (m, 2H), 7.31−7.27 (m, 3H), 4.63 (q, *J* = 6.9, 1H), 1.54 (d, *J* = 6.9, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.3, 135.7, 134.6, 133.1, 131.8, 128.9, 128.63, 128.60, 128.57, 46.2, 17.0; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{15}OS$ [M + H]$^+$ 243.0838, found 243.0835.

(2R,3R*)-3-Phenyl-2-(phenylthio)hex-5-en-3-ol (**7**).* Alcohol **7** was prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **6** (0.125 g, 0.51 mmol) and allylmagnesium chloride (300 μL, 2.0 M solution in THF, 0.60 mmol) in THF (5 mL) at −78 °C for 30 min. ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **7** was formed as a single diastereomer (dr > 99:1). Purification by flash chromatography (3:97 EtOAc−hexanes) afforded alcohol **7** as a yellow oil (0.113 g, 77%). The relative stereochemical configuration of alcohol **7** was assigned by the derivatization of alcohol **7** to sulfone **8**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.35−7.31 (m, 4H), 7.25−7.18 (m, 4H), 5.62−5.55 (m, 1H), 5.16−5.08 (m, 2H), 3.52 (q, *J* = 6.9, 1H), 2.99−2.95 (m, 1H), 2.73 (s, 1H), 2.70−2.67 (m, 1H), 1.32 (d, *J* = 6.9, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 143.3, 135.7, 133.5, 132.3, 129.0, 128.0, 127.2, 127.1, 126.5, 119.7, 77.9, 56.9, 42.8, 17.5; IR (ATR) 3485, 1438, 996, 746, 700, 691 cm^{-1}; HRMS (APCI) *m*/*z* calcd for $C_{18}H_{19}S$ [(M + H) − H_2O]$^+$ 267.1202, found 267.1199. Anal. Calcd for $C_{18}H_{20}OS$: C, 76.01; H, 7.09. Found: C, 75.87; H, 6.92.

Reaction of Alcohol 2 with Potassium Carbonate. To a solution of alcohol **2** (0.022 g, 0.10 mmol, dr 88:12) in MeOH (1.0 mL) was added K_2CO_3 (0.056 g, 0.40 mmol) at 0 °C. After 1 h, the reaction mixture was warmed to 20 °C and stirred for an additional 16 h. To the mixture was then added H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed the presence of only epoxide **5** (dr 89:11). The spectroscopic data (^{1}H NMR, ^{13}C{^{1}H} NMR, IR, and HRMS) for epoxide **5** are consistent with the data reported.[34]

Reaction of Alcohol 4 with Potassium Carbonate. To a solution of alcohol **4** and epoxide **5** (0.012 g, 0.05 mmol, 86:14 ratio; dr of alcohol **4** >99:1) in MeOH (1.0 mL) was added K_2CO_3 (0.030 g, 0.21 mmol) at 0 °C. After 1 h, the reaction mixture was warmed to 20 °C and stirred for an additional 16 h. To the mixture was then added H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed the presence of only epoxide **5** (dr >99:1). The spectroscopic data (^{1}H NMR, ^{13}C{^{1}H} NMR, IR, and HRMS) for epoxide **5** are consistent with the data reported.[34]

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(2R,3R*)-3-Phenyl-2-(phenylsulfonyl)hex-5-en-3-ol (**8**).* To a solution of alcohol **7** (0.028 g, 0.10 mmol) in CH_2Cl_2 (1 mL) was added 3-chloroperbenzoic acid (0.049 g, 70% in H_2O, 0.20 mmol) at 0 °C. After 1 h, the mixture was warmed to 20 °C and stirred for an additional 1 h. To the mixture were then added saturated aqueous $NaHSO_3$ (2 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (1 × 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (33:67 EtOAc−hexanes) afforded sulfone **8** as a white solid (0.033 g, 99%). X-ray quality crystals were grown by the slow evaporation of a solution of sulfone **8** in a 33:67 mixture of EtOAc−hexanes. The relative stereochemical configuration of sulfone **8** was assigned by X-ray crystallographic analysis: mp = 109−113 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66−7.64 (m, 2H), 7.55−7.52 (m, 1H), 7.42−7.39 (m, 2H), 7.32−7.31 (m, 2H), 7.19−7.13 (m, 3H), 5.60−5.53 (m, 1H), 5.11−5.08 (m, 1H), 5.02−5.00 (m, 1H), 3.55 (q, J = 7.2, 1H), 3.06−3.02 (m, 1H), 2.94−2.90 (m, 1H), 1.35 (d, J = 7.2, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 141.7 (C), 139.9 (C), 133.3 (CH), 132.6 (CH), 129.0 (CH), 128.0 (CH), 127.9 (CH), 127.4 (CH), 126.6 (CH), 118.8 (CH_2), 77.8 (C), 68.5 (CH), 41.8 (CH_2), 10.9 (CH_3); IR (ATR) 3501, 1284, 1130, 911, 770, 701 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{20}NaO_3S$ $[M + Na]^+$ 339.1025, found 339.1033.

Representative Procedure for the Addition of Lithium Phenylacetylide to Ketones ((2*R,3*S**)-3-Methyl-2-phenyl-2-(phenylethynyl)oxirane (10)).** To a solution of phenylacetylene (110 μL, 1.00 mmol) in THF (5 mL) was added *n*-butyllithium (550 μL, 1.5 M solution in hexanes, 0.99 mmol) dropwise over 5 min at −78 °C. After 1 h, the solution was warmed to 20 °C and added by cannula to a cooled (−78 °C) solution of ketone **1** (119 mg, 0.705 mmol) in THF (7 mL). After 1 h, the reaction mixture was warmed to 20 °C and stirred for an additional 3 h. To the mixture were then added H_2O (10 mL) and HCl (10 mL, 1.0 M in H_2O). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (1 × 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture revealed that epoxide **10** was formed as a single diastereomer (dr >99:1). Purification by flash chromatography (3:97 EtOAc−hexanes) afforded epoxide **10** as a colorless oil (0.081 g, 49%). The spectroscopic data (^{1}H NMR, ^{13}C{^{1}H} NMR, IR, and HRMS) are consistent with the data reported in the literature:[38] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.52 (m, 2H), 7.47−7.45 (m, 2H), 7.41−7.30 (m, 6H), 3.69 (q, J = 5.4, 1H), 1.10 (d, J = 5.3, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.5, 132.0, 128.7, 128.3, 128.1, 128.0, 127.1, 122.2, 88.9, 82.9, 63.4, 56.2, 13.3; HRMS (ESI) m/z calcd for $C_{17}H_{15}O$ $[M + H]^+$ 235.1117, found 235.1126.

(2R,3S*)-3-Methyl-2-phenyl-2-(phenylethynyl)oxirane (**10**) and (R*)-2-((2S*,3S*)-3-Methyl-2-phenyloxiran-2-yl)-1-phenylpropan-1-one (**11**).* Epoxides **10** and **11** were prepared using the representative procedure for the addition of lithium phenylacetylide to ketones. Lithium phenylacetylide was generated using phenylacetylene (110 μL, 1.00 mmol) and *n*-butyllithium (550 μL, 1.5 M solution in hexanes, 0.99 mmol) in THF (5 mL). This mixture was then added to a solution of 2-bromopropiophenone (100 μL, 0.66 mmol) in THF (7 mL) at −78 °C for 1 h, and the reaction mixture was then warmed to 20 °C for 2 h. ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed a 97:3 mixture of products (**10**:**11**). Epoxides **10** and **11** were formed as a single diastereomer (dr >99:1). Purification by flash chromatography (3:97 EtOAc−hexanes) afforded epoxide **10** as a colorless oil (0.123 g, 80%) and epoxide **11** as a colorless oil (0.007 g, 4%). The spectroscopic data (^{1}H NMR, ^{13}C{^{1}H} NMR, IR, and HRMS) for epoxide **10** (shown above) are consistent with the data reported in the literature.[38]

*Epoxide **11**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.1, 2H), 7.58−7.54 (m, 1H), 7.47−7.43 (m, 2H), 7.26−7.18 (m, 5H), 3.91 (q, J = 7.0, 1H), 3.37 (q, J = 5.3, 1H), 1.29 (d, J = 7.0, 3H), 1.03 (d, J = 5.7, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.7 (C), 137.4 (C), 137.1 (C), 133.1 (CH), 128.64 (CH), 128.57 (CH), 128.0 (CH), 127.6 (CH), 127.5 (CH), 66.3 (C), 58.3 (CH), 47.9 (CH), 15.1 (CH_3), 13.4 (CH_3); IR (ATR) 2973, 1681, 1447, 1212, 1033, 760 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{19}O_2$ $[M + H]^+$ 267.1380, found 267.1384.

(2R,3R*)-2-Phenyl-3-(phenylthio)butan-2-ol and (2R*,3S*)-2-Phenyl-3-(phenylthio)butan-2-ol (**12**).* Alcohols **12** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **6** (0.061 g, 0.25 mmol) and methylmagnesium chloride (0.25 mL, 2.0 M solution in THF, 0.50 mmol) in THF (1 mL) at −78 °C for 30 min. The reaction mixture was warmed to 20 °C and stirred for an additional 1 h. ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohols **12** were formed as a 67:33 mixture of diastereomers. Purification by flash chromatography (30:70 EtOAc−hexanes) afforded alcohols **12** as a colorless oil (0.051 g, 80%) with a diastereomeric ratio of 67:33. A mixture with a diastereomeric ratio of 85:15 was used for characterization: IR (ATR) 3461, 1438, 1023, 745, 699, 566 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{18}NaOS$ $[M + Na]^+$ 281.0971, found 281.0960. Anal. Calcd for $C_{16}H_{18}OS$: C, 74.38; H, 7.02. Found: C, 74.42; H, 6.95.

Major Diastereomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 7.7, 2H), 7.40−7.39 (m, 2H), 7.31 (t, J = 7.7, 2H), 7.26−7.21 (m, 4H), 3.54 (q, J = 7.1, 1H), 3.05 (br s, 1H), 1.63 (s, 3H), 1.24 (d, J = 7.1, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 145.4, 135.6, 132.2, 129.05, 128.2, 127.3, 127.2, 125.8, 76.5, 58.9, 24.6, 18.2.

Minor Diastereomer. ^{1}H NMR (600 MHz, $CDCl_3$, diagnostic peaks) δ 7.45−7.42 (m, 4H), 3.58 (q, J = 7.0, 1H), 2.65 (br s, 1H), 1.68 (s, 3H), 1.16 (d, J = 7.0, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$, diagnostic peaks) δ 145.5, 136.0, 132.0, 129.12, 127.1, 127.0, 125.2, 76.8, 57.0, 29.4, 17.8.

Representative Procedure for the Competition Experiment between Two Ketones for Allylmagnesium Chloride (Ketone 1 and Propiophenone). To a rapidly stirring and cooled (−78 °C) solution of ketone **1** (0.051 g, 0.30 mmol) and propiophenone (40 μL, 0.30 mmol) in THF (3 mL) was added allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) dropwise over 45 min by a syringe pump. After the full volume of the nucleophile was added to the mixture, MeOH (1 mL) was added. The reaction mixture was warmed to 20 °C over 15 min, then concentrated *in vacuo*. The resulting oil was dissolved in $CDCl_3$, then filtered through a plug of SiO_2. ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed a 60:40 mixture of products (**2**:**15**). Alcohol **2** was formed as a 91:9 mixture of diastereomers.

Competition Experiment between Ketone 3 and Propiophenone for Allylmagnesium Chloride. The competition experiment with ketone **3** and propiophenone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **3** (46 μL, 0.30 mmol) and propiophenone (40 μL, 0.30 mmol) in THF (3 mL) with allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) added dropwise over 45 min at −78 °C. ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed a 62:38 mixture of products (**4**:**15**). Alcohol **4** was formed as a single diastereomer (dr >99:1).

Competition Experiment between Ketone 6 and Propiophenone for Allylmagnesium Chloride. The competition experiment with ketone **6** and propiophenone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **6** (0.074 g, 0.30 mmol) and propiophenone (40 μL, 0.30 mmol) in THF (3 mL) with allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) added dropwise over 45 min at −78 °C. ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed a 58:42 mixture of products (**7**:**15**). Alcohol **7** was formed as a single diastereomer (dr >99:1).

Competition Experiment between Ketone 6 and Benzaldehyde for Methylmagnesium Chloride. To a rapidly stirring

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solution of ketone **6** (0.072 g, 0.30 mmol) and benzaldehyde (31 μL, 0.30 mmol) in THF (3 mL) was added methylmagnesium chloride (25 μL, 3.0 M solution in THF, 0.075 mmol) dropwise over 5 min at 20 °C. After 5 h, MeOH (100 μL) was added, and the reaction mixture was concentrated in vacuo. The resulting oil was dissolved in $CDCl_3$, then filtered through a plug of SiO_2. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed the presence of only alcohol **17**. The spectroscopic data (^1H NMR, $^{13}C\{^1H\}$ NMR, IR, and HRMS) of alcohol **17** are consistent with the data reported in the literature.[3]

*2-((tert-Butyldiphenylsilyl)oxy)-1-phenylpropan-1-one (**20**).* A reported procedure[3] was adapted to prepare ketone **20**. To a solution of 2-hydroxypropiophenone (0.270 g, 1.80 mmol) in DMF (1 mL) was added imidazole (0.410 g, 6.02 mmol) and *tert*-butyl(chloro)-diphenylsilane (560 μL, 2.15 mmol). After 24 h, HCl (10 mL, 1.0 M in H_2O) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **20** as a colorless oil (0.644 g, 92%). The spectroscopic data (^1H NMR, $^{13}C\{^1H\}$ NMR) are consistent with the data reported in the literature:[77] IR (ATR) 2932, 1700, 1428, 1112, 957, 704 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}NaO_2$ $[M + Na]^+$ 388.1859, found 388.1871. Anal. Calcd for $C_{25}H_{28}O_2Si$: C, 77.27; H, 7.26. Found: C, 76.99; H, 6.99.

*N-Methoxy-N-methyl-2-((triisopropylsilyl)oxy)propenamide (**22**).* To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.980 g, 10.0 mmol) and ester **21** (1.100 g, 4.01 mmol) in THF (12 mL) was added isopropylmagnesium chloride (10.0 mL, 2.0 M in THF, 20 mmol) dropwise over 20 min at −30 °C. After 1.5 h, the reaction mixture was warmed to −5 °C and stirred for an additional 3 h. To the mixture was then added saturated aqueous NH_4Cl (4 mL) dropwise. The reaction mixture was poured into a 1:4 Et_2O−NH_4Cl solution (40 mL), and the layers were separated. The aqueous layer was extracted with Et_2O (1 × 50 mL) and CH_2Cl_2 (1 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (20:80 EtOAc−hexanes) afforded Weinreb amide **22** as a colorless oil (1.156 g, 99%): ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 4.76−4.71 (m, 1H), 3.66 (s, 3H), 3.10 (s, 3H), 1.27 (d, *J* = 6.4, 3H), 1.06−1.00 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $(CD_3)_2SO$) δ 172.9, 65.4, 60.4, 32.1, 20.4, 17.11, 17.09, 11.3; IR (ATR) 2867, 1690, 1158, 997, 883, 682 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{32}NO_3Si$ $[M + H]^+$ 290.2146, found 290.2143. Anal. Calcd for $C_{14}H_{31}NO_3Si$: C, 58.09; H, 10.79. Found: C, 58.13; H, 10.75.

*3-((Triisopropylsilyl)oxy)butan-2-one (**23**).* To a solution of Weinreb amide **22** (0.576 g, 1.99 mmol) in THF (3.5 mL) was added methylmagnesium chloride (5.0 mL, 2.0 M in THF, 10 mmol) at 0 °C. After 5 h, saturated aqueous NH_4Cl (5 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **23** as a colorless oil (0.417 g, 86%): ^1H NMR (600 MHz, $CDCl_3$) δ 4.23 (q, *J* = 6.7, 1H), 2.22 (s, 3H), 1.31 (d, *J* = 6.7, 3H), 1.11−1.05 (m, 21H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 213.0, 75.6, 24.3, 21.3, 18.1, 18.0, 12.3; IR (ATR) 2945, 2868, 1720, 1125, 883, 682 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{28}NaO_2Si$ $[M + Na]^+$ 267.1751, found 267.1755. Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.87; H, 11.55. Found: C, 63.85; H, 11.67.

*2-Methyl-4-((triisopropylsilyl)oxy)pentan-3-one (**24**).* To a solution of Weinreb amide **22** (2.895 g, 10.00 mmol) in THF (20 mL) was added isopropylmagnesium chloride (25.0 mL, 2.0 M in THF, 50.0 mmol) at 0 °C. After 4 h, saturated aqueous NH_4Cl (5 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **24** as a colorless oil (0.700 g, 26%): ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (q, *J* = 6.9, 1H), 3.29−3.18 (m, 1H), 1.36 (d, *J* = 6.8, 3H), 1.13−1.05 (m, 27H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 217.8, 75.1, 34.7, 21.9, 19.5, 18.3, 18.13, 18.10, 12.4; IR (ATR) 2944, 2868, 1716, 1122, 883, 682 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{32}NaO_2Si$ $[M + Na]^+$ 295.2064, found 295.2071. Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84. Found: C, 66.41; H, 11.79.

(2R,3R*)-2-((tert-Butyldiphenylsilyl)oxy)-3-phenylhex-5-en-3-ol (**25**) and (2R*,3S*)-2-((tert-Butyldiphenylsilyl)oxy)-3-phenylhex-5-en-3-ol (**25′**).* Alcohols **25** and **25′** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **20** (0.195 g, 0.502 mmol) and allylmagnesium bromide (1.00 mL, 1.0 M solution in Et_2O, 1.0 mmol) in Et_2O (1 mL) at −78 °C for 15 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **25** was formed as an 85:15 mixture of diastereomers (**25**:**25′**). Purification by flash chromatography (3:97 EtOAc−hexanes) afforded alcohols **25** and **25′** as a colorless oil (0.201 g, 93%) with a diastereomeric ratio of 85:15. This mixture was used for characterization. The relative stereochemical configurations of alcohol **25** were assigned by the derivatization of alcohol **25** to alcohol **35**: IR (ATR) 2931, 1471, 1428, 1111, 740, 702 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{33}OSi$ $[(M + H) - H_2O]^+$ 413.2295, found 413.2293. Anal. Calcd for $C_{28}H_{34}O_2Si$: C, 78.09; H, 7.96. Found: C, 78.14; H, 8.13.

*Major Diastereomer **25**.* ^1H NMR (600 MHz, $CDCl_3$) δ 7.60−7.58 (m, 2H), 7.55−7.53 (m, 2H), 7.44−7.37 (m, 4H), 7.34−7.21 (m, 7H), 5.62−5.51 (m, 1H), 5.06−4.97 (m, 2H), 4.00 (q, *J* = 6.4, 1H), 2.79 (s, 1H), 2.79−2.71 (m, 1H), 2.63−2.56 (m, 1H), 0.94 (d, *J* = 6.2, 3H), 0.93−0.92 (m, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 144.0, 136.07, 136.06, 134.4, 133.9, 133.0, 129.9, 129.7, 127.92, 127.8, 127.5, 126.8, 126.7, 118.6, 78.4, 76.4, 42.0, 27.0, 19.4, 17.96;

*Minor Diastereomer **25′**.* ^1H NMR (600 MHz, $CDCl_3$, diagnostic peaks) δ 7.73−7.71 (m, 2H), 7.67−7.64 (m, 2H), 5.91−5.78 (m, 1H), 4.04 (q, *J* = 6.4, 1H), 2.90−2.85 (m, 1H), 2.56−2.51 (m, 1H), 1.10 (s, 9H), 0.74 (d, *J* = 6.2, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, diagnostic peaks) δ 142.7, 134.2, 133.3, 130.1, 129.8, 128.0, 127.91, 127.6, 126.6, 126.0, 117.9, 78.7, 76.2, 44.3, 27.3, 19.7, 18.02.

(2R,3R*)-3-Phenyl-2-((triisopropylsilyl)oxy)hex-5-en-3-ol (**27**) and (2R*,3S*)-3-Phenyl-2-((triisopropylsilyl)oxy)hex-5-en-3-ol (**27′**).* Alcohols **27** and **27′** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **26** (0.048 g, 0.16 mmol) and allylmagnesium chloride (120 μL, 2.0 M solution in THF, 0.24 mmol) in THF (2 mL) at −78 °C for 30 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **27** was formed as an 83:17 mixture of diastereomers (**27**:**27′**). Purification by flash chromatography (3:97 EtOAc−hexanes) afforded alcohol **27** as a colorless oil (0.049 g, 89%). The spectroscopic data (^1H NMR, $^{13}C\{^1H\}$ NMR, IR, and HRMS) are consistent with the data reported in the literature:[3] ^1H NMR (400 MHz, $CDCl_3$) δ 7.47−7.46 (m, 2H), 7.33−7.29 (m, 2H), 7.24−7.20 (m, 1H), 5.67−5.56 (m, 1H), 5.10−5.00 (m, 2H), 4.10 (q, *J* = 6.2, 1H), 2.88 (s, 1H), 2.81−2.76 (m, 1H), 2.64−2.58 (m, 1H), 1.14 (d, *J* = 6.3, 3H), 1.02−0.99 (m, 21H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.7, 134.1, 127.7, 126.65, 126.64, 118.3, 78.2, 75.9, 40.8, 18.14, 18.09, 12.7; HRMS (APCI) *m*/*z* calcd for $C_{21}H_{35}OSi$ $[(M + H) - H_2O]^+$ 331.2452, found 331.2446.

(2R,3S*)-2-Phenyl-3-((triisopropylsilyl)oxy)butan-2-ol and (2R*,3R*)-2-Phenyl-3-((triisopropylsilyl)oxy)butan-2-ol (**28**).* Alcohols **28** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **26** (0.154 g, 0.502 mmol) and methylmagnesium chloride (500 μL, 2.0 M solution in THF, 1.00 mmol) in THF (1 mL) at 20 °C for 15 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohols **28** were formed as a 52:48 mixture of diastereomers. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohols **28** as a colorless oil (0.155 g, 96%) with a diastereomeric ratio of 52:48. This mixture was used for characterization: ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2H), 7.41−7.39 (m, 2H), 7.33−7.29 (m, 4H), 7.24−7.19 (m, 2H), 4.17−4.10 (m, 2H), 3.11 (s, 1H), 2.89 (s, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.15−1.13 (m, 4H), 1.12−1.10 (m, 19H), 1.01−0.98 (m, 22H), 0.89 (d, *J* = 6.2, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 128.1, 128.0, 126.8,

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126.6, 125.9, 125.3, 77.0, 76.7, 76.3, 75.8, 28.3, 23.0, 18.41, 18.39, 18.38, 18.3, 18.23, 18.19, 13.0, 12.8; IR (ATR) 3559, 2944, 1110, 1060, 883, 700 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{34}NaO_2Si$ $[M + Na]^+$ 345.2220, found 345.2233. Anal. Calcd for $C_{19}H_{34}O_2Si$: C, 70.75; H, 10.62. Found: C, 71.01; H, 10.72.

(2R,3S*)-3-Methyl-2-((triisopropylsilyl)oxy)hex-5-en-3-ol (**29**) and (2R*,3R*)-3-Methyl-2-((triisopropylsilyl)oxy)hex-5-en-3-ol (**29′**).* Alcohols **29** and **29′** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **23** (0.112 g, 0.458 mmol) and allylmagnesium bromide (1.0 mL, 1.0 M solution in Et_2O, 1.0 mmol) in Et_2O (1 mL) at −78 °C for 15 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **29** was formed as a 80:20 mixture of diastereomers (**29**:**29′**). Purification by flash chromatography (3:97 EtOAc−hexanes) afforded alcohols **29** and **29′** as a colorless oil (0.097 g, 74%) with a diastereomeric ratio of 82:18. This mixture was used for characterization: IR (ATR) 3476, 2944, 2868, 1116, 882, 678 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{33}OSi$ $[(M + H) - H_2O]^+$ 269.2295, found 269.2289. Anal. Calcd for $C_{16}H_{34}O_2Si$: C, 67.07; H, 11.96. Found: C, 67.37; H, 11.87.

*Major Diastereomer **29**.* ^1H NMR (400 MHz, $CDCl_3$) δ 5.98−5.88 (m, 1H), 5.11−5.09 (m, 2H), 3.83 (q, J = 6.3, 1H), 2.41−2.36 (m, 2H), 2.16−2.11 (m, 1H), 1.20 (d, J = 6.2, 3H), 1.123−1.08 (m, 24H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 134.6, 117.9, 75.7, 74.6, 41.2, 23.3, 18.4, 18.30, 12.9;

*Minor Diastereomer **29′**.* ^1H NMR (400 MHz, $CDCl_3$, diagnostic peaks) δ 4.12 (q, J = 7.1, 1H), 1.16 (d, J = 6.4, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, diagnostic peaks) δ 134.5, 117.6, 74.7, 74.4, 43.4, 21.3, 18.32.

(2R,3R*)-3-Isopropyl-2-((triisopropylsilyl)oxy)hex-5-en-3-ol (**30**) and (2R*,3S*)-3-Isopropyl-2-((triisopropylsilyl)oxy)hex-5-en-3-ol (**30′**).* Alcohols **30** and **30′** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **24** (0.033 g, 0.12 mmol) and allylmagnesium bromide (300 μL, 1.0 M solution in Et_2O, 0.30 mmol) in Et_2O (1 mL) at −78 °C for 30 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **30** was formed as a 90:10 mixture of diastereomers (**30**:**30′**). Purification by flash chromatography (2:98 EtOAc−hexanes) afforded alcohols **30** and **30′** as a colorless oil (0.034 g, 90%) with a diastereomeric ratio of 85:15 (**30**:**30′**). This mixture was used for characterization. The relative stereochemical configurations of alcohol **30** were assigned by the derivatization of alcohol **30** to carbamate **40**: IR (ATR) 3568, 2944, 1125, 1015, 998, 883 cm^{-1}; HRMS (ESI) m/z for $C_{18}H_{38}NaO_2Si$ $[M + Na]^+$ 337.2533, found 337.2541. Anal. Calcd for $C_{18}H_{38}O_2Si$: C, 68.72; H, 12.18. Found: C, 68.91; H, 12.34.

*Major Diastereomer **30**.* ^1H NMR (600 MHz, $CDCl_3$) δ 6.02−5.95 (m, 1H), 5.07−5.01 (m, 2H), 4.08 (q, J = 6.5, 1H), 2.54 (s, 1H), 2.39−2.31 (m, 2H), 1.86−1.83 (m, 1H), 1.21 (d, J = 6.5, 3H), 1.10−1.08 (m, 21H), 1.00 (d, J = 7.1, 3H), 0.95 (d, J = 6.8, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 135.8, 116.8, 77.2, 73.0, 37.9, 33.1, 18.9, 18.4, 18.3, 17.8, 17.5, 12.9.

*Minor Diastereomer **30′**.* ^1H NMR (600 MHz, $CDCl_3$, diagnostic peaks) δ 2.56 (s, 1H), 0.91 (d, J = 6.9, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$, diagnostic peaks) δ 135.7, 116.5, 76.8, 73.6, 40.0, 32.7.

(1R,2R*)-1,2-Diphenyl-1-((triisopropylsilyl)oxy)pent-4-en-2-ol and (1R*,2S*)-1,2-Diphenyl-1-((triisopropylsilyl)oxy)pent-4-en-2-ol (**32**).* Alcohols **32** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **31** (0.152 g, 0.412 mmol) and allylmagnesium chloride (310 μL, 2.0 M solution in THF, 0.62 mmol) in THF (4 mL) at −78 °C for 20 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohols **32** were formed as a 55:45 mixture of diastereomers. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohols **32** as a colorless oil (0.147 g, 87%) with a diastereomeric ratio of 52:48. This mixture was used for characterization: ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.25 (m, 4H), 7.23−7.20 (m, 2H), 7.15−7.05 (m, 12H), 6.97−6.95 (m, 2H), 5.70−5.60 (m, 1H), 5.59−5.48 (m, 1H), 5.09−5.04 (m, 1H), 5.01−4.98 (m, 1H), 4.97−4.90 (m, 3H), 4.88 (s, 1H), 3.14 (s, 1H), 2.98 (s, 1H), 2.92−2.79 (m, 2H), 2.64 (dd, J = 14.3, 6.5, 1H), 2.38 (dd, J = 14.3, 7.3, 1H), 0.99−0.98 (m, 11H), 0.94−0.93 (m, 9H), 0.90−0.88 (m, 22H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.2, 141.7, 140.1, 140.0, 134.1, 134.0, 128.42, 128.41, 127.7, 127.6, 127.4, 127.3, 127.2, 127.0, 126.85, 126.84, 126.79, 126.5, 118.1, 118.0, 83.2, 82.2, 78.95, 78.94, 42.7, 41.0, 18.1, 18.0, 17.90, 17.89, 12.6, 12.5; IR (ATR) 3563, 2866, 1091, 1058, 881, 844 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{38}NaO_2Si$ $[M + Na]^+$ 433.2533, found 433.2529.

(2R,3S*)-2-((Triisopropylsilyl)oxy)hex-5-en-3-ol and (2R*,3R*)-2-((Triisopropylsilyl)oxy)hex-5-en-3-ol (**34**).* Alcohols **34** were prepared using the representative procedure for the addition of Grignard reagents to ketones using aldehyde **33** (0.026 g, 0.11 mmol) and allylmagnesium bromide (400 μL, 1.0 M solution in Et_2O, 0.40 mmol) in Et_2O (1 mL) at −78 °C for 15 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **34** was formed as a 51:49 mixture of diastereomers. Purification by flash chromatography (2:98 EtOAc−hexanes) afforded alcohols **34** as a colorless oil (0.022 g, 72%) with a diastereomeric ratio of 47:53. The mixture was used for characterization: ^1H NMR (600 MHz, $CDCl_3$) δ 5.93−5.81 (m, 2H), 5.15−5.08 (m, 4H), 3.95−3.92 (m, 1H), 3.89−3.85 (m, 1H), 3.71−3.68 (m, 1H), 3.44−3.41 (m, 1H), 2.49 (d, J = 4.6, 1H), 2.36−2.31 (m, 2H), 2.27−2.20 (m, 1H), 2.16−2.12 (m, 2H), 1.20 (d, J = 6.2, 3H), 1.14 (d, J = 6.3, 3H), 1.09−1.06 (m, 42H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 135.4, 135.1, 117.3, 117.1, 75.6, 74.6, 71.4, 70.9, 37.7, 36.9, 20.1, 18.3, 18.25, 18.24, 18.20, 16.7, 12.8, 12.5; IR (ATR) 3470, 2942, 1086, 1067, 881, 676 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{32}NaO_2Si$ $[M + Na]^+$ 295.2064, found 295.2063.

(2R,3R*)-3-Phenylhex-5-ene-2,3-diol (**35**) and (2R*,3S*)-3-Phenylhex-5-ene-2,3-diol (**35′**).* To a solution of silyl ether **25** (0.008 g, 0.02 mmol, dr = 86:14) in THF (100 μL) was added tetrabutylammonium fluoride (30 μL, 1.0 M solution in THF, 0.03 mmol). After 2 h, the mixture was concentrated *in vacuo*. Purification by flash chromatography (33:67 EtOAc−hexanes) afforded diol **35** as a colorless oil (0.005 g, 13%) as an 85:15 mixture of diastereomers (**35**:**35′**). The spectroscopic data are consistent with those of the same diol prepared from silyl ether **27** and tetrabutylammonium fluoride.

(2R,3R*)-3-Phenylhex-5-ene-2,3-diol (**35**) and (2R*,3S*)-3-Phenylhex-5-ene-2,3-diol (**35′**).* To a solution of silyl ether **27** (0.174 g, 0.50 mmol, dr 91:9) in THF (3 mL) was added tetrabutylammonium fluoride (600 μL, 1.0 M solution in THF, 0.60 mmol). After 1 h, the mixture was concentrated in vacuo. ^1H NMR spectroscopic analysis of the unpurified reaction mixture revealed that diol **35** was formed as a 91:9 mixture of diastereomers (**35**:**35′**). Purification by flash chromatography (33:67 EtOAc−hexanes) afforded diol **35** as a colorless oil (0.067 g, 70%) as a 91:9 mixture of diastereomers. The mixture was used for characterization: IR (ATR) 3443, 2979, 1447, 1066, 992, 703 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{16}NaO_2$ $[M + Na]^+$ 215.1043, found 215.1040.

*Major Diastereomer **35**.* ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2H), 7.38−7.34 (m, 2H), 7.29−7.24 (m, 1H), 5.62−5.52 (m, 1H), 5.16−5.07 (m, 2H), 3.93 (q, J = 6.4, 1H), 2.86−2.76 (m, 1H), 2.62−2.56 (m, 2H), 2.10 (br s, 1H), 1.14 (d, J = 6.6, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 143.3, 133.4, 128.4, 127.3, 126.5, 119.9, 78.2, 74.0, 40.0, 16.5.

*Minor Diastereomer **35′**.* ^1H NMR (400 MHz, $CDCl_3$, diagnostic peaks) δ 0.93 (d, J = 6.4, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 143.0, 133.6, 128.3, 127.0, 125.8, 119.8, 77.9, 73.6, 43.5, 17.9.

(2R,3R*)-3-Isopropylhex-5-ene-2,3-diol (**36**) and (2R*,3S*)-3-Isopropylhex-5-ene-2,3-diol (**36′**).* To a solution of silyl ether **30** (0.487 g, 1.55 mmol, dr 88:12) in THF (3 mL) was added tetrabutylammonium fluoride (2.0 mL, 1.0 M solution in THF, 2.0 mmol). After 1 h, the mixture was concentrated *in vacuo*. Purification by flash chromatography (25:75 EtOAc−hexanes) afforded alcohol **36** as a colorless oil (0.189 g, 77%) as an 88:12 mixture of diastereomers (**36**:**36′**). This mixture was used for characterization: IR (ATR) 3424, 3076, 2977, 1386, 992, 913 cm^{-1}; HRMS (ESI) m/z calcd for $C_9H_{17}O$ $[(M + H) - H_2O]^+$ 141.1274, found 141.1273.

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Major Diastereomer ***36***. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03−5.92 (m, 1H), 5.17−5.12 (m, 2H), 3.92−3.85 (m, 1H), 2.35 (d, J = 7.5, 2H), 2.11−2.07 (m, 2H), 1.91−1.84 (m, 1H), 1.20 (d, J = 6.5, 3H), 0.99 (d, J = 7.0, 3H), 0.95 (d, J = 7.0, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 135.7, 118.6, 77.2, 71.0, 37.4, 34.0, 17.9, 17.7, 17.5.

Minor Diastereomer ***36′***. $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 135.0, 118.1, 77.0, 72.0, 38.6, 33.5, 17.6, 17.4, 17.3.

(4R,5R*)-4-Allyl-4-isopropyl-2,2,5-trimethyl-1,3-dioxolane* ***(37)*** *and (4R*,5S*)-4-Allyl-4-isopropyl-2,2,5-trimethyl-1,3-dioxolane* ***(37′)***. To a solution of alcohol **36** (0.189 g, 1.19 mmol, dr 88:12) in CH_2Cl_2 (7 mL) was added 2,2-dimethoxypropane (0.391 g, 3.75 mmol) and *p*-toluenesulfonic acid monohydrate (0.027 g, 0.14 mmol). After 19.5 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture revealed that acetal **37** was formed as an 88:12 mixture of diastereomers. Purification by flash chromatography (3:97 EtOAc−hexanes) afforded acetal **37** as a colorless oil (0.152 g, 64%) as an 88:12 mixture of diastereomers (**37**:**37′**). This mixture was used for characterization: IR (ATR) 2984, 1239, 1215, 1031, 1000, 908 cm^{-1}; Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.74; H, 11.14.

Major Diastereomer ***37***. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.97−5.89 (m, 1H), 5.13−5.08 (m, 2H), 4.14−4.11 (m, 1H), 2.38−2.34 (m, 1H), 2.30−2.26 (m, 1H), 2.07−2.00 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.26 (d, J = 6.4, 3H), 0.99 (d, J = 7.1, 3H), 0.90 (d, J = 7.1, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 134.6, 117.6, 106.4, 85.8, 73.9, 36.3, 31.7, 28.7, 26.8, 17.8, 17.3, 15.8.

Minor Diastereomer ***37′***. ^{1}H NMR (600 MHz, $CDCl_3$, diagnostic peaks) δ 5.89−5.82 (m, 1H), 1.97−1.92 (m, 1H), 1.44 (s, 3H), 1.29 (d, J = 6.5, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 134.3, 117.9, 106.3, 85.0, 77.3, 37.7, 30.6, 27.7, 26.7, 18.7, 18.5, 15.1.

3-((4R,5R*)-4-Isopropyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)-propan-1-ol* ***(38)***. To a solution of acetal **37** (0.397 g, 2.00 mmol, dr >99:1) in THF (4 mL) was added a borane dimethyl sulfide complex (2.0 mL, 2.0 M in THF, 4.0 mmol) dropwise at 0 °C. After 1 h, the reaction mixture was warmed to 20 °C and stirred for an additional 16 h. The reaction mixture was cooled to 0 °C, and to the mixture were then added NaOH (3 mL, 1.0 M in H_2O) and H_2O_2 (13 mL, 30% solution in H_2O). After 30 min, the reaction mixture was warmed to 20 °C, and to the mixture was added H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture revealed that acetal **38** was formed as a single diastereomer (dr >99:1). Purification by flash chromatography (33:67 EtOAc−hexanes) afforded acetal **38** as a colorless oil (0.243 g, 56%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (q, J = 6.2, 1H), 3.67 (t, J = 5.9, 2H), 2.14 (br s, 1H), 2.12−2.07 (m, 1H), 1.78−1.54 (m, 4H), 1.44 (s, 3H), 1.35 (s, 3H), 1.25 (d, J = 6.6, 3H), 1.00 (d, J = 6.9, 3H), 0.90 (d, J = 7.3, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 106.3, 85.9, 74.1, 63.7, 31.5, 28.5, 28.1, 26.8, 26.5, 18.0, 17.3, 15.9; IR (ATR) 3386, 2983, 1212, 1009, 754, 527 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{24}NaO_3$ $[M + Na]^+$ 239.1618, found 239.1619.

3-((4R,5R*)-4-Isopropyl-2,2,5-trimethyl-1,3-dioxolan-4-yl)-propyl(4-nitrophenyl)carbamate* ***(39)***. A reported procedure was adapted to prepare carbamate **39**.[105] To a solution of acetal **38** (0.100 g, 0.462 mmol) in THF (2 mL) were added 4-nitrophenyl isocyanate (0.127 g, 0.774 mmol) and tin(II) 2-ethylhexanoate (1 drop). After 24 h, the reaction mixture was concentrated in vacuo and then used directly without purification: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20−8.18 (m, 2H), 7.61−7.59 (m, 2H), 7.47 (br s, 1H), 4.28−4.22 (m, 2H), 4.16−4.12 (m, 1H), 2.04−1.99 (m, 1H), 1.93−1.86 (m, 1H), 1.78−1.71 (m, 1H), 1.65−1.55 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H), 1.25 (d, J = 6.4, 3H), 1.00 (d, J = 6.8, 3H), 0.91 (d, J = 7.3, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.2, 144.3, 142.9, 125.2, 117.9, 106.2, 85.5, 74.2, 66.8, 31.8, 28.4, 27.3, 26.7, 22.7, 18.0, 17.3, 15.7.

(4R,5R*)-4,5-Dihydroxy-4-isopropylhexyl(4-nitrophenyl)-carbamate* ***(40)***. To a 10% HCl solution in MeOH (5.5 mL) was added carbamate **39** (0.209 g, 0.549 mmol). After 1 h, the reaction mixture was concentrated *in vacuo*. To the mixture were then added CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (33:67 EtOAc−hexanes) afforded carbamate **40** as a white solid (0.101 g, 54%). X-ray-quality crystals were grown by the slow evaporation of a solution of carbamate **40** in MeOH. The relative stereochemical configuration of carbamate **40** was assigned by X-ray crystallographic analysis: mp = 92−94 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (d, J = 9.1, 2H), 7.66 (s, 1H), 7.58 (d, J = 9.1, 2H), 4.20 (t, J = 6.6, 2H), 3.95−3.91 (m, 1H), 2.57 (s, 1H), 2.37 (s, 1H), 1.93−1.85 (m, 2H), 1.82−1.77 (m, 1H), 1.65−1.59 (m, 2H), 1.20 (d, J = 6.4, 3H), 0.99 (d, J = 6.9, 3H), 0.95 (d, J = 6.9, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 153.3, 144.4, 142.9, 125.3, 117.9, 77.3, 70.9, 66.8, 33.7, 28.7, 23.5, 18.2, 17.61, 17.56; IR (ATR) 3494, 3214, 1716, 1499, 1235, 749 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{24}N_2NaO_6$ $[M + Na]^+$ 363.1527, found 363.1538.

Competition Experiment between Ketone 26 and Propiophenone for Allylmagnesium Chloride. The competition experiment with ketone **26** and propiophenone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **26** (0.092 g, 0.30 mmol) and propiophenone (40 μL, 0.30 mmol) in THF (3 mL) with allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) added dropwise over 45 min at −78 °C. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed a 30:70 mixture of products (**27**:**15**). Alcohol **27** was formed as an 85:15 mixture of diastereomers.

Competition Experiment between Ketone 31 and Benzophenone for Allylmagnesium Chloride. The competition experiment with ketone **31** and benzophenone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **31** (0.073 g, 0.32 mmol) and benzophenone (0.040 g, 0.21 mmol) in THF (2 mL) with allylmagnesium chloride (250 μL, 0.20 M solution in THF, 0.050 mmol) added dropwise over 45 min at −78 °C. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed a 49:51 mixture of products (**32**:**42**). Alcohol **32** was formed as an 52:48 mixture of diastereomers.

1,2-Diphenylbut-3-en-1-one ***(46)***. To a solution of alcohol **45** (0.227 g, 1.01 mmol) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (0.529 g, 1.25 mmol). After 4 h, a 1:1 saturated aqueous $NaHCO_3$−saturated aqueous $Na_2S_2O_3$ (10 mL) was added and the resulting mixture was stirred for an additional 16 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **46** as a yellow solid (0.189 g, 85%). The spectroscopic data (^{1}H NMR, $^{13}C\{^1H\}$ NMR, IR, HRMS) are consistent with the data reported in the literature:[106] ^{1}H NMR (400 MHz, $CDCl_3$) 7.98−7.96 (m, 2H), 7.53−7.49 (m, 1H), 7.42−7.39 (m, 2H), 7.34−7.31 (m, 4H), 7.25−7.21 (m, 1H), 6.41−6.32 (m, 1H), 5.29 (d, J = 7.7, 1H), 5.23 (d, J = 10.2, 1H), 5.12−5.07 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.5, 138.4, 137.2, 136.4, 133.0, 129.0, 128.9, 128.6, 128.4, 127.2, 117.2, 58.0.

(3R,4R*)-3,4-Diphenylhepta-1,6-dien-4-ol* ***(47)*** *and (3R*,4S*)-3,4-Diphenylhepta-1,6-dien-4-ol* ***(47′)***. Alcohols **47** and **47′** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **46** (0.114 g, 0.50 mmol) and allylmagnesium chloride (380 μL, 2.0 M solution in THF, 0.76 mmol) in THF (5 mL) at −78 °C for 30 min. ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **47** was formed as a 93:7 mixture of diastereomers (**47**:**47′**). Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohols **47** and **47′** as a colorless oil (0.124 g, 94%) with a diastereomeric ratio of 93:7. The mixture was

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used for characterization. The relative stereochemical configuration of alcohol **47** was assigned by the derivatization of alcohol **47** to epoxide **49**: IR (ATR) 3554, 2977, 1446, 997, 915, 742 cm^{-1}; HRMS (APCI) *m/z* calcd for $C_{19}H_{19}$ $[(M + H) - H_2O]^+$ 247.1481, found 247.1486.

*Major Diastereomer **47**.* ^1H NMR (400 MHz, $CDCl_3$) δ 7.21−7.18 (m, 2H), 7.15−7.08 (m, 6H), 6.93−6.91 (m, 2H), 6.38−6.29 m, 1H), 5.53−5.42 (m, 1H), 5.23−5.04 (m, 4H), 3.60 (d, J = 9.7, 1H), 2.84 (dd, J = 14.0, 5.4, 1H), 2.68 (dd, J = 14.0, 9.0, 1H), 2.25 (br s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9 (C), 140.2 (C), 137.7 (CH), 133.7 (CH), 129.4 (CH), 127.7 (CH), 127.5 (CH), 126.4 (CH), 126.34 (CH), 126.28 (CH), 119.6 (CH_2), 117.6 (CH_2), 77.3 (C), 61.7 (CH), 44.8 (CH_2).

*Minor Diastereomer **47′**.* ^1H NMR (400 MHz, $CDCl_3$, diagnostic peaks) δ 6.14−6.05 (m, 1H), 3.66 (d, J = 8.4, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, diagnostic peaks) δ 137.5 (CH), 133.4 (CH), 129.9 (CH), 128.1 (CH), 127.8 (CH), 126.8 (CH), 126.6 (CH), 126.2 (CH), 119.5 (CH_2), 117.5 (CH_2), 61.3 (CH), 45.1 (CH_2).

Competition Experiment between Ketone 46 and Propiophenone for Allylmagnesium Chloride. The competition experiment with ketone **46** and propiophenone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **46** (0.045 g, 0.19 mmol) and propiophenone (27 μL, 0.20 mmol) in THF (2 mL) with allylmagnesium chloride (250 μL, 0.20 M solution in THF, 0.050 mmol) added dropwise over 45 min at −78 °C. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed a 51:49 mixture of products (**47**:**15**). Alcohol **47** was formed as a single diastereomer (dr >99:1).

(1R,2R*)-1,2-Diphenylcyclopent-3-en-1-ol (**48**).* A reported procedure[44] was adapted to prepare alcohol **48**. To a solution of Grubbs II catalyst (0.010 g, 0.012 mmol) in CH_2Cl_2 (1.5 mL) was added a solution of alcohol **47** (0.060 g, 0.23 mmol, dr >99:1) in CH_2Cl_2 (0.5 mL). The resulting mixture was heated to 40 °C in a silicone oil bath. After 3 h, the mixture was cooled to 20 °C and concentrated in vacuo. Purification by flash chromatography (10:90 Et_2O−pentanes) afforded alcohol **48** as a colorless oil (0.044 g, 81%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.46 (m, 2H), 7.37−7.33 (m, 2H), 7.28−7.26 (m, 4H), 7.02−6.99 (m, 2H), 6.07−6.04 (m, 1H), 5.89−5.87 (m, 1H), 4.41 (br s, 1H), 3.07−3.02 (m, 1H), 2.89−2.84 (m, 1H), 1.54 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.0 (C), 136.9 (C), 131.2 (CH), 130.3 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 127.6 (CH), 126.6 (CH), 125.2 (CH), 83.0 (C), 64.1 (CH), 50.7 (CH_2); IR (ATR) 3556, 1601, 1446, 1059, 899, 756 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}$ $[(M + H) - H_2O]^+$ 220.1202, found 220.1209.

(1R,2S*,3R*,5S*)-2,3-Diphenyl-6-oxabicyclo[3.1.0]hexan-3-ol (**49**).* To a solution of alcohol **48** (0.026 g, 0.12 mmol, dr >99:1) in CH_2Cl_2 (1 mL) was added 3-chloroperoxybenzoic acid (0.036 g, 70−75% in H_2O, 0.14 mmol). After 16 h, to the mixture was added saturated aqueous Na_2SO_3 (10 mL), and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10:90 EtOAc−hexanes) afforded epoxide **49** as a white solid (0.024 g, 80%). X-ray-quality crystals were grown by the slow evaporation of a solution of epoxide **49** in MeOH. The relative stereochemical configuration of epoxide **49** was assigned by X-ray crystallographic analysis: mp = 104−105 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 4H), 7.28−7.24 (m, 1H), 7.21−7.19 (m, 3H), 7.00−6.96 (m, 2H), 4.05 (d, J = 2.7, 1H), 3.88 (d, J = 2.9, 1H), 3.68 (s, 1H), 3.26 (s, 1H), 2.59 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.5 (C), 135.8 (C), 128.7 (CH), 128.04 (CH), 127.97 (CH), 127.0 (CH), 126.8 (CH), 125.6 (CH), 78.9 (C), 60.4 (CH), 57.5 (CH), 54.9 (CH), 45.6 (CH_2); IR (ATR) 3697, 2967, 1033, 941, 826, 756 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}O$ $[(M + H) - H_2O]^+$ 235.1117, found 235.1123.

(3R,4R*)-3,4-Diphenylhept-1-en-4-ol (**50**) and (1R*,1R*)-1,2-Diphenylbut-3-en-1-ol (**45**).* Alcohols **50** and **45** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **46** (0.114 g, 0.50 mmol) and *n*-propylmagnesium chloride (380 μL, 2.0 M solution in THF, 0.76 mmol) in THF (5 mL) at 20 °C for 16 h. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **50** was formed as a single diastereomer (dr >99:1). Analysis of the $^{13}C\{^1H\}$ NMR spectrum also revealed the formation of the 1,2-reduction product **45** (dr >99:1). Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohol **50** as a colorless oil (0.033 g, 24%) and alcohol **45** as a colorless oil (0.042 g, 33%). The spectroscopic data (^1H NMR, $^{13}C\{^1H\}$ NMR, IR, and HRMS) of alcohol **45** are consistent with the data reported in the literature.[107]

*Alcohol **50**.* ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.19 (m, 2H), 7.16−7.14 (m, 1H), 7.11−7.09 (m, 5H), 6.90−6.88 (m, 2H), 6.34−6.25 (m, 1H), 5.24−5.15 (m, 2H), 3.62 (d, J = 9.8, 1H), 2.09 (s, 1H), 1.93−1.88 (m, 2H), 1.35−1.23 (m, 1H), 1.00−0.93 (m, 1H), 0.84 (t, J = 7.0, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.1 (C), 140.1 (C), 137.4 (CH), 129.3 (CH), 127.8 (CH), 127.5 (CH), 126.4 (CH), 126.3 (CH), 126.1 (CH), 117.9 (CH_2), 78.5 (C), 62.1 (CH), 42.3 (CH_2), 16.9 (CH_2), 14.4 (CH_3); IR (ATR) 3543, 1677, 1447, 1207, 920, 751 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}$ $[(M + H) - H_2O]^+$ 249.1638, found 249.1636.

Competition Experiment between Ketone 46 and Propiophenone for *n*-Propylmagnesium Chloride. To a rapidly stirring solution of ketone **46** (0.045 g, 0.19 mmol) and propiophenone (27 μL, 0.20 mmol) in THF (2 mL) was added *n*-propylmagnesium chloride (250 μL, 0.20 M solution in THF, 0.050 mmol) dropwise over 5 min at 20 °C. After 16 h, MeOH (1 mL) was added, and the reaction mixture was concentrated in vacuo. The resulting oil was dissolved in $CDCl_3$ and then filtered through a plug of SiO_2. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **51** was the only product formed.

(3R,4R*)-3,4-Diphenylheptan-4-ol (**52**) and (3R*,4S*)-3,4-Diphenylheptan-4-ol (**52′**).* To a solution of alcohol **47** (0.013 g, 0.049 mmol, dr 92:8) in MeOH (1 mL) was added palladium (10%) on carbon (0.005 g, 0.005 mmol), and the reaction mixture was pressurized with H_2 (1 atm). After 20 h, the reaction mixture was filtered over Celite, rinsed with MeOH (10 mL), and concentrated *in vacuo*. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **52** was formed as a 91:9 mixture of diastereomers. Alcohols **52** and **52′** were collected as a white solid (0.012 g, 92%) with a diastereomeric ratio of 91:9 (**52**:**52′**). This mixture was used for characterization: IR (ATR) 3681, 2958, 2844, 2361, 1056, 1014 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{24}NaO$ $[M + Na]^+$ 291.1719, found 291.1724.

*Major Diastereomer **52**.* ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.21 (m, 2H), 7.18−7.15 (m, 6H), 6.93−6.92 (m, 2H), 2.82 (dd, J = 11.5, 2.2, 1H), 2.06−1.99 (m, 1H), 1.93−1.80 (m, 3H), 1.67−1.57 (m, 1H), 1.31−1.21 (m, 1H), 1.03−0.94 (m, 1H), 0.85 (t, J = 7.1, 3H), 0.65 (t, J = 7.1, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.5 (C), 139.9 (C), 130.1 (CH), 127.6 (CH), 127.4 (CH), 126.5 (CH), 126.4 (CH), 126.2 (CH), 79.0 (C), 59.7 (CH), 40.9 (CH_2), 21.5 (CH_2), 16.9 (CH_2), 14.5 (CH_3), 12.62 (CH_3).

*Minor Diastereomer **52′**.* ^1H NMR (400 MHz, $CDCl_3$, diagnostic peaks) δ 0.54 (t, J = 7.2, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, diagnostic peaks) δ 145.5 (C), 140.8 (C), 128.1 (CH), 127.9 (CH), 126.6 (CH), 126.1 (CH), 125.6 (CH), 79.2 (C), 59.1 (CH), 44.2 (CH_2), 22.4 (CH_2), 16.7 (CH_2), 14.3 (CH_3), 12.58 (CH_3).

(3R,4R*)-3,4-Diphenylheptan-4-ol (**52**) and (1R*,2R*)-1,2-Diphenylbut-3-en-1-ol (**53**).* To a solution of alcohols **50** and **51** (0.020 g, 0.075 mmol, ratio 60:40; dr 90:10 for alcohol **50**) in MeOH (1 mL) was added palladium (10%) on carbon (0.007 g, 0.007 mmol), and the reaction mixture was pressurized with H_2 (1 atm). After 20 h, the reaction mixture was filtered over Celite, rinsed with MeOH (10 mL), and concentrated in vacuo. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed a 62:38 mixture of products (**52**:**53**). Alcohols **52** were formed as an 89:11 mixture of products (**52**:**52′**). Alcohol **53** was formed as a single diastereomer (dr >99:1). The spectroscopic data (^1H NMR, $^{13}C\{^1H\}$ NMR, IR, and HRMS) of alcohol **52** are consistent with the data reported for the reduction of alcohol **47** with palladium (10%) on carbon. The spectroscopic data (^1H NMR, $^{13}C\{^1H\}$ NMR, IR, and

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HRMS) of alcohol **53** are consistent with the data reported previously.[108]

*2-(Phenylthio)cycloheptan-1-one (**56**).* A reported procedure[103] was adapted to prepare ketone **56**. To a solution of sodium hydride (0.352 g, 60% in mineral oil, 8.22 mmol) in THF (7 mL) was added thiophenol (0.140 mL, 1.27 mmol) dropwise over 5 min. After 30 min, a solution of ketone **55** (1.012 g, 6.93 mmol) in THF (4 mL) was added to the stirring reaction mixture dropwise over 5 min. After 16 h, to the mixture was added HCl (5 mL, 1.0 M in H_2O). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **56** as a colorless oil (1.088 g, 71%). The spectroscopic data (^{1}H NMR, $^{13}C\{^1H\}$ NMR, and HRMS) are consistent with the data reported in the literature:[109] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.40 (m, 2H), 7.31−7.27 (m, 2H), 7.26−7.22 (m, 1H), 3.78 (dd, J = 10.7, 5.6, 1H), 2.82−2.75 (m, 1H), 2.42−2.37 (m, 1H), 2.29−2.22 (m, 1H), 1.98−1.91 (m, 2H), 1.83−1.79 (m, 1H), 1.67−1.26 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 209.0 (C), 133.8 (CH), 131.9 (CH), 129.0 (CH), 127.6 (CH), 57.4 (CH), 40.0 (CH_2), 30.4 (CH_2), 30.0 (CH_2), 27.1 (CH_2), 25.5 (CH_2); HRMS (APCI) m/z calcd for $C_{13}H_{17}OS$ $[M + H]^+$ 221.0995, found 221.0991.

*2-(Phenylthio)cyclooctan-1-one (**58**).* A reported procedure[103] was adapted to prepare ketone **58**. To a solution of sodium hydride (0.48 g, 60% in mineral oil, 12.0 mmol) in THF (12 mL) was added thiophenol (1.2 mL, 12.0 mmol) dropwise over 5 min. After 30 min, a solution of ketone **57** (1.347 g, 10.2 mmol) in THF (5 mL) was added to the reaction mixture by cannula. After 3 h, to the mixture was added HCl (30 mL, 1.0 M in H_2O). The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **58** as a yellow oil (0.846 g, 72%). The spectroscopic data (^{1}H NMR, $^{13}C\{^1H\}$ NMR) are consistent with the data reported in the literature:[110] HRMS (APCI) m/z calcd for $C_{14}H_{19}OS$ $[M + H]^+$ 235.1151, found 235.1150.

(1R,2R*)-1-Allyl-2-(phenylthio)cycloheptan-1-ol (**59**) and (1R*,2S*)-1-Allyl-2-(phenylthio)cycloheptan-1-ol (**59′**).* Alcohols **59** and **59′** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **56** (0.110 g, 0.50 mmol) and allylmagnesium chloride (375 μL, 2.0 M solution in THF, 0.75 mmol) in THF (5 mL) at −78 °C for 30 min. ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **59** was formed as a 92:8 mixture of diastereomers (**59**:**59′**). Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohol **59** as a colorless oil (0.069 g, 53%) with a diastereomeric ratio of 89:11. This mixture was used for characterization. The relative stereochemical configurations of the two diastereomers were assigned by the derivatization of alcohol **59** to sulfoxide **61**: IR (ATR) 3476, 2926, 1438, 1025, 914, 736 cm^{-1}; HRMS (APCI) m/z calcd for $C_{16}H_{21}S$ $[(M + H) - H_2O]^+$ 245.1358, found 245.1356.

*Major Diastereomer **59**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.31−7.27 (m, 2H), 7.23−7.21 (m, 1H), 5.96−5.86 (m, 1H), 5.17−5.08 (m, 2H), 3.27 (dd, J = 8.9, 1.6, 1H), 2.62−2.56 (m, 1H), 2.53−2.48 (m, 1H), 2.32 (s, 1H), 2.07−2.00 (m, 1H), 1.93−1.87 (m, 3H), 1.78−1.84 (m, 3H), 1.55−1.28 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 136.7 (C), 133.89 (CH), 131.3 (CH), 129.1 (CH), 127.0 (CH), 118.9 (CH_2), 76.3 (C), 61.7 (CH), 45.0 (CH_2), 38.8 (CH_2), 30.6 (CH_2), 28.5 (CH_2), 26.8 (CH_2), 21.5 (CH_2).

*Minor Diastereomer **59′**.* ^{1}H NMR (400 MHz, $CDCl_3$, diagnostic peaks) δ 3.35 (dd, J = 9.9, 2.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 136.3 (C), 133.86 (CH), 131.4 (CH), 129.2 (CH), 126.7 (CH), 118.8 (CH_2), 76.6 (C), 63.1 (CH), 43.2 (CH_2), 38.4 (CH_2), 31.6 (CH_2), 28.0 (CH_2), 27.4 (CH_2), 21.3 (CH_2).

(1R,2R*)-1-Allyl-2-(phenylthio)cyclooctan-1-ol (**60**) and (1R*,2S*)-1-Allyl-2-(phenylthio)cyclooctan-1-ol (**60′**).* Alcohols **60** and **60′** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **58** (0.118 g, 0.504 mmol) and allylmagnesium chloride (380 μL, 2.0 M solution in THF, 0.76 mmol) in THF (5 mL) at −78 °C for 30 min. ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **60** was formed as an 86:14 mixture of diastereomers (**60**:**60′**). Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohol **60** as a yellow oil (0.088 g, 63%). The relative stereochemical configurations of the two diastereomers were assigned by the derivatization of alcohol **60** to sulfoxide **62**: IR (ATR) 3462, 2917, 1438, 988, 912, 736 cm^{-1}; HRMS (APCI) m/z calcd for $C_{17}H_{23}S$ $[(M + H) - H_2O]^+$ 259.1515, found 259.1512.

*Major Diastereomer **60**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.41 (m, 2H), 7.31−7.27 (m, 2H), 7.22−7.18 (m, 1H), 5.96−5.85 (m, 1H), 5.15−5.10 (m, 2H), 3.38 (d, J = 8.0, 1H), 2.86−2.80 (dd, J = 14.1, 6.8, 1H), 2.33 (dd, J = 14.1, 7.8, 1H), 2.28−2.19 (m, 1H), 2.07 (s, 1H), 2.02−1.95 (m, 1H), 1.90−1.71 (m, 3H), 1.67−1.61 (m, 2H), 1.58−1.30 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 136.8 (C), 134.0 (CH), 131.1 (CH), 129.0 (CH), 126.5 (CH), 118.5 (CH_2), 76.5 (C), 59.2 (CH), 43.2 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 26.4 (CH_2), 25.5 (CH_2), 22.8 (CH_2).

*Minor Diastereomer **60′**.* $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, diagnostic peaks) δ 136.7, 133.8, 131.8, 129.3, 127.4, 119.3, 77.7, 42.7, 26.0, 25.9.

(1R,2R*)-1-Allyl-2-((R*)-phenylsulfinyl)cycloheptan-1-ol (**61**).* To a solution of alcohol **59** (0.048 g, 0.18 mmol, dr 89:11) in CH_2Cl_2 (2 mL) was added 3-chloroperbenzoic acid (0.046 g, 70−75% in H_2O, 0.20 mmol) at 0 °C. After 1 h, the mixture was warmed to 20 °C and stirred for an additional 6 h. To the mixture was then added H_2O (3 mL), and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash chromatography (from 20:80 EtOAc−hexanes to 25:75 EtOAc−hexanes) afforded sulfoxide **61** as a white solid (0.032 g, 64%). X-ray-quality crystals were grown by the slow evaporation of a solution of sulfoxide **61** in a 25:75 mixture of EtOAc−hexanes. The relative stereochemical configuration of sulfoxide **61** was assigned by X-ray crystallographic analysis: mp = 131−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.52 (m, 4H), 7.50−7.46 (m, 1H), 6.06−5.95 (m, 1H), 5.30−5.26 (m, 2H), 3.02 (s, 1H), 2.88−2.78 (m, 2H), 2.49 (dd, J = 9.5, 1.6, 1H), 2.00−1.84 (m, 2H), 1.79−1.63 (m, 4H), 1.54−1.52 (m, 1H), 1.49−1.38 (m, 1H), 1.30−1.21 (m, 1H), 0.95−0.84 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.6 (C), 133.5 (CH), 130.4 (CH), 129.1 (CH), 124.3 (CH), 120.0 (CH_2), 76.2 (C), 71.8 (CH), 46.8 (CH_2), 40.3 (CH_2), 28.6 (CH_2), 27.7 (CH_2), 21.8 (CH_2), 18.6 (CH_2); IR (ATR) 3336, 2924, 1144, 1034, 1021, 753 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{23}O_2S$ $[M + H]^+$ 279.1413, found 279.1417.

(1R,2R*)-1-Allyl-2-((R*)-phenylsulfinyl)cyclooctan-1-ol (**62**) (1R*,2S*)-1-Allyl-2-((R*)-phenylsulfinyl)cyclooctan-1-ol (**62′**).* To a solution of alcohol **60** (0.137 g, 0.494 mmol, dr 87:13) in CH_2Cl_2 (3 mL) was added 3-chloroperbenzoic acid (0.085 g, 70−75% in H_2O, 0.49 mmol) at 0 °C. After 1 h, the mixture was warmed to 20 °C and stirred for an additional 15 h. To the mixture were then added saturated aqueous $Na_2S_2O_3$ (10 mL) and Et_2O (20 mL), and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), dried over $MgSO_4$, filtered through a short path of silica, and concentrated in vacuo. ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **62** was formed as an 87:13 mixture of diastereomers (**62**:**62′**). Purification by flash chromatography (from 25:75 EtOAc−hexanes to 50:50 EtOAc−hexanes) afforded sulfoxide **62** as a white solid (0.105 g, 73%). X-ray-quality crystals were grown by the slow evaporation of a solution of sulfoxide **62** in a 50:50 mixture of EtOAc−hexanes. The relative stereochemical configuration of sulfoxide **62** was assigned by X-ray crystallographic analysis: IR (ATR) 3360, 2920, 1443, 1021, 910, 730 cm^{-1}; HRMS (APCI) m/z calcd for $C_{17}H_{23}OS$ $[(M + H) - H_2O]^+$ 275.1464, found 275.1471.

*Major Diastereomer **62**.* ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52−7.46 (m, 4H), 7.45−7.42 (m, 1H), 6.07−6.00 (m, 1H), 5.27−5.21 (m, 2H), 3.10−3.07 (m, 1H), 2.68−2.64 (m, 1H), 3.59 (dd, J = 6.0,

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2.0, 1H), 2.00−1.95 (m, 1H), 1.88−1.76 (m, 3H), 1.63−1.50 (m, 6H), 1.39−1.21 (m, 2H), 0.35−0.27 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 142.4, 133.8, 130.5, 129.2, 124.2, 119.1, 76.2, 70.8, 44.5, 35.1, 29.7, 26.3, 25.0, 22.6, 17.8.

Minor Diastereomer ***62′***. ^1H NMR (600 MHz, $CDCl_3$, diagnostic peaks) δ 5.95−5.88 (m, 1H), 5.21−5.15 (m, 2H), 2.90 (dd, J = 7.5, 1.6, 1H), 2.43−2.39 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 144.0, 133.6, 131.3, 129.1, 126.7, 119.2, 76.5, 72.5, 42.6, 34.9, 29.1, 26.0, 25.8, 23.70, 23.66.

Competition Experiment between Ketone 56 and Cycloheptanone for Allylmagnesium Chloride. The competition experiment with ketone **56** and cycloheptanone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **56** (0.067 g, 0.30 mmol) and cycloheptanone (35 μL, 0.30 mmol) in THF (3 mL) with allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) added dropwise over 45 min at −78 °C. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed a 59:41 mixture of products (**59**:**64**). Alcohol **59** was formed as a single diastereomer (dr > 99:1).

Competition Experiment between Ketone 58 and Cyclooctanone for Allylmagnesium Chloride. The competition experiment with ketone **58** and cyclooctanone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **58** (0.071 g, 0.30 mmol) and cyclooctanone (0.038 g, 0.30 mmol) in THF (3 mL), where allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) was added dropwise over 45 min at −78 °C. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed a 55:45 mixture of products (**60**:**66**). Alcohol **60** was formed as a single diastereomer (dr >99:1).

(1R,2R*)-1-Allyl-2-(phenylthio)cyclohexan-1-ol and (1R*,2S*)-1-Allyl-2-(phenylthio)cyclohexan-1-ol* ***(69)***. Alcohols **69** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **68** (0.133 g, 0.51 mmol) and allylmagnesium chloride (380 μL, 2.0 M solution in THF, 0.76 mmol) in THF (5 mL) at −78 °C for 30 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **69** was formed as a 68:32 mixture of diastereomers. Purification by flash chromatography (3:97 EtOAc−hexanes) afforded the major diastereomer alcohol **69** as a yellow oil (0.055 g, 43%). A mixture of the minor diastereomer alcohol **69** and ketone **68** (ratio 92:8) was isolated as a yellow oil (0.058 g, 46%):

Major Diastereomer. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.43 (m, 2H), 7.30−7.20 (m, 3H), 5.87−5.76 (m, 1H), 5.10−5.04 (m, 2H), 3.17 (dd, J = 9.4, 5.0, 1H), 2.53−2.42 (m, 2H), 2.11 (br s, 1H), 1.91−1.83 (m, 2H), 1.74−1.68 (m, 2H), 1.65−1.56 (m, 1H), 1.51−1.43 (m, 2H), 1.34−1.24 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 135.7 (C), 133.5 (CH), 131.9 (CH), 128.95 (CH), 126.90 (CH), 118.6 (CH_2), 73.2 (C), 57.3 (CH), 45.0 (CH_2), 36.2 (CH_2), 30.4 (CH_2), 25.0 (CH_2), 21.4 (CH_2); IR (ATR) 3466, 2931, 1438, 1025, 913, 736 cm^{-1}; HRMS (APCI) m/z calcd for $C_{15}H_{19}S$ $[(M + H) - H_2O]^+$ 231.1202, found 231.1199.

Minor Diastereomer. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2H), 7.31−7.21 (m, 3H), 5.97−5.87 (m, 1H), 5.18−5.14 (m, 2H), 3.17 (dd, J = 10.1, 3.9, 1H), 2.43 (d, J = 7.3, 2H), 2.38 (br s, 1H), 2.10−2.06 (m, 1H), 1.94−1.91 (m, 1H), 1.78−1.73 (m, 1H), 1.68−1.60 (m, 2H), 1.39−1.30 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 135.8 (C), 133.2 (CH), 131.8 (CH), 129.01 (CH), 126.94 (CH), 118.8 (CH_2), 73.6 (C), 60.1 (CH), 39.9 (CH_2), 35.4 (CH_2), 30.8 (CH_2), 24.7 (CH_2), 22.2 (CH_2).

Competition Experiment between Ketone 68 and Cyclohexanone for Allylmagnesium Chloride. The competition experiment between ketone **68** and cyclohexanone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **68** (0.079 g, 0.30 mmol) and cyclohexanone (31 μL, 0.30 mmol) in THF (3 mL) with allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) added dropwise over 45 min at −78 °C. $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed a 61:39 mixture of products (**69**:**71**). Alcohol **69** was formed as a 67:33 mixture of diastereomers.

2-Chloro-3,3,5,5-tetramethylcyclohexan-1-one ***(74)***. A reported procedure[111] was adapted to prepare ketone **74**. To a solution of 3,3,5,5-tetramethylcyclohexanone (570 μL, 3.26 mmol) in MeCN (4 mL) was added *N*-chlorosuccinimide (0.475 g, 3.56 mmol) and *p*-toluenesulfonic acid monohydrate (0.033 g, 0.37 mmol). The mixture was heated to 82 °C in a silicone oil bath and stirred for 2 h. After cooling to 20 °C, to the mixture was added H_2O (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **74** as a white solid (0.331 g, 54%). X-ray-quality crystals were grown by the slow evaporation of a solution of ketone **74** in a 5:95 mixture of EtOAc−hexanes: mp = 48−50 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (br s, 1H), 2.56 (dd, J = 13.0, 1.8, 1H), 2.25 (d, J = 13.0, 1H), 1.82 (dd, J = 14.4, 1.6, 1H), 1.67 (d, J = 14.6, 1H), 1.18 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.6 (C), 73.2 (CH), 51.7 (CH_2), 50.6 (CH_2), 41.3 (C), 36.1 (C), 32.6 (CH_3), 30.6 (CH_3), 29.8 (CH_3), 24.5 (CH_3); IR (ATR) 2953, 1715, 1368, 902, 811, 739 cm^{-1}; HRMS (APCI) m/z calcd for $C_{10}H_{17}O$ $((M + H) - HCl)^+$ 153.1274, found 153.1272.

3,3,5,5-Tetramethyl-2-(phenylthio)cyclohexan-1-one ***(75)***. A reported procedure[103] was adapted to prepare ketone **75**. To a solution of sodium hydride (0.063 g, 60% in mineral oil, 1.5 mmol) in THF (2 mL) was added thiophenol (140 μL, 1.37 mmol) dropwise over 5 min. After 30 min, a solution of 3,3,5,5-tetramethylcyclohexanone (0.150 mg, 0.795 mmol) in THF (1 mL) was added to the reaction mixture by cannula. After 21 h, HCl (5 mL, 1.0 M in H_2O) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (5:95 EtOAc−hexanes) afforded ketone **75** as a colorless oil (0.087 g, 42%). The spectroscopic data (^1H NMR, $^{13}C\{^1H\}$ NMR, and HRMS) are consistent with the data reported in the literature.[92]

(1R,2S*)-1-Allyl-2-chloro-3,3,5,5-tetramethylcyclohexan-1-ol* ***(77)***. Alcohol **77** was prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **74** (0.198 g, 1.05 mmol) and allylmagnesium chloride (360 μL, 2.0 M solution in THF, 1.3 mmol) in THF (10 mL) at −78 °C for 25 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **77** was formed as a single diastereomer (dr >99:1). Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohol **77** as a colorless oil (0.168 g, 69%). The relative stereochemical configuration of alcohol **77** was assigned by the attempted derivatization of alcohol **77** to epoxide **79**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.85−5.75 (m, 1H), 5.15−5.11 (m, 2H), 3.72 (s, 1H), 2.41−2.35 (m, 1H), 2.30−2.25 (m, 1H), 1.88 (d, J = 2.4, 1H), 1.75 (dd, J = 14.7, 3.2, 1H), 1.57 (dd, J = 14.2, 3.2, 1H), 1.32 (dd, J = 14.6, 2.2, 1H), 1.29 (s, 3H), 1.27−1.24 (m, 1H), 1.24 (s, 3H), 1.02 (s, 3H), 0.88 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 133.3 (CH), 119.0 (CH_2), 78.1 (CH), 75.5 (C), 53.3 (CH_2), 48.3 (CH_2), 46.8 (CH_2), 37.5 (C), 35.9 (CH_3), 33.9 (CH_3), 30.5 (C), 27.9 (CH_3), 23.1 (CH_3); IR (ATR) 3569, 2953, 1368, 1080, 997, 814 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{22}Cl$ $[(M + H) - H_2O]^+$ 213.1405, found 213.1409.

(1R,2S*)-1-Allyl-3,3,5,5-tetramethyl-2-(phenylthio)cyclohexan-1-ol* ***(78)*** *and (1R*,2R*)-1-Allyl-3,3,5,5-tetramethyl-2-(phenylthio)-cyclohexan-1-ol* ***(78′)***. Alcohols **78** and **78′** were prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **75** (0.035 g, 0.15 mmol) and allylmagnesium chloride (150 μL, 2.0 M solution in THF, 0.30 mmol) in THF (2 mL) at −78 °C for 15 min. ^1H NMR and $^{13}C\{^1H\}$ NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **78** was formed as a 94:6 mixture of diastereomers (**78**:**78′**). Purification by flash chromatography (3:97 EtOAc−hexanes) afforded alcohol **78** as a colorless oil (0.023 g, 50%). The

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relative stereochemical configuration of alcohol **78** was assigned by the derivatization of alcohol **78** to sulfoxide **80**.

*Major Diastereomer **78**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2H), 7.29−7.25 (m, 2H), 7.20−7.16 (m, 1H), 5.57−5.47 (m, 1H), 4.93 (dd, J = 10.4, 0.7, 1H), 4.77 (dd, J = 17.0, 0.9, 1H), 2.86 (s, 1H), 2.49 (dd, J = 13.4, 7.5, 1H), 2.12 (s, 1H), 2.05 (dd, J = 13.4, 7.1, 1H), 1.71 (dd, J = 14.4, 2.7, 1H), 1.57 (dd, J = 14.2, 2.7, 1H), 1.32−1.26 (m, 5H), 1.24 (s, 3H), 1.22 (s, 3H), 0.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.4 (C), 133.7 (CH), 130.6 (CH), 129.0 (CH), 126.3 (CH), 118.4 (CH_2), 76.8 (C), 68.2 (CH), 54.2 (CH_2), 49.0 (CH_2), 47.3 (CH_2), 36.8 (C), 36.2 (CH_3), 35.1 (CH_3), 30.3 (C), 27.6 (CH_3), 24.4 (CH_3); IR (ATR) 3529, 1479, 1365, 913, 735, 689 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{28}NaOS$ $[M + Na]^+$ 327.1753, found 327.1755. Anal. Calcd for $C_{19}H_{28}OS$: C, 74.95; H, 9.27. Found: C, 74.86; H, 9.08.

*Minor Diastereomer **78′**.* ^{1}H NMR (500 MHz, $CDCl_3$, diagnostic peaks) δ 5.95−5.85 (m, 1H), 5.19 (dd, J = 10.3, 2.0 Hz, 1H), 5.12 (dd, J = 16.9, 1.7 Hz, 1H), 0.89 (s, 3H).

Reaction of Alcohol 77 with Potassium Carbonate. To a solution of alcohol **77** (0.062 g, 0.27 mmol, dr >99:1) in MeOH (15 mL) was added K_2CO_3 (0.094 g, 0.68 mmol) at 0 °C. After 1 h, the reaction mixture was warmed to 20 °C and stirred for an additional 20 h. To the mixture was then added H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed the presence of only alcohol **77** (dr >99:1).

(1R,2S*)-1-Allyl-3,3,5,5-tetramethyl-2-((S*)-phenylsulfinyl)-cyclohexan-1-ol (**80**) and (1R*,2R*)-1-Allyl-3,3,5,5-tetramethyl-2-((S*)-phenylsulfinyl)cyclohexan-1-ol (**80′**).* To a solution of alcohol **78** (0.060 g, 0.20 mmol, dr 92:8) in CH_2Cl_2 (1 mL) was added a solution of 3-chloroperbenzoic acid (0.049 g, 70% in H_2O, 0.20 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 1 h, the mixture was warmed to 20 °C and stirred for an additional 12 h. To the mixture were then added $NaHSO_3$ (0.030 g) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (1 × 15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (10:90 EtOAc−hexanes to 20:80 EtOAc−hexanes) afforded sulfoxide **80** as a white solid (0.046 g, 72%) with a diastereomeric ratio of 78:22 (**80**:**80′**). The mixture was used for characterization. X-ray-quality crystals were grown by the slow evaporation of a solution of sulfoxide **80** in a 20:80 mixture of EtOAc−hexanes. The relative stereochemical configuration of sulfoxide **80** was assigned by X-ray crystallographic analysis: mp = 124−126 °C; IR (ATR) 3498, 1285, 1130, 992, 687, 536 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{28}NaO_2S$ $[M + Na]^+$ 343.1702, found 343.1703.

*Major Diastereomer **80**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.58 (m 2H), 7.55−7.52 (m, 2H), 7.47−7.43 (m, 1H), 5.25−5.12 (m, 2H), 4.85−4.64 (m, 2H), 2.54−2.48 (m, 1H), 2.44 (s, 1H), 2.13−2.08 (m, 1H), 1.81 (s, 3H), 1.61−1.57 (m, 4H), 1.31 (s, 3H), 1.28 (s, 3H), 0.84 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 144.8, 133.4, 129.9, 129.25, 123.7, 117.9, 79.8, 75.1, 54.2, 49.6, 47.8, 36.0, 35.9, 34.9, 30.4, 27.6, 24.9;

*Minor Diastereomer **80′**.* ^{1}H NMR (400 MHz, $CDCl_3$, diagnostic peaks) δ 4.43 (d, J = 2.3, 1H), 1.73 (s, 3H), 0.83 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 144.7, 133.1, 132.7, 129.29, 126.9, 118.4, 77.3, 76.0, 57.7, 49.1, 48.5, 37.6, 35.7, 35.1, 29.8, 27.3, 23.9.

Competition Experiment between Ketone 74 and Propiophenone for Allylmagnesium Chloride. The competition experiment with ketone **74** and propiophenone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **74** (0.056 g, 0.30 mmol) and propiophenone (40 μL, 0.30 mmol) in THF (3 mL) with allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) added dropwise over 45 min at −78 °C. ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed a 51:49 mixture of products (**77**:**15**). Alcohol **77** was formed as a single diastereomer (dr >99:1).

Competition Experiment between Ketone 75 and Propiophenone for Allylmagnesium Chloride. The competition experiment with ketone **75** and propiophenone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **75** (0.082 g, 0.31 mmol) and propiophenone (40 μL, 0.30 mmol) in THF (3 mL) with allylmagnesium chloride (380 μL, 0.20 M solution in THF, 0.076 mmol) added dropwise over 45 min at −78 °C. ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed a 48:52 mixture of products (**78**:**15**). Alcohol **78** was formed as a single diastereomer (dr >99:1).

(R)-1-Oxa-4-thiaspiro[4.5]decan-6-one (**88**).* A reported procedure was adapted to prepare ketone **88**.[112] A solution of 1,2-cyclohexanedione (1.0 g, 9.0 mmol), 2-mercaptoethanol (0.69 mL, 9.9 mmol), and *p*-toluenesulfonic acid monohydrate (0.10 g, 0.53 mmol) in PhMe (150 mL) was heated to 80 °C in a silicone oil bath. After 16 h, the reaction mixture was filtered through 1 inch of silica. Purification by flash chromatography (from 0:100 Et_2O−hexanes to 10:90 Et_2O−hexanes) afforded ketone **88** as a colorless oil (0.61 g, 40%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40−4.37 (m, 1H), 4.28−4.22 (m, 1H), 3.07−3.04 (m, 2H), 2.78−2.70 (m, 1H), 2.44−2.38 (m, 1H), 2.30−2.15 (m, 2H), 2.03−1.95 (m, 2H), 1.74−1.53 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 205.3 (C), 95.8 (C), 72.0 (CH_2), 40.4 (CH_2), 38.9 (CH_2), 33.0 (CH_2), 26.1 (CH_2), 25.0 (CH_2); IR (ATR) 2940, 1716, 1086, 1070, 885, 761 cm^{-1}; HRMS (ESI) m/z calcd for $C_8H_{13}O_2S$ $[M + H]^+$ 173.0631, found 173.0631.

(5R,6R*)-6-Allyl-1-oxa-4-thiaspiro[4.5]decan-6-ol (**89**).* Alcohol **89** was prepared using the representative procedure for the addition of Grignard reagents to ketones using ketone **88** (0.072 g, 0.42 mmol) and allylmagnesium chloride (305 μL, 2.0 M solution in THF, 0.61 mmol) in THF (4 mL) at −78 °C for 15 min. ^{1}H NMR and ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed that alcohol **89** was formed as a single diastereomer (dr >99:1). Purification by flash chromatography (5:95 EtOAc−hexanes) afforded alcohol **89** as a colorless oil (0.078 g, 87%). The relative stereochemical configurations of alcohol **89** was assigned by the derivatization of alcohol **89** to sulfoxide **92**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.96−5.87 (m, 1H), 5.12−5.09 (m, 2H), 4.42−4.39 (m, 1H), 4.08−4.04 (m, 1H), 2.97−2.95 (m, 2H), 2.60 (dd, J = 14.3, 6.2, 1H), 2.42 (dd, J = 13.8, 8.1, 1H), 2.21 (br s, 1H), 2.08−2.04 (m, 1H), 1.98−1.93 (m, 1H), 1.83−1.80 (m, 1H), 1.71−1.70 (m, 1H), 1.55−1.51 (m, 1H), 1.47−1.40 (m, 1H), 1.36−1.33 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 134.5 (CH), 118.0 (CH_2), 104.5 (C), 75.7 (C), 71.8 (CH_2), 37.9 (CH_2), 37.0 (CH_2), 36.1 (CH_2), 33.3 (CH_2), 24.1 (CH_2), 21.6 (CH_2); IR (ATR) 3485, 2933, 1075, 997, 911, 855 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{17}OS$ $[(M + H) - H_2O]^+$ 197.0995, found 197.0995. Anal. Calcd for $C_{11}H_{18}O_2S$: C, 61.65; H, 8.47. Found: C, 61.36; H, 8.31.

Competition Experiment between Ketone 88 and 4-*tert*-Butylcyclohexanone for Allylmagnesium Chloride. The competition experiment with ketone **88** and 4-*tert*-butylcyclohexanone was performed following the representative procedure for competition experiments with allylmagnesium chloride using ketone **88** (0.030 g, 0.17 mmol) and 4-*tert*-butylcyclohexanone (277 g, 0.18 mmol) in THF (7 mL) with allylmagnesium chloride (230 μL, 0.20 M solution in THF, 0.045 mmol) added dropwise over 45 min at −78 °C. ^{13}C{^{1}H} NMR spectroscopic analysis of the unpurified reaction mixture revealed a 37:63 mixture of products (**89**:**91**). Alcohol **89** was formed as a single diastereomer (dr >99:1).

(5R,6R*)-6-Allyl-6-hydroxy-1-oxa-4-thiaspiro[4.5]decane 4,4-dioxide (**92**).* To a solution of alcohol **89** (0.060 g, 0.28 mmol, dr >99:1) in CH_2Cl_2 (3 mL) was added 3-chloroperbenzoic acid (0.070 g, 70−75% in H_2O, 0.28 mmol) at 0 °C. After 1 h, the mixture was warmed to 20 °C and stirred for an additional 17 h. To the mixture was then added H_2O (3 mL), and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (30:70 EtOAc−hexanes)

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afforded sulfone **92** as a white solid (0.042 g, 61%). X-ray-quality crystals were grown by the slow evaporation of a solution of sulfone **92** in MeOH. The relative stereochemical configuration of sulfone **92** was assigned by X-ray crystallographic analysis: mp = 141−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94−5.84 (m, 1H), 5.18−5.11 (m, 2H), 4.62−4.56 (m, 1H), 4.31−4.24 (m 1H), 3.31−3.20 (m, 2H), 2.82 (s, 1H), 2.72 (dd, J = 14.2, 5.4, 1H), 2.42−2.37 (m, 1H), 1.29−2.23 (m, 1H), 1.98−1.92 (m, 1H), 1.79−1.72 (m, 2H), 1.66−1.60 (m, 3H), 1.42−1.31 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 132.7 (CH), 118.8 (CH_2), 95.9 (C), 76.0 (C), 62.4 (CH_2), 49.9 (CH_2), 38.6 (CH_2), 34.4 (CH_2), 28.9 (CH_2), 21.8 (CH_2), 21.2 (CH_2); IR (ATR) 3509, 2934, 1280, 1116, 1044, 911 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{17}OS$ $[(M + H) - H_2O]^+$ 229.0893, found 229.0887.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02844.

Stereochemical proofs, experimental information, crystallographic data, computational details, copies of ^{1}H and ^{13}C{^{1}H} spectra (PDF)

Accession Codes

CCDC 2123655−2123663 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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