

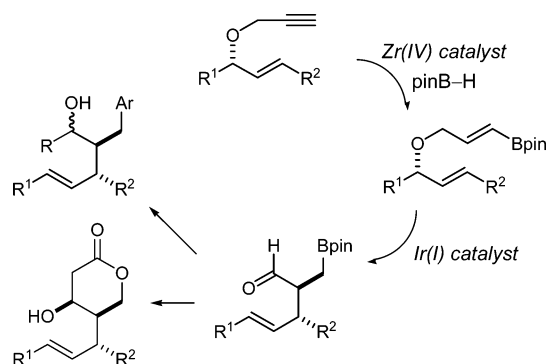
Strategies for Expanding Structural Diversity Available from Olefin Isomerization—Claisen Rearrangement Reactions

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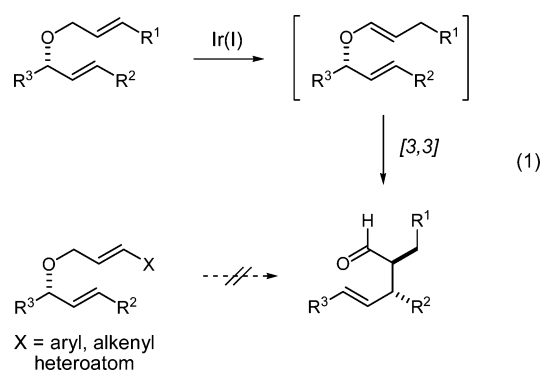


Boron-substituted di(allyl) ethers provide an efficient conduit for expanding the structural diversity available from olefin isomerization—Claisen rearrangement (ICR) reactions. Easily prepared allyl propargyl ethers undergo chemoselective Zr(IV)-catalyzed hydroboration to afford the boron-substituted ICR substrates. The boron-substituted allyl residue undergoes chemoselective Ir(I)-catalyzed olefin isomerization and in situ Claisen rearrangement to afford stereodefined β -boryl aldehyde products. Functionalization of the C—B linkage by oxidation or Suzuki cross-coupling provides a route to Claisen adducts previously inaccessible from the ICR methodology.

Introduction

[3,3] Sigmatropic rearrangements are characterized by their ability to rapidly introduce molecular complexity from simple precursors and to dramatically alter substrate morphology in a single operation.¹ Ireland enolate Claisen and anionic oxy-Cope rearrangements constitute the most extensively utilized [3,3] rearrangements in synthesis activities due, in large part, to the facile substrate preparation and mild reaction conditions offered by these activated reaction variants.² With the goal of imparting similar operational features to aliphatic Claisen rearrangements, we developed olefin isomerization—Claisen rearrangement (ICR) reactions as a strategy for affecting highly stereoselective [3,3] sigmatropic rearrangements.³ The olefin isomerization—Claisen rearrangement methodology is predicated on exploiting

easily prepared di(allyl) ethers as direct progenitors of aliphatic Claisen rearrangements and relies on chemoselective Ir(I)-catalyzed olefin isomerization to arrive at the characteristic allyl vinyl ether Claisen rearrangement precursors (eq 1).⁴ However,



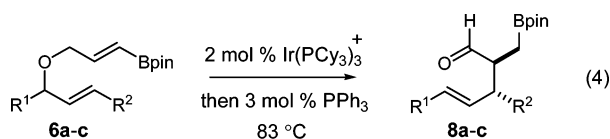
di(allyl) ethers bearing substituents that, due to conjugative stabilization, retard olefin isomerization were not effective ICR substrates. Unfortunately, this family of substrates included aryl-

(1) (a) Ziegler, F. E. *Chem. Rev.* **1988**, 88, 1423. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, 28, 43. (c) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461. (d) Nubbemeyer, U. *Synthesis* **2003**, 961.

(2) (a) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 827. (b) Wilson, S. R. *Org. React. (New York)* **1993**, 43 93. (c) Paquette, L. A. *Tetrahedron* **1997**, 53, 13971.

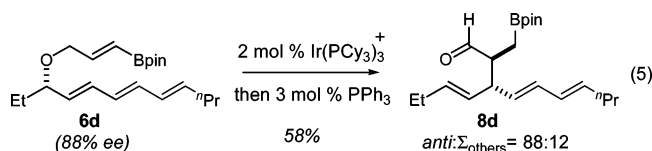
However, conducting the Zr(IV)-catalyzed hydroboration of **5** under microwave irradiation resulted in highly efficient alkyne hydroboration without competing alkene hydroboration.⁷ Thus, the boron-substituted ICR substrates were obtained by Williamson etherification of the allylic alcohols **7** with propargyl bromide (NaH, THF, 65 °C) to afford the allyl propargyl ethers **5a–c** (73–84%). Microwave-accelerated hydroboration of the resulting propargyl ethers under Zr(IV) catalysis (5 mol % of Cp₂Zr(H)Cl, CH₂Cl₂, 100 °C microwave IR probe temperature) then afforded the desired ICR substrates in the form of the boron-containing di(allyl) ethers **6a–c** (75–83%). A similar reaction sequence provided the enantioenriched trienyl allyl ether **6d** from the corresponding 3*S*-trienyl alcohol **7d** indicative of the zirconium-catalyzed hydroboration's faithful chemoselectivity even in the presence of multiple alkene functionalities.

Having secured access to the boron-containing di(allyl) ethers, we were prepared to evaluate these materials as substrates for the ICR bond reorganization. Successfully engaging these substrates in the ICR sequence was predicated on achieving selective vinyl boronate–allyl boronic ester isomerization without competing isomerization of the α -substituted allyl residue.⁸ Subjecting **6** to the standard ICR reaction conditions (2 mol % of Ir(PCy₃)₃⁺, 25:1 CH₂Cl₂/acetone) elicited chemoselective vinyl boronate isomerization to afford the desired *E*-allyl boronate (eq 4). Despite the presence of the boron



ether 6	R ¹	R ²	% yield 8	dr 8
6a	ⁿ Bu	Ph	67	92:8
6b	Ph	Me	65	92:8
6c	1-Np	Me	61	91:9

substituent, steric crowding continues to protect the alternative allyl residue from alkene isomerization. Moreover, olefin isomerization remains highly *E* selective, a significant observation considering that olefin stereochemistry is directly reflected in Claisen diastereoselection. In accord with the optimized ICR reaction conditions, the allyl vinyl ethers emerging from olefin isomerization were directly engaged in thermal [3,3] sigmatropic rearrangement to generate the 2,3-*syn*- β -boryl aldehydes **8a–c** (61–67%, *syn/anti* = 91:9–92:8). The enantioenriched di(allyl) ether **6d** undergoes analogous ICR reorganization to afford the diene-substituted Claisen adduct **8d**; ICR reactions of enantioenriched di(allyl) ethers proceed with near perfect translation of chirality (eq 5).^{3a,c}



(7) For an example of Rh(I)-catalyzed hydroborations accelerated by microwave irradiation, see: Hadebe, S. W.; Robinson, R. S. *Tetrahedron Lett.* **2006**, *47*, 1299–1302.

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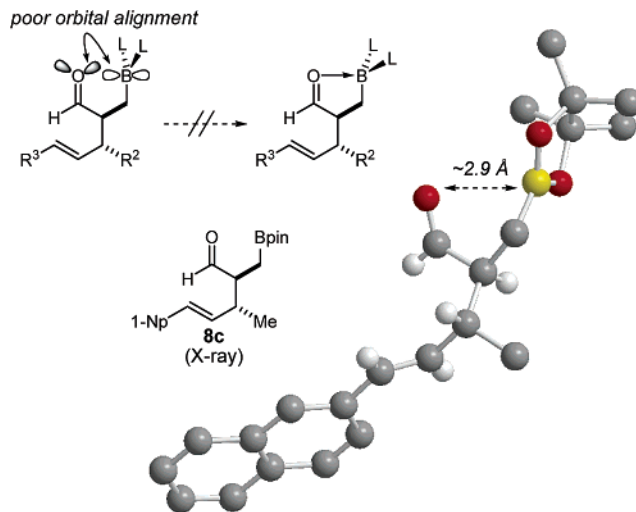
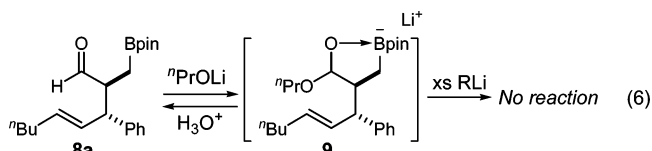


FIGURE 4. X-ray structure of Claisen adduct **8c**.

The structure of the ICR-derived aldehydes **8** offered intriguing possibilities for eliciting unique reactivity patterns during nucleophilic addition to the aldehyde function. We entertained the notion that chelate organization of the α -chiral aldehyde might be achieved by boron coordination of the aldehyde oxygen. Similar chelate organization of alkyl boronic esters has been exploited by Molander to achieve highly diastereoselective carbonyl reductions.⁹ However, X-ray structure analysis of the β -boryl aldehyde **8c** revealed no evidence for this type of chelation (Figure 4). Indeed, the boron atom in **8c** exhibits none of the pyramidalization that would accompany even weak Lewis acid–base association (B–O distance of ~ 2.9 Å). Poor overlap between the oxygen lone pair residing in an sp² hybrid orbital and the vacant boron p orbital is believed to provide the barrier for B–O chelation. These geometric constraints precluding B–O coordination, however, would be largely relieved upon oxygen rehybridization to an sp³ geometry. Consistent with this supposition, reacting **8a** with ⁿPrOLi affords an adduct that is immune to further nucleophilic addition and, following workup, affords the starting aldehyde with no stereochemical erosion (eq 6).¹⁰ These observations in conjunction with corroborating

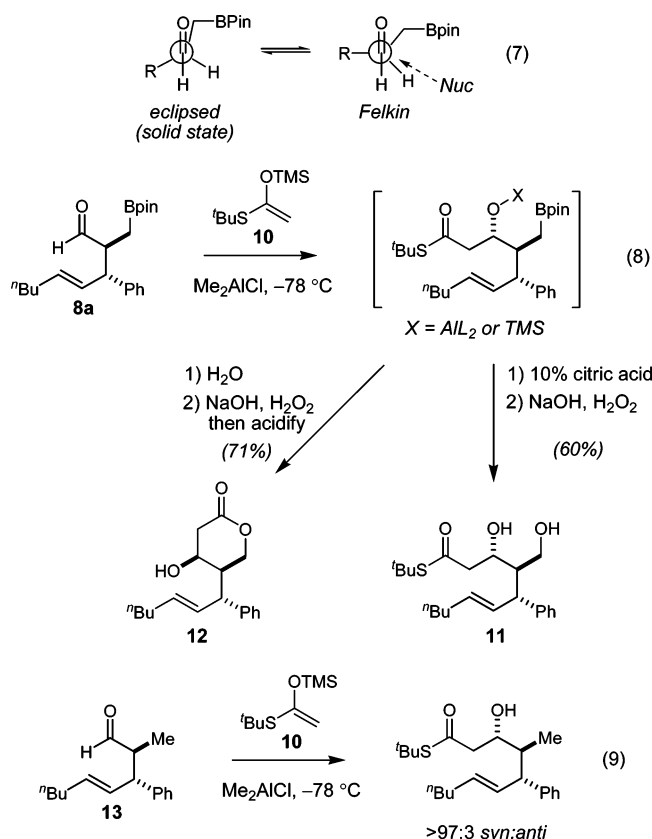


¹H NMR data support the alkoxide-mediated formation of the chelated borate acetal **9** indicative of the effect oxygen rehybridization has on internal Lewis acid–base coordination.¹¹

(9) (a) Molander, G. A.; Bobbitt, K. L.; Murray, C. K. *J. Am. Chem. Soc.* **1992**, *114*, 2759–2760. (b) Molander, G. A.; Bobbitt, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 7517–7518. For other examples of stereoselective nucleophilic additions due to internal boron chelation, see: (c) Curtius, A. D.; Mears, R. J.; Whiting, A. *Tetrahedron* **1993**, *49*, 187–198. (d) Mears, R. J.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 8155–8156. (e) Mears, R. J.; Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3250–3263. (f) Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3362–3374.

(10) Examples of nucleophile-mediated in situ aldehyde protection: (a) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1981**, *22*, 4213–4216. (b) Retz, M. T.; Wenderoth, B.; Peter, R. *J. Chem. Soc., Chem. Commun.* **1983**, 406–408.

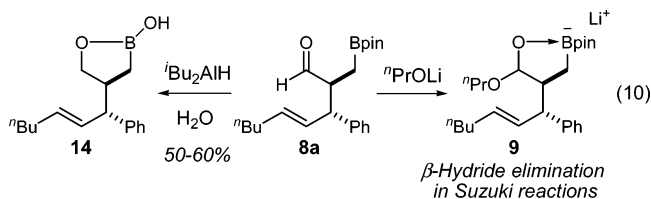
The solid-state conformation of aldehyde **8c** orients the boron-containing alkyl group to eclipse the carbonyl π system (dihedral angle = 4°), an orientation that is reminiscent of the low-energy conformation about the $C_{sp^2}-C_{sp^3}$ bonds identified by Karabatsos (eq 7).¹² A minimal perturbation to this solid-state conformation would yield a Felkin-type orientation of the α stereogenic center, wherein the boronate ester-containing alkyl group functions as the “medium” group.¹³ Consistent with this expectation, the β -boronic aldehyde **8a** undergoes Lewis acid-mediated Mukaiyama aldol addition (1.5 equiv of Me_2AlCl , CH_2Cl_2 , $-78^\circ C$) with silyl ketene acetal **10** to afford, after C–B bond oxidation, the Felkin-derived syn (C_3-C_4) aldol adduct **11** (60%, $\geq 97:3$ syn/anti) (eq 8).¹⁴ Alternatively, δ -lactone **12** can be isolated directly from the addition–oxidation sequence by acidifying the reaction mixture prior to workup (71%, $\geq 97:3$ cis/trans). The aldehyde **13** lacking the β -boronic ester undergoes similar Felkin-selective Mukaiyama aldol addition, reaffirming that the boron substituent in **8** plays no special organizational role in defining stereoselectivity during carbonyl addition (eq 9).¹⁵



Verifying the ICR-derived boronic esters **8** as conduits to structurally diverse Claisen adducts required these materials to function as effective substrates for Suzuki cross-coupling reactions.¹⁶ Initial efforts to directly engage the ICR-derived aldehydes in basic Suzuki reaction conditions elicited considerable epimerization of the α -chiral aldehydes. Protecting the aldehyde as the borate acetal **9** was considered a strategy for

(11) Borate complex **9** was not rigorously characterized; however, 1H NMR analysis of crude reaction mixtures was completely consistent with the proposed structure. These data coupled with the indicated reactivity patterns exhibited by **9** (see eq 6) provided the basis for the structure assignment. See Supporting Information for details of the 1H NMR experiment.

circumventing epimerization and activating the boron moiety toward cross coupling. However, attempted Suzuki cross-coupling of **9** resulted in extensive β -hydride elimination (eq 10). Despite the failure of the boronate acetals as Suzuki



reaction partners, nucleophilic addition to the aldehyde function was expected to deliver similar internally activated boronate species as potential cross-coupling partners. For example, hydride-mediated reduction of aldehyde **8a** afforded a stable intermediate assigned as cyclic borinic acid **14** (50–60%), although the free boronic acid or an oligomeric equivalent cannot be conclusively excluded.¹⁷ In contrast to the pinacolate boronic esters **8** and borate acetal **9**, the borinic acid **14** proved to be an efficient alkyl group donor in the targeted B– C_{alkyl} Suzuki cross-coupling reactions.¹⁸ Considerable optimization of the ensuing cross-coupling reactions revealed a reaction system composed of 5 mol % of $Pd(OAc)_2/25$ mol % of PPh_3 in aqueous Na_2CO_3/t -amyl alcohol afforded efficient coupling of borinic acid **14** with both aryl and heteroaryl bromides (Table 1).¹⁹ Aryl bromides, including 3-bromopyridine and 3-bromoquinoline, participate in efficient coupling with **14** to afford the β -aryl alcohols **15a–f** (36–89%). Only 2-bromopyridine provided notable difficulties as an aryl bromide reaction partner in the cross-coupling reaction.

To probe the additional structural diversity that could be accessed from the ICR–Suzuki cross-coupling sequence, we explored the Claisen-derived aldehydes **8** as possible templates for diversity-oriented synthesis. The ICR-derived aldehyde **8a** was subjected to nucleophilic addition with allylmagnesium

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(13) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2201. See also: (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

(14) (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011–1014. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509. (c) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1975**, 989–990.

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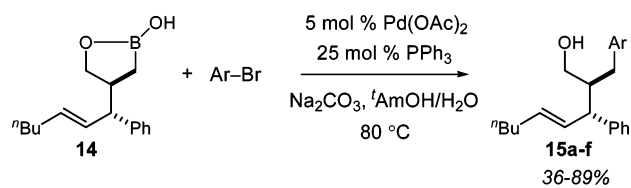
(16) For reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-coupling Reactions*; Wiley-VCH: Weinheim, 1998; p 517. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695 and references therein. (e) Leadbeater, N. E. *Chem. Commun.* **2005**, *23*, 2881–2902. (f) Apukkuttan, P.; Van der Eycken, E.; Dehaen, W. *Synlett* **2005**, 127–133. (g) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.

(17) 1H and ^{13}C NMR spectral data for **14** were fully consistent with the indicated structure. However, our inability to obtain satisfactory mass spectral data for **14** precludes us from conclusively eliminating the free boronic acid alcohol or an oligomeric form of **14** as alternative structures for the species derived from the hydride addition.

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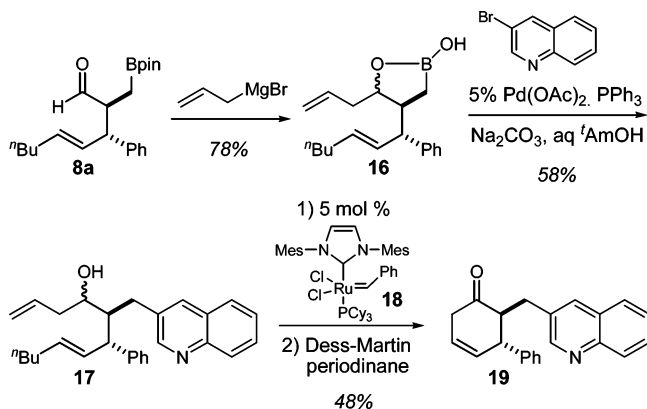
TABLE 1. Suzuki Cross-Coupling of Borinic Acid 14



entry ^a	Ar	% yield ^b
a	C ₆ H ₅	67
b		81
c		67
d		36
e		78
f		89

^a Reaction conditions: Pd(OAc)₂ (5 mol %), PPh₃ (25 mol %), aryl bromide (2 equiv), aq Na₂CO₃/tAmOH, 80 °C. ^b Values reported for purified materials.

SCHEME 1



bromide that, in accord with the corresponding hydride additions, afforded the borinic acid **16** as a mixture of homoallylic alcohol diastereomers (78%, dr ~ 2:1). Cross-coupling of **16** with 2-bromoquinoline under the optimized Suzuki conditions then provided the diaryl alcohol **17** (58%). Engaging **17** in ring-closing metathesis under Grubbs' conditions (5 mol % of **18**) and alcohol oxidation (Dess–Martin) afforded the β,γ -unsaturated ketone **19** as a 92:8 mixture of diastereomers, reflecting the diastereoselection of the initial Claisen rearrangement (48% for two steps) (Scheme 1).²⁰

Conclusion

Olefin isomerization–Claisen rearrangement reactions provide convenient access to highly diastereoselective aliphatic

Claisen rearrangements from easily prepared starting materials. The boron-modified ICR reactions serve to expand the structural diversity available directly from the ICR reactions and from ensuing derivatization of the Claisen adducts. We anticipate that merging the ICR methodology with ensuing Suzuki cross-coupling reactions will further expand the utility of the ICR technology in various synthesis activities.

Experimental Section

Representative Procedure for Synthesis of Di(allyl) Ethers 6. 2-[(1*E*)-3-[(*E*)-1-Phenylhept-1-en-3-yloxyprop-1-enyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6a**). A microwave-compatible reaction vessel was charged with 56 mg of Cp₂Zr(H)Cl²¹ (0.05 equiv, 0.22 mmol) and 0.33 mL of CH₂Cl₂ (3.0 M in alkyne). The resulting suspension was cooled to 0 °C, and 1.00 g of propargylic ether **5a** (4.38 mmol) and 617 mg of pinacolborane (1.1 equiv, 4.82 mmol) were added. The reaction was allowed to warm to ambient temperature and was then heated at 100 °C (internal IR probe) in a microwave reactor for 45 min. The solvent was removed in vacuo, and the residue was purified by flash chromatography (5% EtOAc in hexanes) on Iatrobeads 6RS-8060 silica gel to afford 1.18 g (75%) of the title compound as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 7.42–7.20 (m, 5H), 6.66 (dt, *J* = 18, 4.6 Hz, 1H), 6.49 (d, *J* = 16 Hz, 1H), 6.05 (dd, *J* = 16, 8.0 Hz, 1H), 5.73 (dt, *J* = 18, 1.8 Hz, 1H), 4.15 (ddd, *J* = 15, 4.4, 1.9 Hz, 1H), 3.96 (ddd, *J* = 15, 4.8, 1.8 Hz, 1H), 3.85 (dt, *J* = 6.5, 7.3 Hz, 1H), 1.78–1.50 (m, 2H), 1.27 (s, 12H), 1.40–1.24 (m, 4H), 0.89 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 149.8, 136.5, 132.0, 130.5, 128.4, 127.5, 126.3, 118.6 (br), 83.0, 80.4, 69.5, 35.5, 27.4, 24.6, 22.6, 14.0. MS (EI) *m/z* 356 (M⁺), 341, 326, 299, 270, 257, 199, 173, 167, 155, 143, 131, 117, 105, 91, 85, 77, 67, 57. HRMS *m/z* calcd for C₂₂H₃₃¹¹BO₃, 356.2523; found, 356.2523.

Representative Procedure for ICR Reactions of Di(allyl) Ethers 6: *R**-(*E*,2*R*,3*S*)-3-Methyl-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-5-phenylpent-4-enal (**8a**). A solution of 14 mg of [(C₈H₁₄)₂IrCl]₂ (1.0 mol %, 0.02 equiv of Ir) and 27 mg of PCy₃ (6.0 mol %, 0.06 equiv) in 1.2 mL of CH₂Cl₂ was added to a solution of 11 mg of NaBPh₄ (2.0 mol %, 0.02 equiv) in 1.2 mL of 25:1 CH₂Cl₂/acetone (0.67 M final concentration in **6a**), and the resulting yellow solution was stirred for 5 min at ambient temperature. Di(allyl) ether **6a** (0.500 g, 1.59 mmol) was added. The reaction was stirred for 90 min at ambient temperature whereupon 25 mg of PPh₃ (6.0 mol %, 0.06 equiv) was added, and the resulting solution was heated at 40 °C for 4 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (8% EtOAc in hexanes) on Iatrobeads 6RS-8060 silica gel to afford 0.326 g (65%) of the title compound as a colorless oil. The diastereomer ratio was determined by integration of the vinyl CH resonance from 300 MHz ¹H NMR of the crude product mixture (syn:anti = 92:8). ¹H NMR (300 MHz, CDCl₃): δ 9.76 (d, *J* = 0.8 Hz, 1H), 7.36–7.20 (m, 5H), 6.42 (d, *J* = 16 Hz, 1H), 6.19 (dd, *J* = 16, 7.5 Hz, 1H), 2.85 (m, 1H), 2.70 (m, 1H), 1.24 (s, 6H), 1.21 (s, 6H), 1.12 (d, *J* = 6.9 Hz, 1H), 1.00 (dd, *J* = 16, 10 Hz, 1H), 0.82 (dd, *J* = 16, 5.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 204.8, 137.1, 132.7, 130.1, 128.4, 127.1, 126.0, 83.1, 53.2, 37.8, 24.7, 24.5, 16.4, 6.7 (br). Satisfactory MS data could not be obtained for this compound; copies of the ¹H and ¹³C spectra are provided.

Representative Procedure for the Suzuki Cross-Coupling Reaction of 14: *R**-(*E*,2*S*,3*R*)-2-Benzyl-3-phenylnon-4-en-1-ol (**15a**). A mixture of 3.1 mg of palladium(II) acetate (5 mol %, 0.014 mmol), 11 mg of triphenylphosphine (0.042 mmol), and 75 mg of borinic acid **14** (0.27 mmol) were placed in a CEM microwave tube.^{19a} The tube was sealed and evacuated under vacuum for 30 min and then backfilled with N₂; the evacuate–backfill cycle was

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(21) Buchwald, S.; LaMaire, S.; Nielsen, R.; Watson, B.; King, S. *Org. Synth., Coll. Vol. IX* **1994**, 162.

repeated two additional times.²² *tert*-Amyl alcohol (0.5 mL), 0.060 mL of bromobenzene (0.090 g, 0.57 mmol), and 0.25 mL of aqueous 1.3 M sodium carbonate were added, and the reaction mixture was stirred for 60 min at ambient temperature.²³ The reaction mixture was then heated at 80 °C for 5.5 h (yellow solution → white suspension). The reaction was diluted with water, and the biphasic mixture was extracted with EtOAc (3×). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated. The crude product mixture was purified by flash chromatography (SiO₂, 6:1 hexanes/EtOAc) to afford 54 mg (67%) of the title compound as a colorless oil. Separation of the diastereomers by GC-MS [HP-1 (12 m × 0.20 mm), pressure 21 kPa, method: 70 °C for 2.00 min, ramp at 10 °C/min to 300 °C, hold for 60 min] provided the diastereomer ratio: 4.5% (*T_r* = 18.80), 95.5% (*T_r* = 18.97). IR (thin film) 3389, 3026, 2926, 1601, 1494, 1453, 1030,

(22) For reproducible results, it is essential to remove all oxygen from the **14**/precatalyst mixture using high vacuum prior to introducing the solvent.

(23) For the development of this solvent system for Suzuki cross-coupling reactions, see ref 19b.

970, 700 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.37–7.09 (m, 10H), 5.69 (dd, *J* = 15.2, 8.8 Hz, 1H), 5.58 (dt, *J* = 15.1, 6.1 Hz, 1H), 3.70 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.55 (dd, *J* = 11.3, 4.2 Hz, 1H), 3.34 (t, *J* = 9.1 Hz, 1H), 2.55 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.46 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.14 (m, 1H), 2.03 (q, *J* = 6.8 Hz, 2H), 1.33 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 144.0, 140.9, 132.0, 131.9, 129.0, 128.6, 128.3, 127.9, 126.2, 125.8, 62.1, 51.2, 47.7, 35.2, 32.2, 31.5, 22.2, 13.9. MS (EI) *m/z* 308 (M⁺), 290, 233, 199, 173, 117, 91. HRMS (EI) *m/z* calcd for C₂₂H₂₈O, 308.2140; found, 308.2147.

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Supporting Information Available: Experimental procedures, characterization data, ¹H and ¹³C NMR spectra, and X-ray diffraction data are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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