

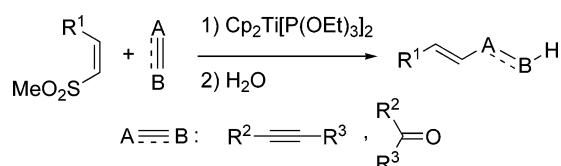
Titanocene(II)-Promoted Stereoselective Alkenylation Utilizing (Z)-Alkenyl Sulfones

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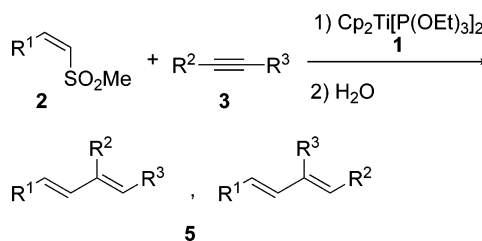
The stereoselective alkenylation of unsaturated compounds by means of a (Z)-alkenyl sulfone-titanocene(II) system is described. Treatment of alkynes and (Z)-alkenyl methyl sulfones with the titanocene(II) reagent $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$ produced conjugated dienes. This alkenylation system is also applicable to polar $\text{C}=\text{O}$ bonds; the simple mixing of carbonyl compounds, (Z)-alkenyl methyl sulfones, and the titanocene(II) reagent formed allylic alcohols. The advantages of alkenylation are that it requires no prepreparation of the alkenylmetal reagent and that it proceeds with complete stereoselectivity.

Introduction

Alkenylation is one of the most important transformations for the construction of unsaturated compounds. Alkenylmetal reagents are frequently employed as major tools for this purpose. For example, their transition-metals-catalyzed reactions with alkenyl halides or sulfonates,¹ such as the Kumada,² Suzuki,³ Stille,⁴ and Hiyama couplings,⁵ provide a useful method for the C–C bond formation between sp^2 carbon atoms. Although a variety of methods have been developed, including the oxidative addition of alkenyl halides to low-valent metal species and hydro- and carbometallation of alkynes,⁶ preparation of the alkenylmetals employed in the previously stated reactions is troublesome in some cases.

Recently we reported the titanocene(II)-promoted ($\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$, **1**) vinylation of alkynes and carbonyl compounds with vinyl pivalate.⁷ We also found that various alkynyl phenyl

SCHEME 1. Alkenylation of Alkynes **3** with (Z)-Alkenyl Methyl Sulfones **2**



sulfones reacted with (Z)-alkenyl methyl sulfones (**2**) in the presence of **1** to form the alkenylation products, 1-(phenylsulfonyl)-1,3-dienyltitanium compounds. These compounds produced titanium vinylvinylidene complexes upon treatment with

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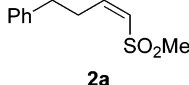
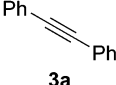
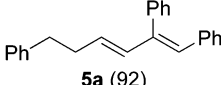
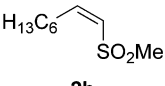
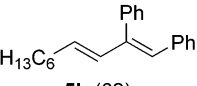
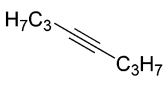
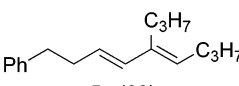
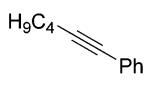
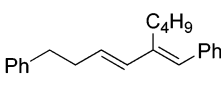
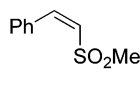
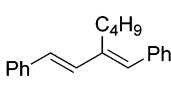
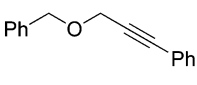
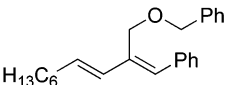
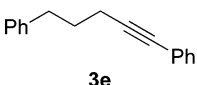
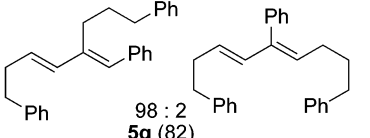
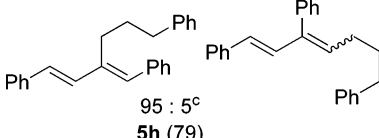
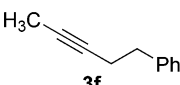
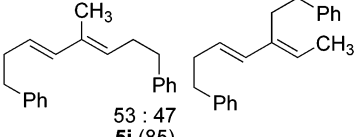
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TABLE 1. Stereoselective Preparation of Conjugated Dienes 5^a

entry	alkenyl sulfone 2	alkyne 3	reaction conditions ^b	product (yield / %)
1			I	 5a (92)
2		3a	I	 5b (62)
3	2a		II	 5c (60)
4	2a		III	 5d (59)
5		3c	III	 5e (69)
6	2b		II	 5f (66)
7	2a		II	 98 : 2 5g (82)
8	2c	3e	II	 95 : 5 ^c 5h (79)
9	2a		II	 53 : 47 5i (85)

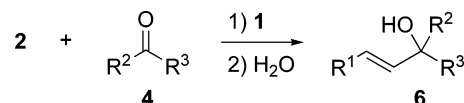
^a Preparation was performed with the general procedure A described in the experimental section, unless otherwise noted. ^b Conditions I: carried out at 0 °C for 30 min and then at 25 °C for 1 h. Conditions II: carried out at 0 °C for 30 min and then at 25 °C for 2 h. Conditions III: carried out at 0 °C for 13 h. ^c The configuration of the minor isomer was not determined.

another equivalent of **1**.⁸ These findings prompted us to investigate the synthetic utility of the titanocene(II)-promoted alkenylation of unsaturated compounds using alkenyl sulfones. Here we describe alkenylation of simple alkynes (**3**) (Scheme 1) and carbonyl compounds (**4**) (Scheme 2) that provide new routes to conjugated dienes (**5**) and allylic alcohols (**6**).⁹ The advantages of these reactions are that they require no preformation of alkenylmetal species and that they are applicable to the alkenylation of both nonpolar alkynes and polar carbonyl compounds.

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SCHEME 2. Alkenylation of Carbonyl Compounds **4** with (*Z*)-Alkenyl Methyl Sulfones **2**



Results and Discussion

Alkenylation of Alkynes. When symmetric alkynes **3a** and **3b** were treated with **2** (2 equiv) in the presence of **1** (3 equiv) at 0–25 °C for 1.5–2.5 h, **5a–c** were obtained in good yields (entries 1–3, Table 1). Although (*Z*)-alkenyl phenyl sulfones

(9) For the preliminary results of alkenylation using (*Z*)-4-phenylbuten-1-yl phenyl sulfone, see ref 7.

TABLE 2. Stereoselective Preparation of Secondary Allylic Alcohols **6** by the Reaction of Aldehydes **4**^a

entry	alkenyl sulfone 2	aldehyde 4	reaction conditions ^b	product (yield / %)
1	2a	4a	I	6a (74)
2	2b	4a	I	6b (52)
3	2c	4b	I	6c (71)
4	2a	4c	I	6d (64)
5	2a	4d	I	6e (65) ^c
6	2c	4d	I	6f (69) ^c
7 ^d	2a	4e	II	6g (42)
8 ^d	2c	4e	II	6h (35)
9 ^d	2c	4f	II	6i (66)

^a Preparation was performed with the general procedure B described in the experimental section, unless otherwise noted. ^b Conditions I: carried out at 0 °C for 30 min and then at 25 °C for 2 h. Conditions II: carried out at 0 °C for 13 h. ^c A mixture of diastereomers. ^d Performed with the general procedure C described in the experimental section.

can also be employed for the alkenylation, their stereoselective preparation is rather troublesome because of photoisomerization of their precursors, (*Z*)-alkenyl phenyl sulfides.¹⁰ In contrast, (*Z*)-alkenyl methyl sulfides were resistant to photoisomerization, and the sulfones **2** were readily obtained in pure forms by their oxidation. The reaction proceeded with complete stereoselectivity; the dienes **5** showed an (*E*)-configuration with respect to the double bond that was originated from alkenyl sulfones **2**, and the two substituents that were derived from alkynes **3** were *cis* to each other. The reactions of **2** with phenylacetylene derivatives **3c–e** proceeded with excellent regioselectivity, and the dienes **5** that have a phenyl group at the terminal carbon were predominantly obtained. No regioselectivity was observed when alkyl substituted unsymmetric alkynes were subjected to the reaction with **2** (see entry 9).

Alkenylation of Aldehydes and Ketones. Treatment of aliphatic aldehydes **4a–d** with the alkenyl sulfones **2** in the

presence of **1** at 0–25 °C for 2.5 h formed various allylic alcohols **6a–f** with (*E*)-configuration stereoselectively (entries 1–6, Table 2). Aromatic aldehydes such as benzaldehyde, however, were found to be rather poor substrates in this reaction; the reaction was complicated and the allylic alcohols **6** were obtained in moderate yields (see entries 7 and 8, Table 2). The α,β -unsaturated aldehyde **4f** reacted with the sulfone **2c** at its carbonyl group to produce the allylic alcohol **6i** selectively, and product via the coupling with its carbon–carbon double bond was not detected (entry 9, Table 2).

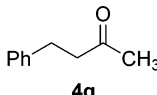
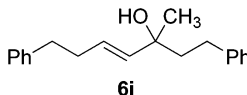
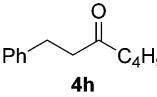
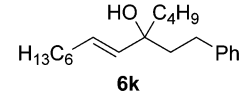
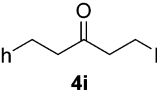
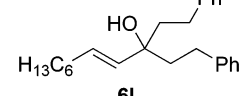
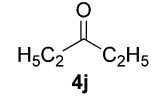
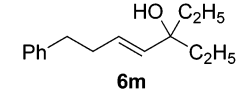
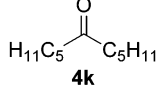
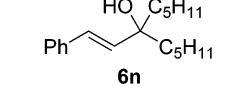
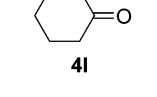
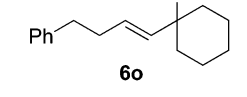
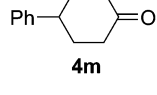
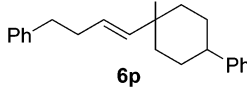
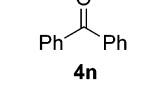
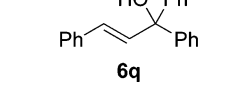
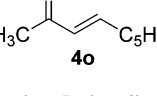
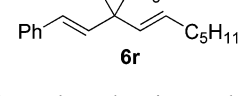
Recently, transition-metal-catalyzed alkenylation of carbonyl compounds has been extensively studied.¹¹ Systems utilizing Rh(cod)₂OTf–H₂¹² and Ni(cod)₂–Et₃B¹³ are employed for the alkenylation with enynes. Nickel-catalyzed alkenylation using alkynes¹⁴ or alkenes¹⁵ has also been developed. However, these reactions generally can be applied only to aldehydes, and they

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TABLE 3. Stereoselective Preparation of Tertiary Allylic Alcohols **6** by the Reaction of Ketones **4**^a

entry	alkenyl sulfone 2	ketone 4	reaction conditions ^b	product (yield / %)
1	2a		I	 (6j) (73)
2	2b		I	 (6k) (66)
3	2b		I	 (6l) (77)
4	2a		I	 (6m) (69)
5	2c		I	 (6n) (82)
6	2a		I	 (6o) (69)
7	2a		I	 (6p) (67) ^c
8 ^d	2c		II	 (6q) (71)
9 ^d	2c		II	 (6r) (50)

^a Preparation was performed with the general procedure B described in the experimental section, unless otherwise noted. ^b Conditions I: carried out at 0 °C for 30 min and then at 25 °C for 2 h. Conditions II: carried out at 0 °C for 13 h. ^c Single isomer. ^d Performed with the general procedure C described in the experimental section.

sometimes afford regioisomeric mixtures. A CrCl₂-mediated reaction of alkenyl halides with carbonyl compounds, known as the Nozaki–Hiyama–Kishi (NHK) reaction, is frequently

(13) For recent examples, see (a) Miller, K. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, *126*, 15342. (b) Miller, K. M.; Colby, E. A.; Woodin, K. S.; Jamison, T. F. *Adv. Synth. Catal.* **2005**, *347*, 1533. (c) Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 3077. (d) Moslin, R. M.; Jamison, T. F. *Org. Lett.* **2006**, *8*, 455. (e) Moslin, R. M.; Miller, K. M.; Jamison, T. F. *Tetrahedron* **2006**, *62*, 7598.

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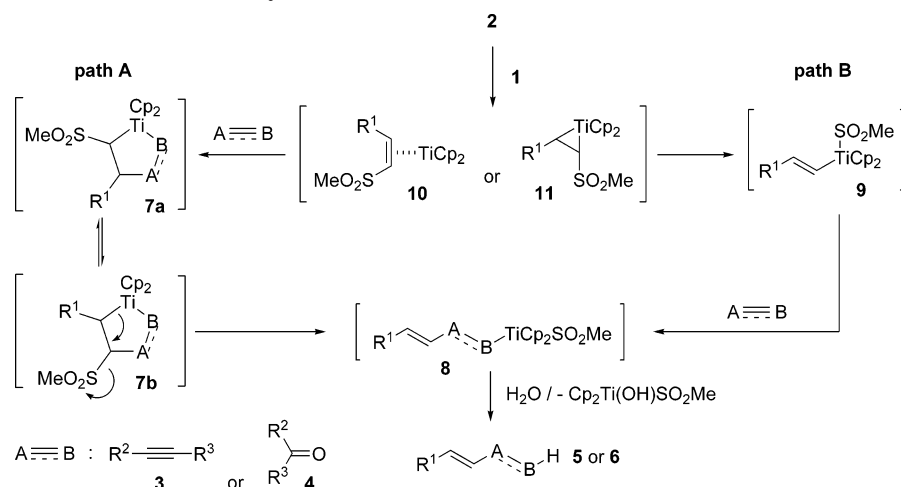
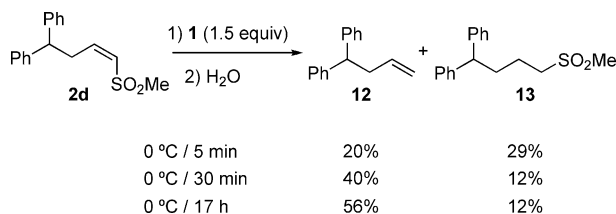
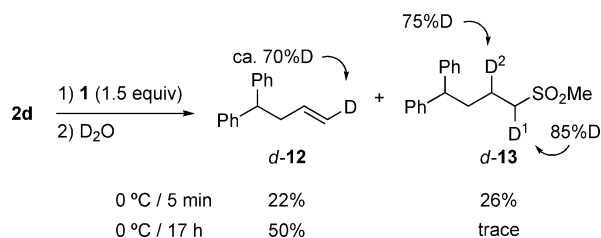
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employed for the preparation of allylic alcohols.¹⁶ Although aldehydes are good substrates for the NHK reaction, ketones are generally much less reactive toward the organochromium intermediates. In contrast, the present titanocene(II)-mediated reaction is highly effective for the alkenylation of ketones. The reactions of various acyclic, cyclic, and aromatic ketones **4** with **2** formed the corresponding tertiary allylic alcohols **6** with

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SCHEME 3. Two Plausible Reaction Pathways

SCHEME 4. Reduction of the (*Z*)-Alkenyl Methyl Sulfone **2d** with **1**SCHEME 5. Formation of the Deuterio Olefin *d*-12 and the Dideuterio Sulfone *d*-13

(*E*)-configuration in good yields (Table 3). Treatment of the α,β -unsaturated ketone **4o** with **2c** also formed the α -alkenyl allylic alcohol **6r** with complete stereoselectivity (entry 9, Table 3).

Reaction Pathway. As we described in the previous paper,⁷ the titanocene(II)-promoted cross-coupling of unsaturated compounds is expected to proceed via the formation of five-membered titanacycles (path A in Scheme 3). Compounds **2** react with unsaturated compounds **3** or **4** in the presence of **1** to form two titanacycle intermediates **7a** and **7b**, which exist in equilibrium. The subsequent elimination of the methylsulfonyl group via **7b** produces the dienylyltitaniums or titanium alkoxides of allylic alcohols **8** that produce the conjugated dienes **5** or allylic alcohols **6** upon hydrolysis. Similar reactions via the formation of five-membered titana- and zirconacycles from divalent metal species and unsaturated compounds have been investigated and employed for diene-, enyne-, and diyne-intramolecular couplings¹⁷ and for one-pot synthesis of aromatic and heteroaromatic compounds.¹⁸

An alternative pathway that involves the formation of alkenyltitanium species **9** (path B) should also be considered. Desulfurizative titanation of **2** with **1** via the π -complexes **10** or titanacyclopropanes **11** affords **9**. The subsequent carbomet-

allation or Grignard-type carbonyl addition of **9** produces **8**. Marek et al. reported the formation of alkenylzirconium species by the reaction of both (*E*)- and (*Z*)-alkenyl sulfones with zirconocene(II)-olefin complexes and their subsequent reactions with electrophiles.¹⁹ When (*Z*)-alkenyl methyl sulfone **2d** was treated with **1** at 0 °C for 5 min, the terminal olefin **12** was produced in 20% yield with the saturated sulfone **13** (Scheme 4). The yield of **12** increased with increasing reaction time.²⁰ Deuteration of the organotitanium intermediate produced the deuterated olefin *d*-12 and dideuterated sulfone *d*-13 (Scheme 5).

Although there is no decisive experimental evidence that clarifies the mechanism for the formation of the trans-deuterated olefin *d*-12, the above results might support the alkenylation via the formation of the alkenyltitanium species generated by the tertiary alkylation of titanium vinylcarbene complexes was reported by us.²¹ Indeed, the conjugated diene **5j** was obtained in good yields by the reaction of **3a** with

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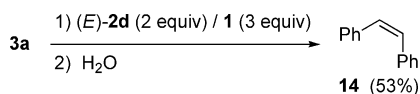
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(20) The reaction of **2d** with **1** at 25 °C for 2 h formed **12** in a lower yield (36%) and also formed a substantial amount (27%) of a stereoisomeric mixture of 1,1,8,8-tetraphenylocta-3,5-diene (**15**, Supporting Information), which would be produced by titanocene(II)-promoted self-coupling of **2d**.

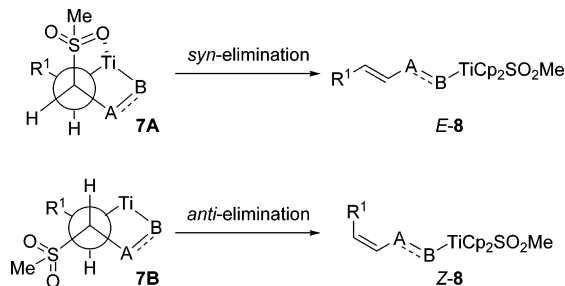
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TABLE 4. Reactions of the Alkenyl Sulfone **2d** with **3a** and **4g** under Different Conditions

entry	unsaturated compound	conditions	product (yield/%)
1	3a	A	5j (86)
2	3a	B	5j (88)
3	4g	A	6s (65)
4	4g	B	6s (80)

SCHEME 6. Reaction of the (*E*)-Alkenyl Methyl Sulfone (*E*)-**2d** with **3a**

SCHEME 7. Stereochemical Outcome for Reaction Pathway A



2d carried out with the pretreatment of **2d** with **1** at 0 °C for 17 h (entry 1, Table 4). However, when **2d** and **3a** were added simultaneously to a THF solution of **1** at 25 °C, **5j** was also obtained in comparable yield (entry 2). In the case of alkenylation of 4-phenylbutan-2-one (**4g**) with **2d**, the alkenylation product **6s** was obtained with better yield when the reaction was carried out without pretreatment of **2d** with **1** (entry 4). Although further investigation is needed to understand the mechanism of these reactions, we tentatively assume that the pathway involving the five-membered titanacycle intermediates (path A) is more reliable.

The stereochemistry of the present alkenylation is also of interest. The reaction of **2** proceeded with the inversion of configuration to form the (*E*)-alkenes **5** and **6**. In contrast, the alkenyl sulfone (*E*)-**2d** was completely inactive toward alkenylation of **3a**, and the reaction ended up with the formation of (*Z*)-stilbene (**14**) and with a substantial amount of (*E*)-**2d** (40%, Scheme 6).²²

The above stereochemistry-dependent reactivity is completely different from similar alkenylation of carbonyl compounds such as the NHK reaction, which generally proceeds using both stereoisomers of alkenyl halides with the retention of configuration via the alkenylchromium intermediates.¹⁶ The stereochemistry of the present alkenylations might be rationalized by the formation of the titanacycle intermediate **7** with retention of the configuration of (*Z*)-**2** and followed by the subsequent

syn-elimination of methylsulfonyl group via the conformation **7A**, as shown in Scheme 7. The preferential syn-elimination over anti-elimination is explained by the intramolecular coordination of the sulfonyl oxygen to the titanium atom depicted in **7A**.

Conclusion

We have established a versatile alkenylation of unsaturated compounds utilizing **2**. This new method is applicable both to alkynes bearing a nonpolar carbon–carbon triple bond and to carbonyl compounds bearing a polar carbon–oxygen double bond. The procedure is straightforward, and the stereoselectivity is excellent. Therefore, the present alkenylation will have a wide synthetic application to construct unsaturated systems.

Experimental Section

General Methods. THF was distilled from sodium and benzophenone. Preparative thin layer chromatography (PTLC) was carried out using Wakogel B-5F. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were recorded in CDCl₃, and chemical shifts (δ) are quoted in parts per million from tetramethylsilane for ¹H and CDCl₃ for ¹³C spectroscopy. IR absorptions are reported in cm⁻¹.

Synthesis of (3*E*,5*E*)-1-Phenyl-5-propylnona-3,5-diene (5c**).**
General Procedure A. Finely powdered molecular sieves 4A (60 mg), magnesium turnings (16 mg, 0.66 mmol), and Cp₂TiCl₂ (149 mg, 0.6 mmol) were placed in a flask and were dried by heating with a heat gun in vacuo (2–3 mmHg). After the contents were cooled, THF (1.5 mL) and P(OEt)₃ (0.21 mL, 1.2 mmol) were added successively with stirring at 25 °C. After 3 h, the reaction mixture was cooled to 0 °C. A THF (1 mL) solution of **2a** (84 mg, 0.4 mmol) was added dropwise over 5 min to the mixture, and then the mixture was stirred for 30 min. Next, a THF (1 mL) solution of **3b** (22 mg, 0.2 mmol) was added dropwise over 10 min. The mixture was stirred for an additional 30 min at 0 °C and then for 2 h at 25 °C. The reaction was quenched by addition of 1 M NaOH. The insoluble materials were filtered off through celite and were washed with ether. The layers were separated, and the aqueous layer was extracted with ether. After the combined organic extracts were dried with Na₂SO₄, the solvent was evaporated. Purification of the residue by PTLC (hexane) resulted in **5c** (29 mg, 60%): ¹H NMR δ 0.91 (t, *J* = 7.3 Hz, 6H), 1.32–1.48 (m, 4H), 2.07 (dt, *J* = 7.5, 7.3 Hz, 2H), 2.12–2.21 (m, 2H), 2.39 (dt, *J* = 7.5, 7.5 Hz, 2H), 2.71 (t, *J* = 7.9 Hz, 2H), 5.35 (t, *J* = 7.3 Hz, 1H), 5.59 (dt, *J* = 15.8, 6.8 Hz, 1H), 5.98 (d, *J* = 15.8 Hz, 1H), 7.12–7.32 (m, 5H); ¹³C NMR δ 13.9, 14.3, 22.2, 23.0, 29.0, 30.2, 34.9, 36.3, 125.7, 126.1, 128.2, 128.4, 131.1, 134.2, 138.0, 142.1; IR (neat) 3086, 3062, 3026, 2958, 2871, 1604, 1496, 1455, 1377,

(22) The terminal olefin **12** was produced in a 10% yield by this reaction.

1339, 1076, 1031, 964, 745, 698 cm^{-1} ; Anal. Calcd for $\text{C}_{18}\text{H}_{26}$: C, 89.19; H, 10.81. Found: C, 89.23; H, 10.57.

Synthesis of (*E*)-2-Benzyl-1,7-diphenylhept-4-en-3-ol (6a).
General Procedure B. A solution of **1** in THF (1.5 mL) was prepared from Cp_2TiCl_2 (149 mg, 0.6 mmol), magnesium turnings (16 mg, 0.66 mmol), $\text{P}(\text{OEt})_3$ (0.21 mL, 1.2 mmol), and molecular sieves 4A (60 mg). A THF (1 mL) solution of **2a** (84 mg, 0.4 mmol) was added dropwise over 5 min to the solution of **1**, and the mixture was stirred for 30 min. A THF (1 mL) solution of **4a** (45 mg, 0.2 mmol) was added dropwise over 10 min to the mixture, and the mixture was stirred for an additional 30 min at 0 °C and then for 2 h at 25 °C. The usual workup and purification by PTLC (hexane/AcOEt, 9:1) resulted in **6a** (53 mg, 74%): ^1H NMR δ 1.41 (s, 1H), 2.04–2.19 (m, 1H), 2.30–2.45 (m, 3H), 2.53 (d, $J = 7.0$ Hz, 2H), 2.70 (t, $J = 7.5$ Hz, 2H), 2.78 (dd, $J = 13.7, 7.1$ Hz, 1H), 4.01 (bs, 1H), 5.51 (dd, $J = 15.5, 6.3$ Hz, 1H), 5.64 (dt, $J = 15.4, 6.5$ Hz, 1H), 7.03–7.38 (m, 15H); ^{13}C NMR δ 33.9, 35.2, 35.5, 35.6, 48.0, 72.7, 125.8, 125.9, 128.20, 128.24, 128.3, 128.4, 129.1, 129.2, 131.4, 131.8, 140.8, 141.1, 141.5; IR (neat) 3409, 3060, 3026, 2925, 1603, 1495, 1453, 1030, 973, 749, 699 cm^{-1} ; Anal. Calcd for $\text{C}_{26}\text{H}_{28}\text{O}$: C, 87.60; H, 7.92. Found: C, 87.46; H, 8.32.

Synthesis of (*E*)-1,1,3-Triphenylprop-2-en-1-ol (6q).²³ General Procedure C. To a THF (1.5 mL) solution of **1**, which was prepared from Cp_2TiCl_2 (149 mg, 0.6 mmol), magnesium turnings (16 mg, 0.66 mmol), $\text{P}(\text{OEt})_3$ (0.21 mL, 1.2 mmol), and molecular sieves

4A (60 mg), a THF (1 mL) solution of **2c** (109 mg, 0.6 mmol) was added dropwise over 5 min, and the mixture was stirred for 30 min. A THF (1 mL) solution of **4n** (55 mg, 0.3 mmol) was added dropwise over 10 min, and the mixture was stirred for an additional 13 h at 0 °C. The usual workup and purification by PTLC (hexane/AcOEt, 9:1) resulted in **6q** (61 mg, 71%): mp 100–103 °C; ^1H NMR δ 2.40 (m, 1H), 6.65 (d, $J = 15.9$ Hz, 1H), 6.83 (dd, $J = 15.9, 0.7$ Hz, 1H), 7.19–7.46 (m, 15H); ^{13}C NMR δ 79.4, 126.7, 126.9, 127.3, 127.7, 128.2, 128.5, 129.2, 135.2, 136.6, 146.0; IR (KBr) 3555, 3530, 3083, 3056, 3026, 1598, 1489, 1446, 1154, 1065, 1028, 976, 757, 738, 700 cm^{-1} ; Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{O}$: C, 88.08; H, 6.34. Found: C, 88.07; H, 6.31.

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Supporting Information Available: Procedure for the deuteration experiment and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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