Zr-Catalyzed Olefin Alkylations and Allylic Substitution Reactions with Electrophiles

Judith de Armas, Stanley P. Kolis, and Amir H. Hoveyda*

Contribution from the Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

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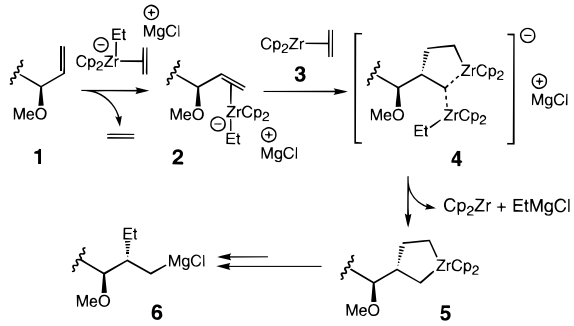
Abstract: Disubstituted aryl olefins undergo efficient alkylations in the presence of 5 mol % Cp_2ZrCl_2, *n*-BuMgCl, and alkyl tosylates or alkyl bromides. In one class of reactions (Table 1), the resulting alkyl zirconocene (initial alkylation product) undergoes β-hydride abstraction with a hydrogen atom from within the substrate to afford allylic alkylation products (Scheme 5). In another category of reactions, where cyclic allylic ethers (chromenes) are used (Table 2), Zr-alkoxide elimination occurs after the C−C bond formation to effect a net allylic substitution. It is proposed that these reactions involve the nucleophilic attack of substrate-derived zirconates or zirconocene−Grignard reagents on various tosylates and bromides. There is little or no competitive electrophile alkylation by the *n*-alkyl Grignard reagent. Several mechanistic and synthetic aspects of these Zr-catalyzed C−C bond forming reactions are examined and discussed.

Introduction

During the past several years, research in these laboratories has involved the development of regio- and stereoselective Zr-catalyzed C−C bond forming reactions with olefinic substrates and alkyl Grignard reagents.[1] Both the diastereo- and enantioselective Zr-catalyzed processes were used at several critical stages in the first enantioselective total syntheses of fluvirucin B_1[2] and nebivolol.[3] Nevertheless, a number of limitations remain associated with Zr-catalyzed alkylations. One shortcoming is the lack of generality of effective alkylating agents:[4] only EtMgCl, and to a lesser extent *n*-Pr- and *n*-BuMgCl, can be utilized for efficient catalytic asymmetric C−C bond formation. The latter two reagents afford the derived *i*-Pr- and *sec*-Bu adducts, respectively.

One strategy that addresses the above drawback presented itself from our detailed investigation of the diastereoselective Zr-catalyzed ethylmagnesations of allylic and homoallylic alcohols and ethers.[5] As shown in Scheme 1, our mechanistic

Scheme 1



studies suggested that the active alkylation agent is the zirconate **2**, rather than olefin **1**. That is, contrary to the usual mode of reactivity observed for electrophilic metal−alkene complexes,[6] **2** serves as the nucleophile. Addition of the electron-rich **2** to electrophilic **3** leads to the selective formation of metallacyclopentane **5**, via bimetallic **4**. On the basis of this paradigm, we began to examine whether olefin−zirconate complexes such as **2** react with other classes of carbon electrophiles, thereby offering an alternative Zr-catalyzed alkylation where a wider range of alkylating agents can be used. The initial results of our studies on the Zr-catalyzed alkylation of disubstituted alkenes and allylic substitution of unsaturated ethers with alkyl tosylates and bromides are reported herein.

Initial Mechanistic Considerations. We decided to focus our studies on *cis*-disubstituted olefins, since previous research indicate that such substrates should be most suitable for enantioselective catalysis.[1c] We envisioned two distinct classes of reactions. As depicted in Scheme 2, one class of transformations relates to alkylation of zirconate **7** by an appropriate electrophile (E^+) to afford **8**. The resulting alkylzirconocene **8**

(1) Zr-catalyzed diastereoselective alkylations: (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079−5080. (b) Morken, J. P.; Hoveyda, A. H. *J. Org. Chem.* **1993**, *58*, 4237−4244. Zr-catalyzed enantioselective alkylations: (c) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6697−6698. (d) Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097−7104. Zr-catalyzed kinetic resolution through enantioselective alkylation: (e) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123−3124. (f) Visser, M. S.; Harrity, J. P. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 3779−3780. (g) Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 2343−2351.

(2) Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302−10316.

(3) Johannes, C. W.; Visser, M. S.; Weatherhead G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340−8347.

(4) For previous studies from these laboratories to address this issue, see: (a) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273−7274. (b) Heron, N. M.; Adams, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205−6206. (c) Adams, J. A.; Heron, N. M.; Koss, A.-M.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 854−860.

(5) Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614−6624.

(6) For example, see: (a) Eisenstein, O.; Hoffmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4308−4320. (b) Fujimoto, H.; Koga, N. *Tetrahedron Lett.* **1982**, *23*, 4357−4360.

10.1021/ja000693j CCC: $19.00 © 2000 American Chemical Society
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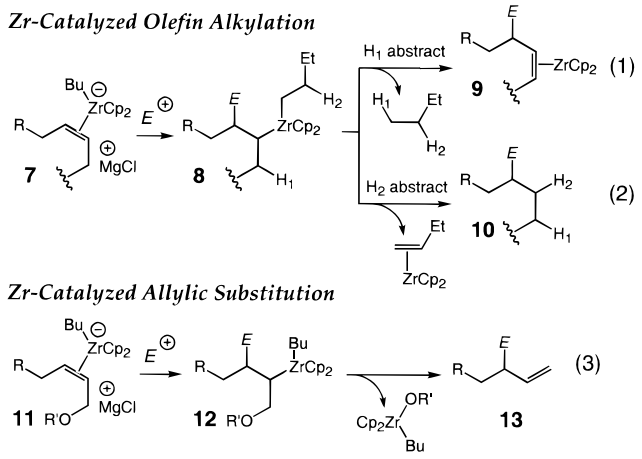
Scheme 2



could then follow two pathways: (1) β-Hydride abstraction[7] (eq 1), where a hydrogen within the substrate is involved (H_1), to deliver **9**. (2) β-Hydride abstraction (eq 2), where a hydrogen within the *n*-alkyl group (H_2) participates in the reaction, to afford **10**. A second category of processes would utilize allylic ethers as substrates (eq 3, Scheme 2). Here, alkylation of zirconate **11**, formation of **12** and subsequent Zr-alkoxide elimination would lead to the formation of **13**. The overall process thus represents a net Zr-catalyzed allylic substitution. In all cases, the zirconocene unit would readily re-enter another catalytic cycle. From the viewpoint of utility in regio- and stereoselective synthesis, routes in eqs 1 and 3 are more attractive, since the resulting olefin may be used for subsequent functionalization. In all instances, a longer chain alkyl Grignard reagent would be used, since reaction with EtMgCl could lead to competitive or adventitious ethylmagnesation.[1]

Regioselective Zr-Catalyzed Alkylation of Indenes. To initiate our studies, we opted for disubstituted aryl olefins as substrates for two reasons: (i) The aryl moiety can stabilize the adjacent polarized C−Zr bond and facilitate the formation of the requisite zirconate (cf. **7** in Scheme 2). (ii) The aryl group is sterically and electronically modifiable, so that various influences on the C−C bond formation can be gauged. As illustrated in entry 1 of Table 1, we established that treatment of indene (**14**) with 5 mol % Cp_2ZrCl_2 in the presence of *n*-BuMgCl (2 equiv) and tosylate **15** (1 equiv) at 22 °C leads to the efficient and rapid formation of **16** as a single olefin isomer (<2% trisubstituted alkene) and in 92% yield after silica gel chromatography; similar results are obtained with *n*-BuMgBr. *When **14** is treated with the same conditions but in the absence of Cp_2ZrCl_2, <2% conversion is observed* (400 MHz ^{1}H NMR). The data in entry 2 indicate that, with **14** as the substrate, alkynyl electrophiles participate efficiently in the Zr-catalyzed alkylation. This observation and the fact that the above transformation proceeds without formation of side products arising from alkyne coupling (<2%) are noteworthy in light of the fact that alkynes are among the most favored zirconocene ligands.

Various functional units (e.g., alkenes and alkynes) can be imported as part of the alkylating agent, a factor that is important to the synthetic utility of these transformations. Subsequent structural modification involving the functional group within the electrophile and the alkene unit within the initial substrate nucleus can afford more complex polycyclic structures. The example shown in Scheme 3, concerning an intramolecular Pauson−Khand reaction (**24**→**25**),[8] is illustrative. The structural identity of tetracycle **25** was determined through X-ray crystallography.

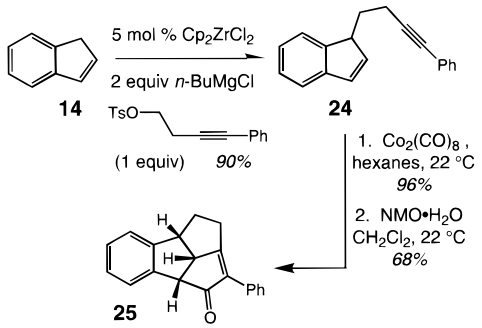
(7) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1988**, *110*, 3171−3175.

Table 1. Zr-Catalyzed Alkylation of Indenes with Alkyl Tosylates[a]

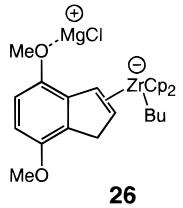
entry	substrate	electrophile	product	yield (%)[b]
1	**14**	**15**	**16**	92
2	**14**	**17**	**18**	90
3	**19**	*n*-C_8H_{17}OTs **20**	**21**	65
4	**22**	*n*-C_8H_{17}OTs **20**	**23**	27[c]

[a] Conditions: 5 mol % Cp_2ZrCl_2, 2 equiv (entries 1−2) or 5 equiv (entries 3−4) *n*-BuMgCl, 1 equiv electrophile, 22 °C, 4−6 h. [b] Isolated yields after silica gel chromatography. [c] 30% conv; 69% **22** and 66% **20** recovered.

Scheme 3

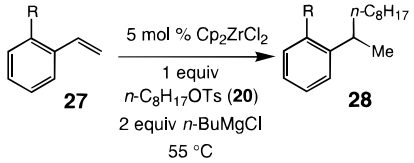


Effect of Neighboring Lewis Basic Groups on the Rate of Catalytic Alkylation. In our previous work on Zr-catalyzed ethylmagnesation, we determined that these transformations can be strongly affected by the chelating ability of an adjacent Lewis basic functional group.[1a,5] To establish whether similar effects exist here, the catalytic alkylations shown in entries 3−4 of Table 1 were carried out. The facile reaction in entry 3 (with **19**) and the sluggish process in entry 4 (with **22**) suggest that a chelation-based stabilization of the zirconate complex, as shown in **26**, may be operative (see below for the possible involvement of the zirconocene−Grignard intermediate).[9] Such complexation may facilitate the catalytic alkylation by stabilizing the substrate−metal complex to overcome the adverse steric influence of the ortho substituent.



26

Scheme 4



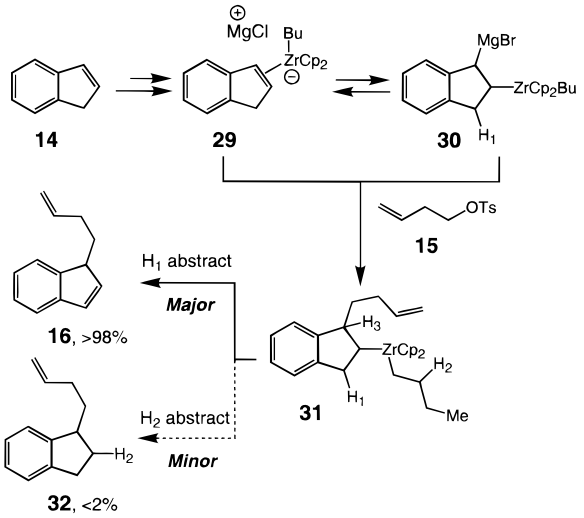
	conv (%) (after 30 min)	isolated yield (%) (after 4 h)
27a R = H	35	84
27b R = OMe	72	70
27c R = *n*-Pr	<2	<2

To probe the above mechanistic issue further, styrenyl substrates **27a**−**c** were subjected to the Zr-catalyzed alkylation conditions.[10] As illustrated in Scheme 4 (see % conv after 30 min), *o*-methoxy styrene **27b** is the most reactive; importantly, the *o*-alkyl styrene **27c** is inert to the catalytic alkylation conditions. These results provide additional evidence that the presence of a Lewis basic site in the proximity of the reacting alkene is beneficial and can readily overcome adverse steric elements.

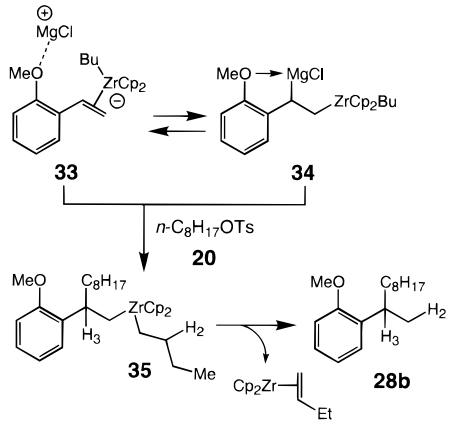
The higher reactivity of **27b** vs **27a** cannot be due to the fact that the aryl group in the first substrate is more electron-rich. The aromatic ring in the less reactive **22** is likely as electron-rich as that in **19** (cf. Table 1), but it is only in the more reactive **19** that the resident Lewis base can provide effective chelation. In light of the results in Scheme 4, comparison of the reactivity of **19** and **14** may well suggest that a more electron-rich aryl unit diminishes reaction efficiency. Thus, the OMe group in **19** and **27b** may not only be overcoming unfavorable steric effects through chelation (compare to **27b** to **27a**) but also rate-reducing electronic effects (compare **19** and **22**).

Origin of Olefin Regioselectivity in Catalytic Alkylations of Indenes. Catalytic reactions in Table 1 likely proceed through the pathway presented by eq 1 in Scheme 2, whereas those shown in Scheme 4 probably occur by the route illustrated in eq 2. As illustrated in Scheme 5, alkylation may occur either by zirconate **29** or by zirconocene−Grignard complex **30** (more on this issue later). With substrates **14**, **19**, and **22**, β-hydride abstraction (via **31**) exclusively involves a substrate hydrogen (H_1 abstraction to give **16**) in preference to the abstraction of a hydrogen atom (H_2) from the Zr-bound *n*-Bu group. Such selectivity with indene substrates is probably due to relatively facile β-hydride abstraction of benzylic vs aliphatic protons (styrenes only have one type of β-hydride).[11] As expected, the alternative benzylic C−H (H_3) is less reactive as a result of unfavorable steric interactions.[11] These considerations imply that if Cp_2ZrBu_2 (precursor to Cp_2Zr−butene complex) is used as the catalyst, the reaction should proceed in the presence of MeMgCl (1−2 equiv), although the latter does not bear an alkyl unit that contains a β-hydride. Indeed, treatment of indene (**14**) with 5 mol % Cp_2ZrBu_2, 2 equiv MeMgCl, and 1 equiv **20** (THF, 22 °C) leads to the formation of the desired alkylation product in 69% isolated yield.

Scheme 5



Scheme 6



A similar mechanistic scenario may be envisioned for styrenyl substrates (Scheme 6).[10] In this case, however, the dialkylzirconocene that results from alkylation (**35**) preferably undergoes β-H abstraction involving a CH_2 unit of the Bu ligand (H_2); the competing process with the neighboring benzylic proton (H_3) is expected to be less favored because of steric reasons. In line with these mechanistic models, when d_9−BuMgCl is used in the catalytic alkylation of **14**, the desired product is obtained with <2% deuterium incorporation. In contrast, under similar conditions, **28b** is isolated from Zr-catalyzed alkylation of **27b** with deuterium incorporation at the CH_3 position (based on ^{13}C NMR analysis; H_2 = D in **28b**, Scheme 6).

The Nature of the Alkylating Agent. On the basis of the above discussions, it is plausible to propose that it is either the intermediate zirconate (e.g., **29** Scheme 5) or the derived zirconocene−Grignard system (e.g., **30** in Scheme 5) that is responsible for the catalytic alkylation. The electron-rich bimetallic Grignard reagent should be a highly potent alkylating agent, such that there is little or no competing reaction by *n*-BuMgCl. Nonetheless, it may be suggested that rapid β-H abstraction of intermediate zirconocene−Grignards such as **30** and **34** (Schemes 5 and 6, respectively) may lead to the formation of the corresponding allylmagnesium halides (e.g., **39**, Scheme 7) which may then undergo alkylation.[12] That is,

(8) (a) Schreiber, S. L.; Crowe, W. E.; Shambayati, S. *Tetrahedron Lett.* **1990**, *31*, 5289−5292. (b) Krafft, M. E.; Chirico, X. *Tetrahedron Lett.* **1994**, *35*, 4511−4514. (c) Schore N. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford: 1991; 1037−1064.

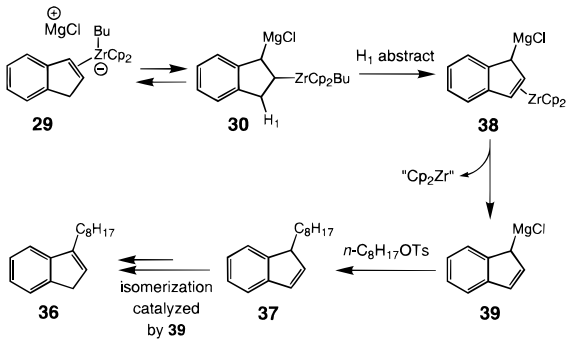
(9) Similar to **19**, but unlike **22**, indene **14** reacts readily with **20** to afford the corresponding alkylation adduct in 88% isolated yield.

(10) While our studies were in progress, a related Zr-catalyzed alkylation of terminal styrenes was reported: Terao, J.; Watanabe, T.; Saito, K.; Kambe, N.; Sonoda, N. *Tetrahedron Lett.* **1998**, *39*, 9201−9204.

(11) Negishi, E.; Nguyen, T.; Maye, J. P.; Choueiri, D.; Suzuki, N.; Takahashi, T. *Chem. Lett.* **1992**, 2367−2370.

(12) Recent kinetic studies indicate that allylmagnesium halides can be several orders of magnitude more nucleophilic than alkylmagnesium halides. See: Holm, T. *J. Org. Chem.* **2000**, *65*, 1188−1192.

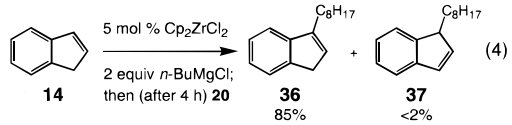
Scheme 7



the transformations depicted in Table 1 and Schemes 3 and 4 may constitute Zr-catalyzed *formation* of Grignard reagents that undergo efficient alkylation with the appropriate electrophiles. To address this issue, the following experiments were carried out:

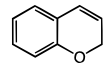
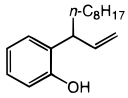
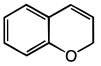
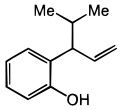
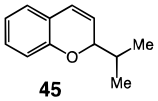
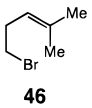
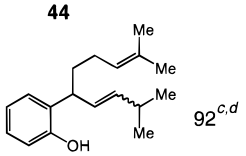
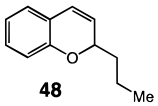
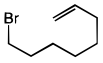
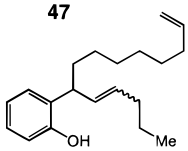
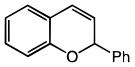
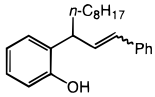
(1) Treatment of **27b** with 5 mol % Cp_2ZrCl_2 and 2 equiv *n*-BuMgCl (2 h) and quenching with D_2O (to signal the presence of any benzylic Grignard reagents formed) leads to the formation of substantial amounts of polymeric products, recovered **27b** and <2% *o*-methoxy-ethylbenzene.

(2) As shown in eq 4, when indene is treated with 5 mol % Cp_2ZrCl_2 and 2 equiv *n*-BuMgCl (2h, 22 °C) and alkyl tosylate **20** is added subsequently, trisubstituted olefin **36** is isolated as the only product (85% yield after silica gel chromatography); there is <2% of **37**, which is the alkylation product obtained when the reaction is performed under the conditions used for transformations in Table 1. A plausible rationale for the difference between the outcome of reactions when the alkylating agent is present the entire time (Table 1) vs when it is added after treatment of the substrate with the zirconocene catalyst and *n*-BuMgCl (eq 4) is illustrated in Scheme 7. In the absence of an alkylating agent, zirconocene−Grignard reagent **30** undergoes a β-H abstraction (with H_1) to afford **38**; because H_1 is a benzylic proton, this process is expected be relatively facile.[11] Subsequent dissociation of zirconocene yields indenylmagnesium chloride **39**. Upon addition of tosylate **20**, alkylation occurs and **37** is generated. However, due to the presence of **39**, which may be a better kinetic base than *n*-BuMgCl,[12] the thermodynamically more favored trisubstituted olefin **36** can be formed exclusively. In support of this scenario, when **14** is subjected to the conditions shown in eq 4, but a sample of authentic **37** (30%) is also introduced to the reaction mixture along with tosylate **20**, only **36** is obtained at the end of the reaction time (<2% recovered **37**). These findings, and their comparison to the outcome of the related catalytic reactions, clearly indicate that **39** is not generated under the conditions used in Table 1; reactions shown in Table 1 afford <5% of the derived trisubstituted alkylation adducts. Otherwise, particularly in the late stages of the catalytic process, when most of the electrophile is consumed, the basic Grignard reagent would promote substantial olefin isomerization.



Zr-Catalyzed Allylic Substitution Reactions. To examine the feasibility of a Zr-catalyzed allylic substitution (cf. eq 3 in Scheme 2), catalytic reactions of a variety of chromenes were investigated (Table 2). As shown in entry 1 of Table 2, the catalytic alkylation proceeds smoothly at 55 °C to afford **41** in 77% yield after silica gel chromatography. As before, <2% conversion is observed in the absence of Cp_2ZrCl_2. *The above observation thus represents a Zr-catalyzed allylic substitution reaction, where an electrophile—not a nucleophile—serves as the alkylating agent.* The catalytic alkylation shown in entry 2 of Table 2 highlights the effectiveness of the Zr-catalyzed alkylation (**42**→**44**). In this case, a secondary alkyl tosylate readily undergoes reaction, leading to C−C bond formation in an efficient manner. The examples in entries 3−4 indicate that bromides easily participate in alkylation without complications arising from elimination and formation of the derived diene.[13] Three additional points regarding the catalytic allylic substitu-

Table 2. Zr-Catalyzed Allylic Substitution Reactions of Chromenes with Alkyl Tosylates and Alkyl Bromides[a]

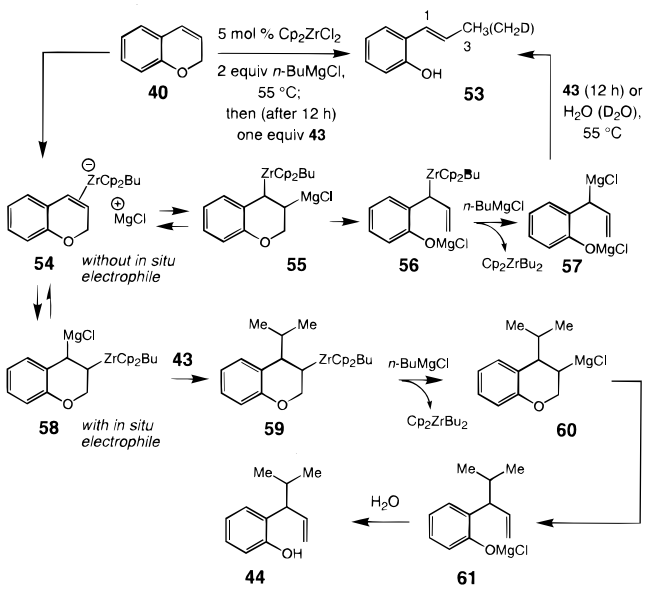
entry	substrate	electrophile	product	yield (%)[b]
1	 **40**	*n*-C_8H_{17}OTs **20**	 **41**	77[c]
2	 **42**	 **43**	 **44**	71[c]
3	 **45**	 **46**	 **47**	92[c,d]
4	 **48**	 **49**	 **50**	70[c,e]
5	 **51**	*n*-C_8H_{17}OTs **20**	 **52**	82[c,e]

[a] Conditions: 5 mol % Cp_2ZrCl_2, 2 equiv *n*-BuMgCl, 1 equiv electrophile, 55 °C, 12 h; >95% conv in all cases. [b] Isolated yield after silica gel chromatography. [c] Entry 1 afforded 9:1 (terminal:trisubstituted) mixture of olefin regioisomers; entries 2−5 afforded a single alkene regioisomer. [d] **47** is isolated as a 3:1 *E*:*Z* mixture. [e] **50** and **52** are isolated as a 1:1 *E*:*Z* mixture.

(13) The high substitution pattern of the alkene in **46** is required for efficient reaction; catalytic alkylations of tosylate of 1-tosyloxy-3-butene and 1-bromo-3-butene proceed to 25−30% conversion. This is likely due to the formation of Cp_2Zr-butadiene **i**, generated as the result of bromide or OTs elimination. Since butadiene represents a relatively robust ligand for Cp_2Zr, ligand exchange with the chromene substrate may be inhibited and the reaction rate reduced. Such unsaturated tosylates and bromides react efficiently with the more reactive **14**, but adventitious elimination can presumably more effectively compete with alkylation in the case of less reactive chromenes. The following observations support this contention: (i) The Zr-catalyzed alkylation of **40** proceeds efficiently with 1-bromo-7-octene (80% isolated yield after silica gel chromatography). (ii) The reaction of **40** with 1-tosyloxy-3-butene proceeds *further* with *lower* equiv of the electrophile (25% conv with 2 equiv tosylate; 45% conv with 1 equiv tosylate, 100% conv based on tosylate, with 0.7 equiv tosylate).

i

Scheme 8



tions in Table 2 are: (i) Competitive alkylation of the tosylates and bromides by *n*-BuMgCl is at best a minor pathway. In all reactions, where only one equiv of the electrophile is used, conversion is >95% (400 MHz ^{1}H NMR).[14] The preferential nucleophilicity of the purported substrate-zirconates or the derived zirconocene−Grignard (cf. **29** and **30**, Scheme 7) over *n*-BuMgCl, despite the fact that the latter is present in larger excess, is noteworthy. (ii) Most products are formed with little or no contamination by other olefin regioisomers; **41** is obtained as a 9:1 mixture of terminal and trisubstituted olefins (85% total yield), whereas **44**, **47**, **50**, and **52** are isolated as a single regioisomer (400 MHz ^{1}H NMR). The formation of the minor olefin regioisomer in the reaction of **40** is likely due to adventitious isomerization upon workup. When the reaction mixture is quenched with a saturated solution of NH_4Cl (vs $NaHCO_3$), a 1:1 mixture of terminal and trisubstituted olefin products are isolated. (iii) Catalytic alkylations in entries 3−4 afford mixtures of olefin stereoisomers (3:1 *Z*:*E* for **47** and 1:1 *Z*:*E* for **50** and **52**).[15,16]

Similar to our studies regarding catalytic alkylation of styrenes (cf. Scheme 4) and indenes (cf. Table 1), we have determined that the reactions shown in Table 2 do not involve the Zr-catalyzed formation of Grignard reagents represented by **57** in Scheme 8, which then undergo uncatalyzed alkylation. When **40** is treated with 5 mol % Cp_2ZrCl_2 and 2 equiv *n*-BuMgCl at 55 °C for 12 h, and the resulting solution is treated with tosylate **43**, only substituted styrene **53** is isolated (<2% **44** is detected by 400 MHz ^{1}H NMR). When the reaction mixture is quenched with D_2O, substantial deuterium incorporation at C3 is observed (<5% D incorporation at C1). These observations suggest that in the absence of an electrophile, zirconate intermediate **54** may be converted to zirconocene−Grignard reagent **55**; subsequent Mg-alkoxide elimination leads to the formation of allylzirconocene **56**, which may undergo ligand exchange with *n*-BuMgCl to afford **57**.[17] These results indicate that, similar to *n*-BuMgCl, **57** is not sufficiently reactive to effectively react with **43**, thus underlining the potent nucleophilicity of the substrate zirconate (**54**) or the derived bimetallic zirconocene−alkylmagnesium halide intermediate (**55**). In contrast, as also shown in Scheme 8, with the alkylating agent available in situ, reaction via either **54** or **58** leads to the formation of **59**; subsequent Zr−Mg ligand exchange and Mg-alkoxide elimination allows for the formation of **44**.

Conclusions

We disclose a Zr-catalyzed C−C bond forming reaction, where electrophiles serve as alkylating agents. A plausible mechanistic rationale involves reaction of the electrophiles with zirconates or the corresponding zirconocene−Grignard reagents derived from alkene substrates. In one class of reactions (eq 1 and Table 1), the zirconocene resulting from zirconate alkylation undergoes β-H abstraction involving a hydrogen within the substrate to afford a net allylic alkylation adduct. In another category of transformations (eq 3 and Table 2), involving allylic ethers, Zr-alkoxide elimination after zirconate alkylation leads to a net allylic substitution. The accessibility of various cyclic disubstituted alkenes, the availability of chiral optically pure zirconocenes,[18] and the efficiency of the processes reported herein foreshadow future exciting developments in catalytic enantioselective C−C bond formation. These studies, along with research to enhance the generality of these classes of Zr-catalyzed reactions (wider range of substrates and electrophiles), the attendant mechanistic studies and applications to natural product synthesis are in progress and will be reported shortly.

Experimental Section

General. Infrared (IR) spectra were recorded on a Perkin-Elmer 781 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^{1}H NMR spectra were recorded on a Varian GN-400 (400 MHz) or Varian UI-500 (500 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a Varian G2−400 (100 MHz) or Varian UI-500 (125 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.7 ppm). Microanalyses were performed by Robertson Microlit Laboratories (Madison, New Jersey). High-resolution mass spectrometry was performed by the University of Illinois Mass Spectrometry Laboratories.

All reactions were conducted in oven (135 °C) and flame-dried glassware under an inert atmosphere of dry argon. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl; toluene was distilled from sodium metal. All Grignard reagents were made with flame dried magnesium turnings purchased from Strem. Biscyclopentadienyl zir-

(14) The 400 MHz ^{1}H NMR spectrum of the unpurified product mixture exhibits <2% of any decomposition materials.

(15) It may be suggested that Zr-alkoxide elimination of the initial Zr−alkene complex (cf. **11**, Scheme 2) leads to the formation of an allyl zirconocene that then serves as the nucleophile. Our previous mechanistic studies indicate that, unlike acyclic allylic ethers, cyclic allylic ethers are not readily converted to allylzirconocenes in the presence of Cp_2ZrCl_2 and *n*-BuMgCl. This difference in reactivity is likely related to the inability of oxygen atoms in cyclic ethers to coordinate effectively with the transition metal center. See: ref 1d.

(16) Formation of a mixture of *cis*- and *trans*-olefin isomers in reactions of substituted chromenes (entries 3−5, Table 2) may be due to initial formation of alkylmagnesium halide diastereomers (cf. **60**, Scheme 8), which undergo subsequent stereoselective elimination.

(17) A similar mechanism involving Zr-alkoxide elimination might also be suggested.

(18) For reviews regarding the utility of chiral metallocenes in asymmetric alkylation of olefinic substrates, see: (a) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262−1284. (b) Hoveyda, A. H.; Heron, N. M. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer-Verlag: Berlin, 1999; pp 431−454. For a recent report on an enantioselective Fe-catalyzed olefin alkylation, see: (c) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978−979. For a recent Pd-catalyzed asymmtric addition of dialkylzinc reagents to cyclic allylic ethers, see: (d) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1805−1805.

conocene dichloride was purchase from Boulder Scientific and recrystallized from anhydrous toluene. Alkyl bromides were purchased from Aldrich and distilled from anhydrous calcium chloride. Indene and styrene were purchased from Aldrich and distilled over calcium hydride.

Representative Experimental Procedure for the Zr-Catalyzed Alkylation of Indene. A 10 mL flame-dried round-bottom flask was charged with 100 mg (0.86 mmol) of indene **14**, 194 mg (0.86 mmol) of tosylate **15**, and 3.36 mL of THF. To this mixture was added 12.6 mg (0.043 mmol) Cp_2ZrCl_2 and 0.95 mL (1.72 mmol) of a 1.8 M solution of *n*-BuMgCl (tetrahydrofuran) in a dropwise fashion. The resulting mixture was allowed to stir at 22 °C for 4.5 h. The solution was then cooled to 0 °C (ice bath). At this point, the reaction was quenched by the dropwise addition of 3 mL of a saturated solution of $NaHCO_3$. The resulting mixture was washed with 3 × 25 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a pale yellow oil. Preparative thin-layer chromatography with pentane as the eluant afforded 135 mg (0.79 mmol, 92%) of the desired alkylation product **16**.

Representative Experimental Procedure for the Zr-Catalyzed Alkylation of Chromenes. A 10 mL flame-dried round-bottom flask was charged with 100 mg (0.76 mmol) of chromene **40**, 216 mg (0.76 mmol) of tosylate **20**, and 3.37 mL of THF. To this mixture was added 11.1 mg (0.038 mmol) of Cp_2ZrCl_2 and 0.980 mL (1.52 mmol) of a 1.55 M solution of *n*-BuMgCl (tetrahydrofuran) in a dropwise fashion. The flask was equipped with a condenser, and the resulting mixture was heated at 55 °C for 12 h. The reaction mixture was then allowed to cool slowly to 0 °C. Once at 0 °C, the reaction was quenched by the dropwise addition of 3 mL of a saturated solution of $NaHCO_3$. The resulting mixture was then washed with 3 × 25 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a pale yellow oil. Silica gel chromatography (20:1 pentanes:Et_2O) afforded 143 mg (0.58 mmol, 77%) of the desired alkylation product **41**.

3-(3-Butenyl)-indene (16): IR (NaCl) 3069 (m), 2930 (m), 1640 (m), 1464 (m) 1369(w), 916 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (1H, dd, J = 7.6, 0.8 Hz), 7.36 (1H, dd, J = 7.6, 0.8 Hz), 7.26 (1H, ddd, J = 7.6, 7.6, 0.8 Hz), 7.20 (1H, ddd, J = 7.6, 7.6, 0.8 Hz), 6.82 (1H, d, J = 5.6 Hz), 6.56 (1H, dd, J = 5.6, 1.6 Hz), 5.92−5.80 (1H, m), 5.09−4.96 (2H, m), 3.50 (1H, m), 2.25−2.08 (2H, m), 2.07−1.96 (1H, m), 1.68−1.56 (1H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ 147.5, 144.1, 138.8, 138.4, 130.6, 126.3, 124.6, 122.7, 120.9, 114.7, 49.9, 31.6, 30.8. HRMS Calcd for $C_{13}H_{14}$: 170.1096. Found: 170.1095. Anal. Calcd for $C_{13}H_{14}$: C, 91.71; H, 8.21. Found: C, 91.46; H, 8.10.

3-(3-Butynyl)-indene (18): IR (NaCl) 3308 (m), 3069 (w), 2930 (m), 2118 (w), 1464 (m). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (1H, d, J = 6.0 Hz), 7.38 (1H, d, J = 6.0 Hz), 7.29 (1H, dd, J = 6.0, 5.6 Hz), 7.22 (1H, dd, J = 6.0, 6.0 Hz), 6.86 (1H, dd, J = 4.6, 1.6 Hz), 6.57 (1H, dd, J = 4.6, 1.2 Hz), 3.69−3.64 (1H, m), 2.33−2.22 (1H, m), 2.03 (1H, t, J = 2.0 Hz), 1.88−1.78 (1H, m). ^{13}C NMR (500 MHz, $CDCl_3$) δ 147.6, 145.0, 138.9, 132.2, 127.4, 125.5, 123.6, 121.8, 84.8, 69.8, 49.9, 30.9, 17.1. HRMS Calcd for $C_{13}H_{12}$: 168.0939. Found: 167.0858. Anal. Calcd for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.83; H, 7.01.

3-(Octyl)-6,7-methoxyindene (23): IR (NaCl) 2924 (s), 2855 (m), 1489 (m), 1464 (w), 1300 (w), 1218 (m), 117 (w), 1073 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (1H, s), 6.92 (1H, s), 6.71 (1H, dd, J = 5.5, 1.8 Hz), 6.46 (1H, dd, J = 5.5, 1.8 Hz), 3.91 (3H, s), 3.90 (1H, s), 3.42−3.36 (1H, m), 1.92−1.82 (1H, m), 1.50−1.21 (13H, m), 0.88 (3H, t, J = 7.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.8, 147.8, 141.2, 138.9, 137.5, 131.0, 107.9, 105.3, 57.0, 56.8, 51.3, 32.6, 32.5, 30.6, 30.2, 30.0, 28.3, 23.4, 14.8. HRMS Calcd for $C_{19}H_{28}O_2$: 288.2089. Found: 288.2087. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.35; H, 9.75.

3-(4-Phenyl-3-butynyl)-indene (24): IR (NaCl) 3061 (m), 2925 (m), 1490 (s), 1460 (m), 1441 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, J = 6.8 Hz), 7.42−7.35 (3H, m), 7.32−7.18 (5H, m), 6.84 (1H, dd, J = 5.6, 1.2 Hz), 6.61 (1H, dd, J = 5.6, 1.6 Hz), 3.74−3.68 (1H, m), 2.49 (2H, t, J = 7.2 Hz), 2.28−2.15 (1H, m), 1.94−1.82 (1H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.9, 144.3, 138.4, 131.5, 131.4, 128.2, 127.6, 126.6, 124.8, 122.9, 121.1, 89.7, 81.5, 49.3, 30.5, 29.7, 20.0, 17.5. HRMS Calcd for $C_{19}H_{16}$: 244.1252. Found: 244.1250. Anal. Calcd for $C_{19}H_{16}$: C, 93.40; H, 6.60. Found: C, 93.43; H, 6.83.

Tetracycle 25: IR (NaCl) 3018 (m), 2907 (m), 1598 (m), 1490 (s), 1462 (m), 1456 (m), 1441 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 5.6 Hz), 7.45−7.40 (2H, m), 7.38−7.32 (2H, m), 7.30−7.14 (4H, m), 4.24−4.20 (1H, m), 3.85−3.78 (2H, m), 2.99−2.91 (1H, m), 2.87−2.77 (2H, m), 1.99−1.92 (1H, m). ^{13}C NMR (400 MHz, $CDCl_3$) δ 181.2, 147.6, 141.9, 133.7, 132.1, 129.5, 129.1, 128.9, 128.6, 127.7, 126.3, 125.9, 60.2, 54.0, 44.5, 32.1, 30.0.

2-(2-Methoxyphenyl)-decane (28b): IR (NaCl) 2962 (m), 2930 (s), 2855 (m), 1602 (w), 1495 (m), 1464 (w), 1287 (w), 1237 (m), 1036 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.12 (2H, m), 6.92 (1H, t, J = 7.3 Hz), 6.85 (1H, d, J = 8.0 Hz), 3.81 (3H, s), 3.22−3.12 (1H, m), 1.66−1.42 (2H, m), 1.34−1.08 (12H, m), 0.87 (3H, t, J = 6.8 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.7, 137.0, 127.4, 127.1, 121.2, 111.1, 56.1, 37.8, 32.6, 32.4, 30.5, 30.3, 30.0, 28.4, 23.4, 21.7, 14.8. HRMS Calcd for $C_{17}H_{28}O$: 248.2140. Found: 248.2147. Anal. Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 81.86; H, 11.37.

2-(1-Octylprop-2-enyl)-phenol (41): IR (NaCl) 3471 (br), 2930 (s), 2855 (m), 1590 (w), 1457 (m), 1331 (w), 1212 (w), 916 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.09 (2H, m), 6.90 (1H, ddd, J = 7.6, 7.3, 1.1 Hz), 6.89 (1H, dd, J = 7.8, 0.9 Hz), 6.04−5.96 (1H, m), 5.15−5.11 (2H, m), 4.93 (1H, s), 3.52−3.46 (1H, m), 1.75 (2H, dd, J = 15.1, 7.4 Hz), 1.40−1.19 (12H, m), 0.87 (3H, t, J = 7.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) 154.4, 142.3, 130.2, 129.2, 128.1, 121.6, 116.9, 115.5, 44.4, 34.0, 32.6, 30.3, 30.2, 30.0, 28.2, 23.3, 16.0. HRMS Calcd for $C_{17}H_{26}O$: 246.1984. Found: 246.1980. Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 83.04; H, 10.90.

2-(1-(1-Methylethyl)prop-2-enyl)-phenol (44): IR (NaCl) 3069 (br), 2962 (s), 2873 (m), 1590 (w), 1501 (m), 1457 (s), 1381 (w), 1331 (w), 916 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.04 (2H, m), 6.91 (1H, dd, J = 7.6, 7.6 Hz), 6.77 (1H, d, J = 8.4 Hz), 6.05 (1H, ddd, J = 17.2, 9.6, 9.6 Hz), 5.14−5.04 (2H, m), 4.72 (1H, s), 3.22 (1H, dd, J = 8.8, 8.8 Hz), 2.14−2.02 (1H, m), 1.08 (3H, d, J = 6.8 Hz), 0.80 (3H, d, J = 6.8 Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.0, 140.1, 129.7, 128.8, 126.9, 120.8, 115.8, 115.4, 51.7, 31.2, 21.2, 21.0. HRMS Calcd for $C_{12}H_{16}O$: 176.1201. Found: 176.1205. Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.94; H, 8.85.

2-(1-(4-Methylpent-3-enyl)-4-methylpent-2-enyl)-phenol (47): IR (NaCl) 3465 (br), 2962 (s), 1590 (w), 1451 (m), 1212 (w), 1092 (w), 966 (w). ^{1}H NMR (400 MHz, $CDCl_3$; *cis* and *trans*) δ 7.20−7.04 (4H, m), 6.94−6.86 (2H, m), 6.82 (1H, d, J = 7.2 Hz), 6.76 (1H, d, J = 8.0 Hz), 5.66−5.48 (2H, m), 5.42−5.28 (2H, m), 5.18−5.08 (3H, m), 4.86 (1H, s), 3.83 (1H, m), 3.38 (1H, m), 2.80−2.64 (1H, m), 2.38−2.24 (1H, m), 2.30−1.86 (9H, m), 1.85−1.58 (9H, m), 1.56 (3H, d, J = 5.2 Hz), 1.04−0.92 (9H, m), 0.87 (3H, d, J = 6.4 Hz). ^{13}C NMR (400 MHz, $CDCl_3$; *cis* and *trans*) δ 153.9, 153.0, 138.6, 132.0, 131.2, 129.5, 127.8, 127.1, 126.6, 123.8, 120.4, 116.0, 115.5, 42.1, 36.6, 35.4, 33.4, 31.0, 26.9, 26.0, 25.6, 23.0, 22.7, 22.4, 17.6. HRMS Calcd for $C_{18}H_{26}O$: 258.1984. Found: 258.1992. Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, =10.14. Found: C, 83.26; H, 10.09.

2-(1-(Pent-2-enyl)-oct-8-enyl)-phenol (50): IR (NaCl) 3471 (br), 2930 (s), 2861 (m), 1640 (w), 1596 (w), 1457 (m), 1325 (w), 1206 (w), 910 (m). ^{1}H NMR (500 MHz, $CDCl_3$; *cis* and *trans*) δ 7.17 (1H, d, J = 6.0 Hz), 7.14−7.02 (3H, m), 6.93−6.87 (2H, m), 6.80 (1H, d, J = 6.8 Hz), 6.76 (1H, d, J = 6.4 Hz), 5.86−5.75 (2H, m), 5.62−5.56 (1H, m), 5.54−5.46 (1H, m), 5.12 (1H, s), 5.01−4.90 (4H, m), 4.86 (1H, s), 3.84−3.77 (1H, m), 3.43−3.37 (1H, m), 2.20−1.98 (10H, m), 1.80−1.56 (4H, m), 1.44−1.20 (20H, m), 0.94−0.84 (6H, m). ^{13}C NMR (500 MHz, $CDCl_3$; *cis* and *trans*) δ 153.9, 153.2, 139.2, 133.0, 132.7, 131.5, 131.1, 130.0, 128.3, 127.8, 127.3, 121.9, 120.9, 120.8, 116.2, 115.8, 114.1, 43.0, 37.0, 35.2, 34.6, 33.8, 33.6, 29.7, 29.5, 29.4, 29.1, 29.0, 28.9, 27.5, 27.4, 22.7, 13.8, 13.6. HRMS Calcd for $C_{20}H_{30}O$: 286.2297. Found: 286.2295. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.59; H, 10.52.

2-(1-Octyl-3-phenyl-allyl)-phenol (52): IR (NaCl) 3522 (br), 3031-(m), 2924 (s), 2855 (s), 1602 (m), 1501 (s), 1457 (s), 1331 (m), 1243 (s), 972 (s). ^{1}H NMR (400 MHz, $CDCl_3$; *cis* and *trans*) δ 7.38−7.05 (14H, m), 6.96−6.74 (4H, m), 6.58 (1H, d, J = 16.0 Hz), 6.47 (1H, d, J = 16.03 Hz), 6.40−6.27 (2H, m), 4.85 (1H, s), 4.82 (1H, s), 3.69 (1H, dd, J = 14.4, 7.2 Hz), 3.42 (1H, dd, J = 15.2, 8.2 Hz), 1.87−

1.75 (4H, m), 1.42−1.14 (24H, m), 0.87 (6H, t, $J = 6.8$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$; *cis* and *trans*) δ 153.1, 152.2, 144.5, 137.0, 136.3, 133.1, 130.0, 129.7, 128.8, 127.9, 127.4, 127.1, 127.0, 126.0, 124.6, 123.2, 120.9, 120.7, 116.0, 115.6, 49.7, 49.6, 42.7, 42.6, 36.0, 34.3, 31.9, 29.7, 29.6, 29.5, 29.4, 27.7, 22.8, 14.2. HRMS Calcd for $C_{23}H_{30}O$: 322.2297. Found: 322.2291.

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Supporting Information Available: Crystallographic details for **25** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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