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Alkenes as Chelating Groups in Diastereoselective Additions of Organometallics to Ketones

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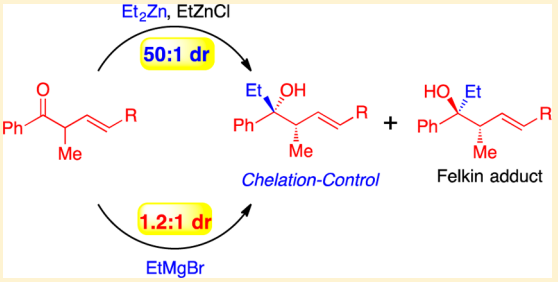
Supporting Information

ABSTRACT: Alkenes have been discovered to be chelating groups to Zn(II), enforcing highly stereoselective additions of organozincs to β,γ-unsaturated ketones. ^{1}H NMR studies and DFT calculations provide support for this surprising chelation mode. The results expand the range of coordinating groups for chelation-controlled carbonyl additions from heteroatom Lewis bases to simple C−C double bonds, broadening the 60 year old paradigm.



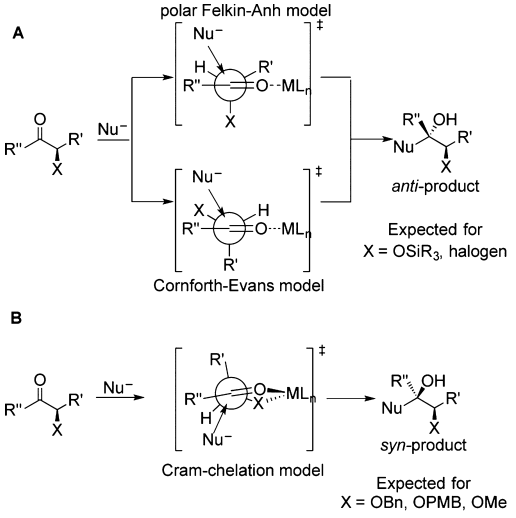
1. INTRODUCTION

Diastereoselective additions of organometallic nucleophiles to α-chiral carbonyl compounds has been a topic of significant interest for over 60 years.[1] During this time, several models have been advanced to predict the stereochemical outcome of such additions to α- and β-chiral aldehydes, ketones, and imines.[2] Among these models the Felkin−Ahn,[3] Cornforth−Evans,[4] and Cram-chelation models[5] are the most generally accepted (Scheme 1).

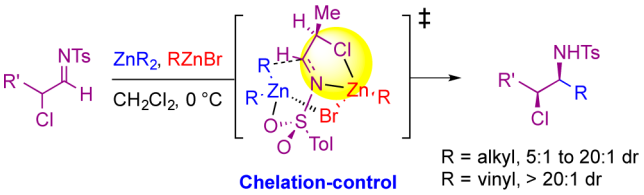
It is well known that α- and β-silyloxy aldehydes and ketones react with nucleophiles via the Felkin−Anh pathway with few exceptions (Scheme 1A).[2,6] We recently demonstrated, however, that a remarkable class of Lewis acids, RZnX (X = halide or OSO_2R), promotes the addition of a wide range of alkyl and vinyl organozinc reagents to α- and β-silyloxy aldehydes and ketones via *chelation control* with very high diastereomeric ratios (Scheme 1B).[7]

On the basis of these results, we hypothesized that less Lewis basic substituents, such as halides of C−X bonds, might also coordinate to RZnX, leading to chelation control. As shown in Scheme 2 we developed a highly diastereoselective method for chelation-controlled additions to α-chloro *N*-sulfonyl aldimines with dr's as high as 20:1.[8]

Scheme 1. Models for Additions to Carbonyl Groups: (A) Felkin−Ahn and Cornforth−Evans and (B) Cram-Chelation



Scheme 2. Chelation-Controlled Addition of Organozinc Reagents to α-Chloro Imines



In spite of these advances, the boundary conditions defining effective chelating groups remain to be fully described. Typically, heteroatoms containing basic, unhindered lone pairs are utilized in chelation-directed processes, but the above work has shown that even hindered and weakly basic heteroatoms can participate. We contemplated whether it would be possible to expand beyond heteroatoms by using simple alkenes as chelating groups to effect facial control in additions to carbonyls.

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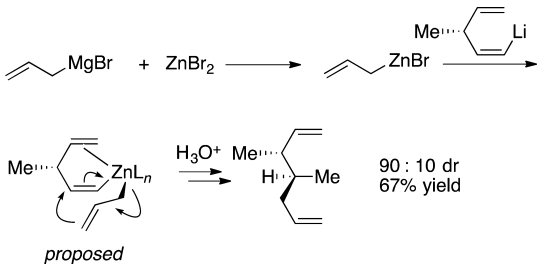
The strength of a metal−π interaction depends on both the nature of the alkene and the metal center, as described by the Dewar−Chatt−Duncanson model.[9] This model involves a synergistic interaction with donation of the alkene π-orbital to the metal and π-back-bonding from a filled d-orbital of the metal to the π^*-orbital of the alkene. The Dewar−Chatt−Duncanson model explains well why stable olefin complexes of d^{10} metals such as Ni(0), Pd(0), or Pt(0) are abundant.[10] In contrast, other d^{10} metals, such as Zn(II), Cd(II), or Hg(II), do not usually form olefin complexes. The ability of a metal to back-bond to an olefin is related to its promotion energy;[11] the higher the promotion energy, the lower the propensity for back-bonding. Hg(II) has a promotion energy of 12.8 eV, and some examples of binding with arene derivatives are known.[12] For Zn(II) and Cd(II), the promotion energies are higher (17.1 and 16.6 eV, respectively). Coordination of π-systems to these metals arises predominantly from σ-donation, which explains the lability and, therefore, the scarcity of such systems.[13] Olefin complexes with Zn(II) are intramolecular and/or exist only in the solid state.[14] To the best of our knowledge, no intermolecular π-interactions of this kind have been observed in solution.

Not surprisingly, very few examples of Zn−π interactions acting as stereocontrol elements have been proposed. In seminal work, Marek, Beruben, and Normant demonstrated that the presence of a terminal double bond in the allylzincation resulted in a high degree of acylic stereocontrol (Scheme 3).[14a]

Scheme 3. Diastereoselective Olefin-Directed Allylzincation



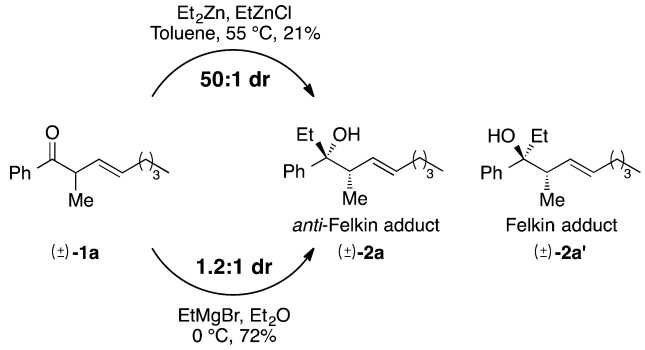
Interaction of zinc with an aryl ring has also been proposed to explain the reversal of diastereoselectivity in Simmons−Smith halocyclopropanation reactions.[15] Elegant studies by Yamamoto and co-workers have demonstrated that coordination of double and triple bonds to aluminum(III) can change reaction chemoselectivity.[16]

With this backdrop, we asked whether racemic β,γ-enones could undergo chelation-controlled additions by means of coordination of the carbonyl *and alkene* moieties to zinc. Herein, we substantiate this hypothesis with the counter-intuitive discovery that chiral β,γ-enones undergo highly diastereoselective additions, albeit in low yield due to competing aldol processes. NMR and computational studies provide support for chelation of the β,γ-enones to Zn(II). This study hints that even weak metal π-interactions can be used to control diastereoselectivity and expands the boundaries of groups that undergo stereoselective chelation-controlled carbonyl additions.

2. RESULTS AND DISCUSSION

2.1. Proof of Concept. To determine whether or not racemic β,γ-enones would undergo chelation-controlled addition reactions, we prepared ketone **1a** (Scheme 4; see

Scheme 4. Selectivity of the Ethyl Addition to Ketone 1a



Experimental Section for details). Ketone **1a** was treated with $ZnEt_2$ and EtZnCl under a wide variety of conditions, giving mixtures of addition product and aldol byproducts, with the aldol products predominating in all cases. Nonetheless, when racemic **1a** was exposed to $ZnEt_2$ (3 equiv) and EtZnCl (2 equiv) in toluene and heated to 55 °C, the chelation-controlled **2a** and Felkin **2a′** addition products formed with a surprising diastereomeric ratio of 50:1 (determined by GC). In contrast, treatment of **1a** with EtMgBr at 0 °C in diethyl ether generated **2a** and **2a′** with only 1.2:1 dr. The high selectivity with organozinc reagents provides *proof of concept* that the addition proceeds *via a chelation-controlled pathway*. As mentioned, all attempts to shift the balance between aldol processes and the addition reaction by changing solvents, concentrations, reagent ratios, zinc Lewis acids, temperatures, organozinc reagents, and addition rates led to similar or lower yields of the addition products. It should also be emphasized that no stereoselectivity was obtained in coordinating solvents due to binding to the zinc Lewis acid.

2.2. Exploration of Chelation by NMR. ^{1}H NMR has been widely used to study alkene−metal coordination in solution.[17,18] We therefore decided to probe the binding of racemic β,γ-enones to EtZnCl by treatment of **1a** with 4 equiv of EtZnCl in CD_2Cl_2.[19] The chemical shift variations ($\Delta\delta$) with respect to the free substrate are reported in Table 1 (entry 1). Notably, both vinyl protons shift downfield upon addition of EtZnCl. Such downfield shifts are generally observed on binding of olefins to d^0 metals,[8] which is consistent with σ-donation of the alkene to the metal and little or no back-bonding. In contrast, upfield shifts have been reported with d^{10} metals, such as Pd(0) and Pt(0).[18] The different magnitudes of the shifts for the β and γ protons in Table 1 (entry 1) are consistent with unsymmetrical binding of the olefin to the metal, a characteristic also observed with d^0 metal−olefin complexes,[20] and expected for geometrically constrained chelate formation.

To further probe interactions between enones and EtZnCl, a series of γ-aryl substituted β,γ-unsaturated ketones (**1b−d**) were examined. ^{1}H NMR experiments analogous to those executed with **1a** were performed (Table 1, entries 2−4). When the phenyl group is substituted with an electron-donating group, the observed $\Delta\delta$ increases (entry 2 vs 3). In contrast, with an electron-withdrawing aryl group, the $\Delta\delta$ decreases (entry 2 vs 4). These results indicate that stronger interactions with the zinc center occur when there is more electron density on the π-system. The greater $\Delta\delta$ values observed for the γ protons are consistent with the larger δ^+ character of the double

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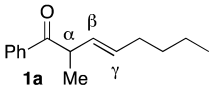
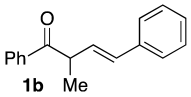
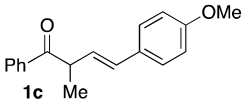
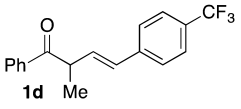
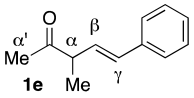
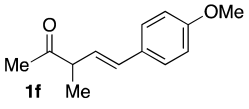
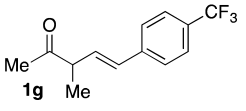
Table 1. ^{1}H NMR Binding Study of EtZnCl with β,γ-Unsaturated Ketones 1a–g

entry	substrate	equiv. EtZnCl	α(Δδ)[a]	β(Δδ)[a]	γ(Δδ)[a]	α′(Δδ)[a]
1	 **1a**	4	0.31	0.23	0.39	–
2	 **1b**	4	0.23	0.02	0.18	–
3	 **1c**	4	0.24	0.05	0.24	–
4	 **1d**	4	0.18	0	0.11	–
5	 **1e**	4	0.26	-0.04	0.12	0.34
6	 **1f**	4	0.27	-0.03	0.14	0.35
7	 **1g**	4	0.28	-0.05	0.12	0.35

[a]Chemical shift variations with respect to the free β,γ-unsaturated ketones **1a–g**.

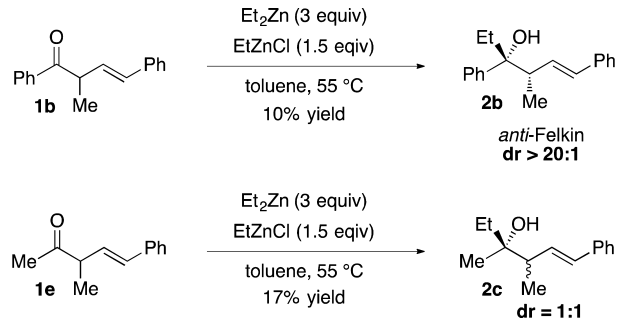
bond at benzylic position. It also suggests that coordination preferentially occurs at the β position.

Similar ^{1}H NMR studies were then conducted on the methyl ketones **1e–g** (Table 1, entries 5–7). To our surprise, the results obtained were drastically different from those in entries 1–4. Irrespective of the electron density of the double bond, the $\Delta\delta$ values were almost unchanged compared to the reference compound **1e** (entries 5 vs 6 and 7). Moreover, the chemical shift variations are systematically greater for the α' protons relative to the α proton, which is opposite that expected for chelation.[6e] Together, these results suggest that substrates **1e–g** do not undergo alkene chelation.

2.3. Reactivity Studies with α-Phenyl and α-Methyl Ketones. On the basis of the contrasting results from the NMR studies above, we examined additions to phenyl ketone **1b** and methyl ketone **1e** (Scheme 5) under the conditions employed in Scheme 4. The phenyl ketone **1b** underwent addition in the presence of EtZnCl to give the chelation-controlled adduct **2b** with a very high selectivity (dr >20:1) consistent with the chelation observed in the ^{1}H NMR spectra. On the other hand, the methyl ketone **1e** afforded a 1:1 mixture of diastereomers **2c** and **2c′**, in agreement with the absence of chelation features in the ^{1}H NMR spectra of **1e** and its analogues. Although the tertiary alcohols are the minor products in these reactions, the observed stereoselectivities clearly point to distinct reaction manifolds. These unanticipated reaction outcomes are explored computationally in the next section.

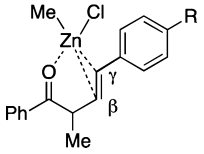
2.4. Exploration of the Reaction Pathways Using Computational Methods. To gain insight into the factors

Scheme 5. Addition of Et_2Zn to Ketones 1b and 1e in the Presence of EtZnCl



giving rise to the observed diastereoselectivities and ^{1}H NMR chemical shift changes in Scheme 5 and Table 1, respectively, DFT calculations were undertaken.[21] First, the ground-state geometries were calculated for the adduct between the β,γ-unsaturated ketone and MeZnCl. Coordination of the alkene to the Zn(II) center was readily found even when a solvation model (toluene, CPCM) was exmployed. Table 2 shows how alkene binding is modulated by the electronic properties of the γ-aryl substituent. In agreement with ^{1}H NMR binding studies, a substrate with an electron donor group (R = OMe) coordinates more strongly than a substrate with an electron-withdrawing group (R = CF_3), as evidenced by the Zn–alkene distances. Comparison of the Zn–C_β and Zn–C_γ bond lengths also suggests a stronger coordination between the metal center and the β carbon, which is consistent with the ^{1}H NMR observations described above.

Table 2. Selected Distances and Relative Enthalpies Calculated at the B3LYP/LANL2DZ Level in Toluene (CPCM) after Coordination of 1b–d with MeZnCl



entry	R	ΔH (kcal/mol)[a]	Zn–C_β (Å)	Zn–C_γ (Å)	C=C (Å)
1	H	−1.7	3.421	3.845	1.354
2	OMe	−2.1	3.420	3.840	1.355
3	CF_3	−1.8	3.427	3.855	1.354

[a]Enthalpy difference calculated between the mono- and tricoordinated complexes.

Next, the transition states for the additions of $ZnMe_2$ were calculated using MeZnCl as Lewis acid. The lowest energy transition states leading to the *anti*-Felkin adduct (**TS-1**) and the Felkin adduct (**TS-2**) incorporate two zinc atoms each (Figure 1). This general model for dialkylzinc addition to carbonyls has been extensively studied both experimentally and computationally.[22–24] The more Lewis acidic MeZnCl serves to activate the carbonyl. The zinc atom of the $ZnMe_2$ complexes to both the choride and the carbonyl of this initial adduct, causing nucleophilic activation of the $ZnMe_2$. In the lowest energy transition state, chelation occurs between the alkene and the zinc of the MeZnCl. The Zn–alkene distances are comparable to those previously observed in the solid state for Zn(II)–π coordination.[14c] The Zn–π coordination forces the alkene moiety to orient *syn* to the C=O bond (O=CC_βC$_\gamma$

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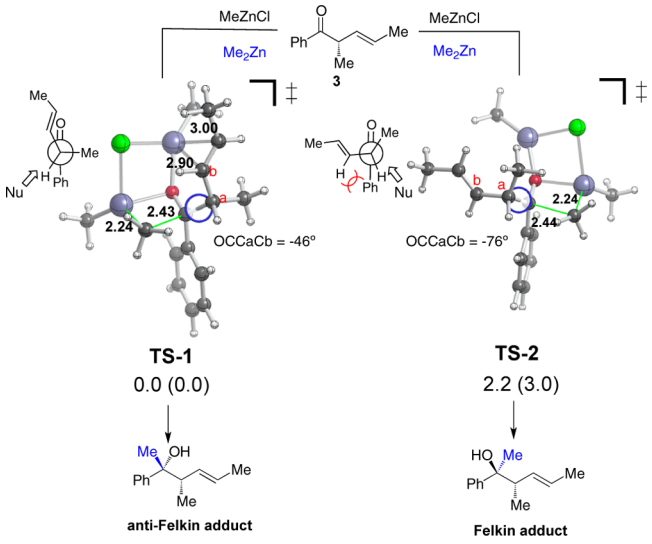

Figure 1. Relative free energies and enthalpies (in parentheses), in kcal/mol, calculated for the methyl addition to ketone **3**, calculated at the B3LYP/LANL2DZ level in toluene (CPCM). Selected bond distances are in angstroms.

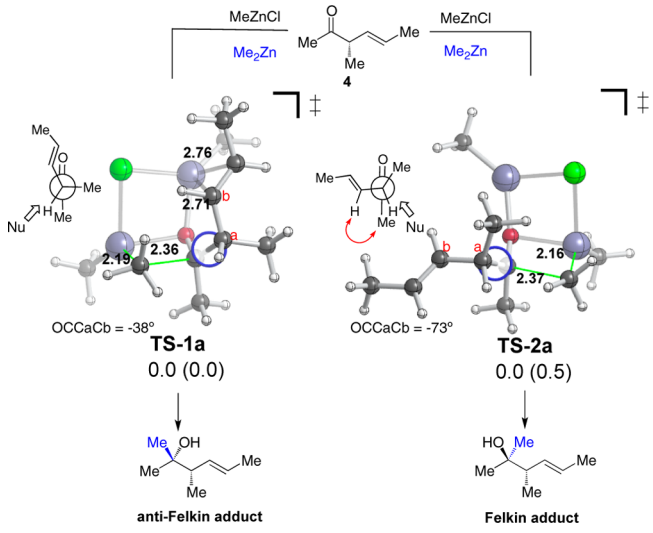

Figure 2. Relative free energies and enthalpies (in parentheses), displayed in kcal/mol, calculated for the methyl addition to ketone **4**, calculated at the B3LYP/LANL2DZ level in toluene (CPCM). Selected bond distances are in angstroms.

dihedral = −46°). This orientation minimizes the steric interactions between the α-methyl and the phenyl ring in the *anti*-Felkin approach (see left Newman projection in Figure 1). Other conformations were >5 kcal/mol higher in energy (see Supporting Information for structures).

In contrast, the lowest energy transition state leading to the Felkin adduct (**TS-2**) does not involve alkene chelation to the Zn and is significantly higher in energy (2−3 kcal/mol).[25] It was possible to locate transition-state structures for the Felkin approach with Zn−π chelation, but severe steric interactions between the α-methyl and the phenyl ring cause them to be an additional ∼3 kcal/mol higher in energy than **TS-2** (see Supporting Information). Notably, the relative energies between the two diastereomeric transition states are in excellent agreement with the experimentally determined diastereoselectivities, which favor the chelation-controlled product by >20:1 dr.[26]

In contrast to the phenyl ketone, computations show a negligible energy difference between the two lowest energy diastereomeric transition-state structures for the methyl ketone (Figure 2, **TS-1a** and **TS-2a**). Again, the lowest energy transition-state structure leading to the *anti*-Felkin product shows chelation between the π-system and the Zn, whereas that leading to the Felkin product is not chelated. However, **TS-2a**, which leads to the Felkin product, is now nearly isoenergetic with **TS-1a**, predicting low diastereoselectivty, in accord with that observed (Scheme 5). The unfavorable steric interactions present between the phenyl ketone and the α-alkenyl substituent that destabilize **TS-2** (see right Newman projection in Figure 1) are diminished in **TS-2a** (see right Newman projection in Figure 2) due to the smaller methyl ketone group (see Supporting Information).

3. CONCLUSIONS

In summary, on the basis of the ability of Lewis acidic alkyl zinc halides and pseudohalides to promote chelation-controlled additions with carbonyl compounds possessing α- or β-silyloxy and α-halo groups, which are typically regarded as ineffective chelating groups, we hypothesized that alkenes might act similarly. Experimentally, this hypothesis was validated with β,γ-enones undergoing chelation-controlled additions of alkylzinc reagents in the presence of Lewis acid EtZnCl with diastereoselectivities as high as 50:1. The proposed chelation control is also supported by DFT calculations and solution ^{1}H NMR binding studies with β,γ-unsaturated ketones. To our surprise, we found that the nature of the substrate played a dramatic role in the proclivity to form Zn−π interactions, which showed excellent correlation with both solution binding studies and computations. Importantly, these results show that metal−alkene interactions, even with metal centers for which no solution-phase η^2-alkene adducts are known, can be sufficient to control diastereoselectivity in carbonyl addition reactions. These insights show that the range of effective coordinating groups for chelation-controlled carbonyl additions and related processes extends beyond highly basic heteroatoms, augmenting the long-standing paradigm. In a broader synthetic context, such interactions may enable control of stereo- and chemoselectivities of related chemical processes.

4. EXPERIMENTAL SECTION

4.1. General Methods. All water- and air-sensitive reactions were performed under an N_2 atmosphere using flame-dried glassware and standard Schlenk and vacuum line techniques. The progress of reactions was monitored by thin-layer chromatography (TLC) and visualized by UV or by staining with ceric ammonium molybdate or potassium permanganate. Silica gel (230−400 mesh) was used for flash chromatography. The ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were obtained using a 500 and 125 MHz Fourier transform NMR spectrometer, respectively. ^{1}H NMR were referenced to tetramethylsilane in $CDCl_3$ (δ = 0 ppm), and ^{13}C{^{1}H} NMR spectra were referenced to residual solvent ($CDCl_3$, δ = 77.16 ppm). Coupling constants are reported in hertz. Toluene, acetonitrile, and dichloromethane were dried through alumina columns and degassed before use. Ethyl zinc chloride was synthesized according to a method reported in the literature.[27] Other reagents were obtained from commercial sources and used without further purification. ***CAUTION: Care must be taken when handling pyrophoric dialkylzinc reagents.***

4.2. Quantum Mechanical Methods. All geometries were optimized using DFT at the B3LYP/LANL2DZ[28] level of theory in toluene (unless otherwise noted) with the CPCM[29] solvation model as implemented in GAUSSIAN09.[30] All stationary points were

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characterized as transition states (one and only one imaginary frequency) or minima (zero imaginary frequencies). Various methods were assessed to compare with the solid-state geometry of the zinc–alkene coordination (see Supporting Information, Figure C1).

4.3. Synthesis of the β,γ-Unsaturated Ketones 1a–d. β,γ-Unsaturated benzyl ketones **1a–d** were synthesized from benzaldehyde in a three-step sequence, involving a Barbier crotylation, an olefin cross-metathesis, and a Dess–Martin periodinane oxidation.

*General Procedure for the Synthesis of Compounds **1a–d**.* To a solution of benzaldehyde (1.0 g, 9.42 mmol) in a THF/$NH_4Cl_{aq.sat}$ mixture (25:25 mL) were added crotyl chloride (1.38 mL, 14.13 mmol) and zinc powder (1.23 g, 18.84 mmol). The reaction mixture was stirred at room temperature for 12 h. The media was then filtered, and most of the THF removed *in vacuo*. The media was then extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 2-methyl-1-phenylbut-3-en-1-ol (1.0 g, 6.22 mmol, 45:55 diastereomer mixture) as a light yellow oil in 66% yield, without further purification. Part of this homoallylic alcohol (100 mg, 0.62 mmol) was taken up in dry degassed DCM (3 mL). A terminal alkene (1-hexene, styrene, 4-methoxy styrene, or 4-trifluoromethylstyrene for **1a–d**, respectively, 1.86 mmol) and second-generation Grubbs catalyst (26 mg, 31.0 μmol) were then added. The reaction mixture was heated at reflux under N_2 for 12 h. The reaction media was concentrated *in vacuo*, and the crude mixture was purified by silica gel flash chromatography. The resulting pure crossed alcohols were then taken up in dry DCM (0.2 M), and a 15% solution of Dess–Martin periodinane in DCM (1.2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The white solid that formed was filtered off and washed with cold diethyl ether (5 mL). The filtrate was concentrated *in vacuo* and purified by silica gel flash chromatography to yield β,γ-unsaturated ketones **1a–d**.

*(E)-2-Methyl-1-phenyloct-3-en-1-one (**1a**).* The general procedure was applied with 1-hexene (0.23 mL, 1.86 mmol) as coupling partner. The title compound **1a** (79 mg, 0.37 mmol) was obtained as a colorless oil in 39% yield over the three steps. Spectral data obtained were in accordance with the literature.[31]

*(E)-2-Methyl-1,4-diphenylbut-3-en-1-one (**1b**).* The general procedure was applied with styrene (0.21 mL, 1.86 mmol) as coupling partner. The title compound **1b** (76 mg, 0.32 mmol) was obtained as a colorless oil in 34% yield over the three steps. Spectral data obtained were in accordance with the literature.[31]

*(E)-4-(4-Methoxyphenyl)-2-methyl-1-phenylbut-3-en-1-one (**1c**).* The general procedure was applied with 4-methoxystyrene (0.25 mL, 1.86 mmol) as coupling partner. The title compound **1c** (89 mg, 0.33 mmol) was obtained as a colorless oil in 36% yield over the three steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.41 (d, *J* = 6.8 Hz, 3H), 3.78 (s, 3H), 4.29 (apparent quintet, *J* = 6.9 Hz, 1H), 6.20 (dd, *J* = 15.9, 8.2 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.80–6.83 (m, 2H), 7.24–7.28 (m, 2H), 7.43–7.48 (m, 2H), 7.52–7.56 (m, 1H), 8.00–8.03 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 17.9, 45.0, 55.4, 114.1, 127.6, 127.7, 128.7, 128.8, 129.9, 131.2, 133.1, 136.6, 159.3, 201.4. IR (neat): 3060, 3032, 2966, 2930, 2872, 2836, 1679, 1606, 1510, 1447, 1247, 1174, 1031, 969, 819, 701. HRMS (CI): *m*/*z* $[C_{18}H_{18}O_2]^+$ calcd 266.1307, found 266.1312.

*(E)-2-Methyl-1-phenyl-4-(4-(trifluoromethyl)phenyl)but-3-en-1-one (**1d**).* The general procedure was applied with 4-trifluoromethylstyrene (0.27 mL, 1.86 mmol) as coupling partner. The title compound **1d** (70 mg, 0.23 mmol) was obtained as a colorless oil in 24% yield over the three steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.44 (d, *J* = 6.8 Hz, 3H), 4.35 (apparent quintet, *J* = 6.9 Hz, 1H), 6.49 (dd, *J* = 16.0, 7.3 Hz, 1H), 6.55 (d, *J* = 16.0 Hz, 1H), 7.43 (br d, *J* = 8.2 Hz, 2H), 7.48 (br t, *J* = 7.7 Hz, 2H), 7.53 (br d, *J* = 8.2 Hz, 2H), 7.55–7.59 (m, 1H), 7.99–8.03 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 17.9, 44.9, 124.3 (q, *J* = 271.9 Hz), 125.6 (q, *J* = 3.8 Hz), 126.6, 128.7, 128.9, 129.5 (q, *J* = 32.5 Hz), 130.4, 132.7, 133.4, 136.4, 140.6, 200.9. IR (neat): 3060, 2975, 2933, 1683, 1615, 1448, 1414, 1325, 1165, 1122, 1067, 1016, 972, 822, 705. HRMS (ESI): *m*/*z* $[C_{18}H_{15}F_3O + H]^+$ calcd 305.1153, found 305.1152.

4.4. Synthesis of the β,γ-Unsaturated Ketones 1e–g. β,γ-Unsaturated ketones **1e–g** were synthesized from acetaldehyde in a three-step sequence, involving a Barbier crotylation, a Heck reaction, and a Dess–Martin periodinane oxidation.

*General Procedure for the Synthesis of Compounds **1e–g**.* To a solution of acetaldehyde (1.0 g, 22.70 mmol) in a THF/$NH_4Cl_{aq.sat}$ mixture (50:50 mL) were added crotyl chloride (3.32 mL, 34.05 mmol) and zinc powder (2.97 g, 45.40 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction media was then filtered, and most of the THF removed *in vacuo*. The resulting solution was then extracted with DCM (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 3-methylpent-4-en-2-ol (1.18 g, 11.80 mmol, 45:55 diastereomer mixture) as a light yellow oil in 52% yield, without further purification. To a mixture of $Pd(OAc)_2$ (4.5 mg, 20.0 μmol) and tris(*o*-tolyl)phosphine (12 mg, 40.0 μmol) under nitrogen was added a dry degassed solution of the prepared homoallylic alcohol (100 mg, 1.0 mmol) in MeCN (5 mL). Freshly distilled triethylamine (0.14 mL, 1.0 mmol) and an aryl bromide (bromobenzene, 4-bromoanisole, or 4-bromobenzotrifluoride for **1e–g**, respectively, 2.0 mmol) were then added. The mixture was heated under reflux for 12 h. The reaction media was concentrated *in vacuo*, taken up in DCM (10 mL), and washed with $NH_4Cl_{aq.sat}$ (3 × 5 mL) and brine (5 mL). The organic layer was filtered, dried, and concentrated *in vacuo* to give a crude mixture, which was purified by silica gel flash chromatography. The resulting pure crossed alcohol was then taken up in dry DCM (0.2 M), and a 15% solution of Dess–Martin periodinane in DCM (1.2 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The white solid that formed was filtered off and washed with cold diethyl ether (5 mL). The filtrate was concentrated *in vacuo* and purified by silica gel flash chromatography to yield β,γ-unsaturated ketones **1e–g**.

*(E)-3-Methyl-5-phenylpent-4-en-2-one (**1e**).* The general procedure was applied with bromobenzene (0.21 mL, 2.0 mmol) as coupling partner. The title compound **1e** (49 mg, 0.28 mmol) was obtained as a colorless oil in 15% yield over the three steps. Spectral data obtained were in accordance with the literature.[32]

*(E)-5-(4-Methoxyphenyl)-3-methylpent-4-en-2-one (**1f**).* The general procedure was applied with 4-bromoanisole (0.25 mL, 2.0 mmol) as coupling partner. The title compound **1f** (73 mg, 0.36 mmol) was obtained as a white solid in 19% yield over the three steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.26 (d, *J* = 6.9 Hz, 3H), 2.18 (s, 3H), 3.32 (apparent quintet, *J* = 7.2 Hz, 1H), 3.80 (s, 3H), 6.01 (dd, *J* = 15.8, 8.5 Hz, 1H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.83–6.87 (m, 2H), 7.27–7.32 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 16.3, 28.2, 51.5, 55.4, 114.2, 126.7, 127.6, 129.8, 131.7, 159.4, 209.7. IR (neat): 2963, 2933, 2837, 1710, 1606, 1512, 1452, 1356, 1252, 1168, 1032, 968, 813. HRMS (ESI): *m*/*z* $[C_{13}H_{16}O_2 + H]^+$ calcd 205.1229, found 205.1230. T_{fus}: 34–35 °C.

*(E)-3-Methyl-5-(4-(trifluoromethyl)phenyl)pent-4-en-2-one (**1g**).* The general procedure was applied with 4-bromobenzotrifluoride (0.28 mL, 2.0 mmol) as coupling partner. The title compound **1g** (39 mg, 0.16 mmol) was obtained as a colorless oil in 8% yield over the three steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.30 (d, *J* = 6.9 Hz, 3H), 2.21 (s, 3H), 3.39 (apparent quintet, *J* = 7.4 Hz, 1H), 6.30 (dd, *J* = 15.9, 8.4 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 7.45 (br d, *J* = 8.2 Hz, 2H), 7.56 (br d, *J* = 8.2 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 16.3, 28.4, 51.3, 124.3 (q, *J* = 271.8 Hz), 125.7 (q, *J* = 3.7 Hz), 126.6, 129.6 (q, *J* = 32.4 Hz), 130.9, 131.7, 140.4, 208.9. IR (neat): 2978, 2935, 2876, 1717, 1616, 1416, 1357, 1325, 1165, 1123, 1067, 1016, 971, 820. HRMS (ESI): *m*/*z* $[C_{13}H_{13}F_3O - H]^-$ calcd 241.0840, found 241.0836.

4.5. General Procedure for the Additions to the β,γ-Unsaturated Ketones. In a drybox, to a Schlenk flask containing the β,γ-unsaturated ketone (0.3 mmol) were added successively dry toluene (1.5 mL), EtZnCl (78 mg, 0.6 mmol), and Et_2Zn (0.45 mL, 0.9 mmol, 2 M in toluene). The flask was taken out of the glovebox and heated under nitrogen at 55 °C for 48 h. The reaction mixture was then cooled to 0 °C and carefully quenched successively with water (1 mL) and 1 N HCl (1 mL). The layers were separated, and the aqueous

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one was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel flash chromatography (using 90:10 hexanes/EtOAc eluent).

*(±)-(3R,4S,E)-4-Methyl-3-phenyldec-5-en-3-ol (**2a**).* The general procedure was applied to **1a** (65 mg, 0.3 mmol) to give the title compound **2a** (16 mg, 63 μmol) as a colorless oil, in 21% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.68 (t, *J* = 7.4 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H), 1.27−1.41 (m, 4H), 1.79−1.94 (m, 3H), 2.04 (q, *J* = 6.7 Hz, 2H), 2.51 (apparent quintet, *J* = 7.5 Hz, 1H), 5.37 (ddt, *J* = 15.3, 8.7, 1.3 Hz, 1H), 5.54 (dt, *J* = 15.3, 6.7 Hz, 1H), 7.19−7.24 (m, 1H), 7.30−7.35 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 7.8, 13.9, 15.5, 22.2, 31.7, 32.4, 33.3, 47.3, 78.5, 125.9, 126.1, 127.7, 131.2, 132.9, 144.6. IR (neat): 3518 (br), 3087, 3059, 3027, 2963, 2928, 2874, 2857, 1494, 1458, 1446, 1376, 1164, 976, 907, 759, 701. HRMS (CI): *m*/*z* [$C_{17}H_{26}O - C_8H_{15}^{\bullet}$]$^+$ calcd 135.0810, found 135.0810. dr = 50:1 determined by GC analysis. Determination of the relative stereochemistry was realized by performing an ozonolysis/$NaBH_4$ reduction sequence and comparing with the data available for the resulting diol in the literature.[33]

*(±)-(3R,4S,E)-4-Methyl-3,6-diphenylhex-5-en-3-ol (**2b**).* The general procedure was applied to **1b** (71 mg, 0.3 mmol) to give the title compound **2b** (8 mg, 30 μmol) as a colorless oil, in 10% yield. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.69 (t, *J* = 7.4 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 1.83 (br s, 1H), 1.85−1.99 (m, 2H), 2.72 (dq, *J* = 8.9, 6.9 Hz, 1H), 6.24 (dd, *J* = 15.9, 8.9 Hz, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 7.19−7.25 (m, 2H), 7.28−7.33 (m, 2H), 7.33−7.40 (m, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 7.9, 15.6, 33.7, 48.0, 79.1, 126.0, 126.3, 126.4, 127.3, 128.0, 128.7, 131.5, 132.0, 137.6, 144.7. IR (neat): 3582 (br), 3496 (br), 3082, 3059, 3026, 2969, 2931, 2876, 1599, 1494, 1447, 1371, 1262, 1161, 1073, 1030, 967, 909, 751, 701. HRMS (ESI): *m*/*z* [$C_{19}H_{22}O$ + Na]$^+$ calcd 289.1568, found 289.1584. dr > 20:1 determined by ^{1}H NMR analysis. Determination of the relative stereochemistry was realized by performing an ozonolysis/$NaBH_4$ reduction sequence and comparing with the data available for the resulting diol in the literature.[33]

4.6. General Procedure for the ^{1}H NMR Study. In a glovebox, the β,γ-unsaturated ketone (0.127 mmol) was taken up in dry CD_2Cl_2 (0.3 mL + 0.3 mL rinse) and transferred into a screw-cap NMR tube. After sealing, the tube was taken out of the glovebox to record the reference NMR spectra. The tube was then taken back into the glovebox and EtZnCl (0.127 mmol, 16 mg) was added. The tube was closed and taken out of the glovebox, and a second spectrum was recorded (ketone + 1 equiv of EtZnCl). The NMR tube was introduced one last time into the glovebox, where more EtZnCl (0.381 mmol, 49 mg) was added. The tube was closed and taken out of the glovebox, and another NMR spectrum was recorded (ketone + 4 equiv of EtZnCl). Comparison of the chemical shifts for these three cases was systematically examined.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

A text file of all computed molecule Cartesian coordinates in a format for convenient visualization. ^{1}H and ^{13}C{^{1}H} NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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