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One-pot sequential cross-metathesis/hydride reduction: highly stereoselective synthesis of primary (*E*)-allylic alcohols from terminal olefins

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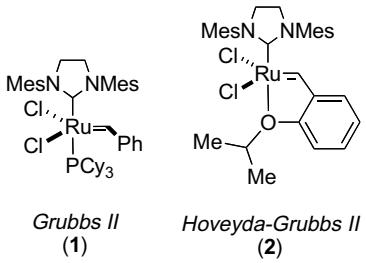
Abstract

Several di- and trisubstituted primary (*E*)-allylic alcohols have been prepared from the corresponding terminal olefins in a highly stereoselective manner (>20:1 *E*/*Z*) by sequencing olefin cross-metathesis (CM) with hydride reduction (DIBAL-H) in good yields utilizing only commercially available reagents in a one-pot fashion. The method is a reliable alternative to the direct CM of terminal olefins with allyl alcohol, which is not always stereoselective but rather highly substrate dependent.

Keywords: One-pot; Cross-metathesis; Synthesis; Primary (*E*)-allylic alcohol

1. Introduction

Streamlining linear sequences of chemical reactions are a routine tactic when carrying out an efficiency-driven synthesis, be it toward the preparation of building blocks, a natural product target/analogue, or a pharmaceutical intermediate. One-pot and tandem reactions are excellent examples of such tactics, which both accelerate product preparation and reduce cost by consolidating time-consuming purification steps (i.e., chromatography).[1] In the context of sequencing CM with other transformations, methodologies can be classified into those carried out in a one-pot fashion and those that are not.[2] We and others have focused efforts on the former in order to maximize efficiency.[3] Olefin cross-metathesis is a powerful methodology for the elaboration of olefinic substrates, particularly terminal alkenes, due largely to the advent of powerful catalysts such as the Grubbs 2nd generation catalyst (**1**) and the Hoveyda–Grubbs 2nd generation catalyst (**2**) (Fig. 1).[4]



Grubbs II (**1**) *Hoveyda-Grubbs II* (**2**)

Fig. 1. Structures of olefin CM catalysts Grubbs II (**1**) and Hoveyda–Grubbs II (**2**).

We recently reported a sequential CM/phosphorus-based olefination sequence for the rapid and stereoselective preparation of either (2*E*,4*E*)- or (2*Z*,4*E*)-dienoates by (1) performing a CM between a terminal olefin and crotonaldehyde (**3**) to stereoselectively afford an intermediary α,β-enal (>20:1 *E*:*Z*); and (2) utilizing either the Wittig (one-pot) or Horner–Wadsworth–Emmons reaction as the second step.[3g] Continuing with our program directed at

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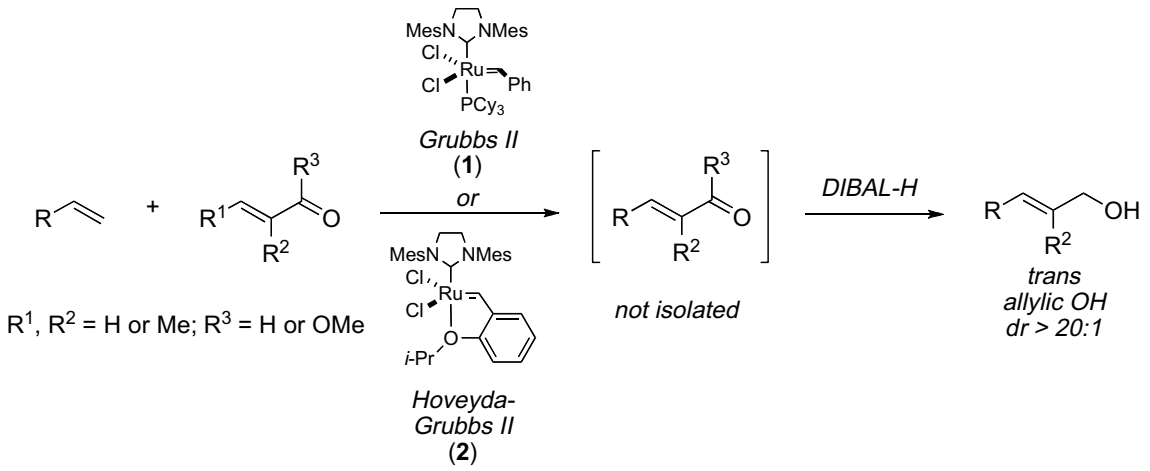


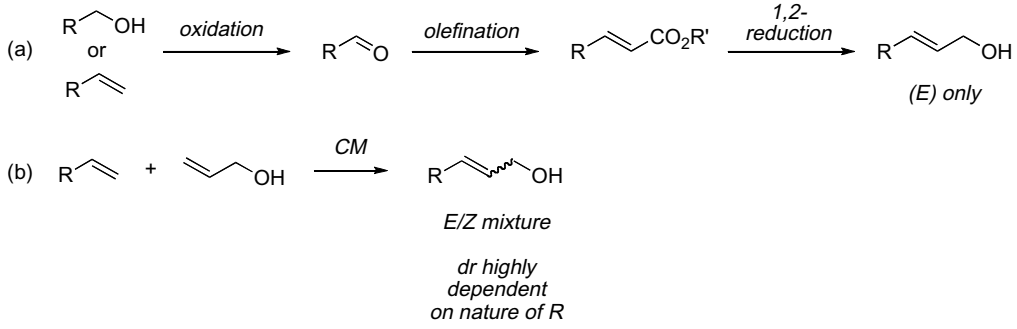
Scheme 1. Generalized one-pot sequential CM/hydride reduction of terminal olefins.

sequencing CM with non-metathesis reactions, we report our findings on the use of DIBAL-mediated reduction as the second step, which afford primary (*E*)-allylic alcohols in good yields and excellent stereoselectivities (>20:1 *E*:*Z*) when either crotonaldehyde (**3**), methacrolein (**4**) or methyl acrylate (**5**) are used as coupling partners (Scheme 1).

Primary (*E*)-allylic alcohols are excellent substrates for a variety of transformations such as the Sharpless asymmetric epoxidation reaction,[5] which has been heavily utilized in the iterative synthesis of polyketide-derived natural products.[6,7] These substrates are typically prepared in the three-step sequence due to the need for redox manipulation: (1) oxidation of a primary alcohol or terminal olefin to the aldehyde; (2) olefination of the resulting aldehyde with a phosphorus-based reagent (e.g., phosphorane, phosphonate); and (3) 1,2-reduction of the enoate to the primary (*E*)-allylic alcohol (Scheme 2a). A shorter alternative route features a CM between a terminal olefin, which can be likened to an aldehyde surrogate vis-à-vis traditional olefination chemistry, and allyl alcohol (Scheme 2b). While this short route is attractive, the stereoselectivity of the transformation is highly dependent on the nature of 'R' such that an increase in steric bulk favors the (*E*) geometric isomer.[8]

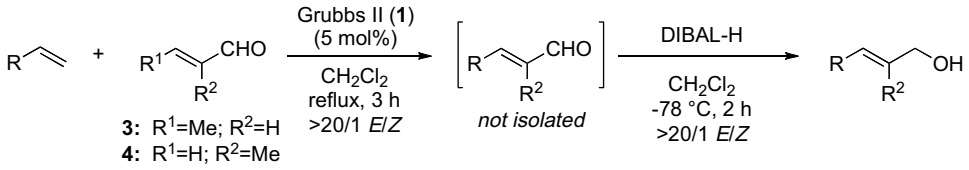
By sequencing (1) the highly (*E*)-selective CM reaction of an electron-rich terminal olefin and an electron-poor olefin (i.e., acrolein, acrylate, etc.)[8] with (2) a hydride reduction step, the stereochemical fidelity of the product is preserved. Table 1 shows a variety of terminal olefins that were subjected to this one-pot method.[9] Styrene (**6**) and a series of TBS-protected α,ω alkenols were treated with 3 equiv of either crotonaldehyde (**3**) or methacrolein (**4**) and 5 mol % Grubbs II (**1**) in refluxing CH_2Cl_2 for 3 h to afford intermediary α,β-enals in high yield and high dr (>20:1 *E*/*Z* by ^{1}H NMR).[10] As these reactions proceed cleanly and in high yield (a priori requirements for efficient one-pot procedures), the reaction mixtures were subsequently cooled to −78 °C and treated with excess DIBAL-H (commercially available solution in hexanes), affording exclusively primary (*E*)-allylic alcohols **10**–**15** in synthetically useful yields (59–74%). The temperature regime was necessary to avoid undesired 1,4 reduction. The substitution of the double bond is controlled by choice of coupling partner (**3** or **4**).

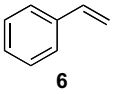
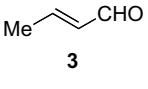
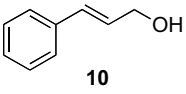
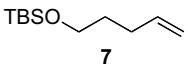
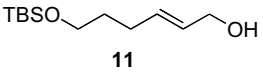
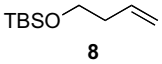
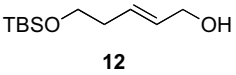
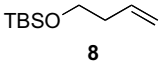
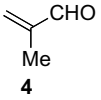
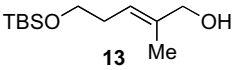
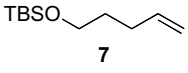
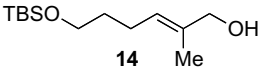
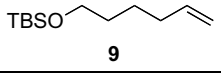
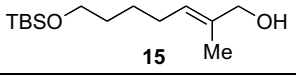
With these results in hand, we turned our attention to more synthetically useful terminal olefins (Table 2).[11] The allylation and crotylation reaction of aldehydes represent formidable alternatives to the acetate and propionate aldol



Scheme 2. Routes to primary (*E*)-allylic alcohols: (a) traditional; (b) CM.

Table 1
One-pot sequential CM/hydride reduction method for the stereoselective synthesis of primary (*E*)-allylic alcohols with the Grubbs II catalyst (**1**)



Entry	Olefin	Coupling partner (3 equiv)	Product	Yield[a] (%) dr > 20:1 (*E*/*Z*)[b]
1	 **6**	 **3**	 **10**	70
2	 **7**	**3**	 **11**	74
3	 **8**	**3**	 **12**	72
4	 **8**	 **4**	 **13**	56
5	 **7**	**4**	 **14**	69
6	 **9**	**4**	 **15**	59

[a] Yields refer to the average of two runs.
[b] Ratio determined by ^{1}H NMR.

reactions, respectively. These methodologies have been leveraged in the stereoselective total synthesis of natural products, particularly those of polyketide origin.[12] As the products of these reactions are terminal olefins, they represent excellent substrates for our methodology. Toward this goal, a variety of protected homoallylic alcohols **16**–**21** were prepared using established procedures and subjected to our method. For these substrates, we found that the combination of 10 mol % Hoveyda–Grubbs II catalyst (**2**) and 3 equiv of methyl acrylate (**5**) gave the best results.[13] In addition, after the addition of DIBAL-H at −78 °C, the reaction mixture was warmed −45 °C and stirred for 2 h. Of note are chemoselective CM entries 3 and 6, which afford alcohols **24** and **27** due to the bulky TBS protecting group that sterically shields the allylic site.[14] Synthetically useful yields (54–74%) were obtained for both allylated (entries 1–4) and crotylated (entries 5–6) substrates.

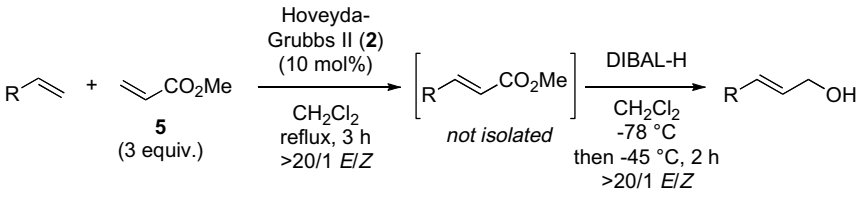
In summary, we have developed a convenient one-pot sequential CM/hydride reduction method for the rapid synthesis of di- and trisubstituted primary (*E*)-allylic alcohols from terminal olefins in good yields as one geometric isomer. The method utilizes only commercially available reagents and should find utility in the elaboration of synthetic intermediates. We will continue to probe the utility and demonstrate the value sequencing CM with other reactions and those results will be presented in due course.

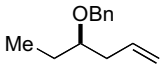
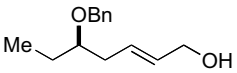
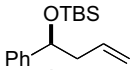
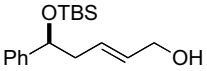
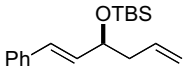
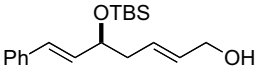
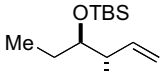
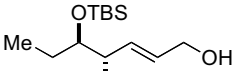
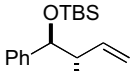
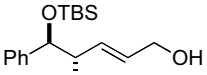
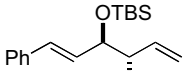
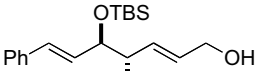
2. Experimental procedures

2.1. Representative procedure for CM/hydride reduction sequence (Tables 1 and 2)

To a solution of olefin (0.48 mmol) and α,β-unsaturated carbonyl partner (1.45 mmol) in deaerated CH_2Cl_2 (3.0 mL) was added catalyst **1** or **2** (5–10 mol %). The reaction mixture was heated to 40 °C under an Ar atmosphere and stirred for 3 h. The reaction mixture was cooled to −78 °C, and DIBAL-H (1 M in hexanes, 1.8 mL, 1.80 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 2 h and quenched by the slow addition of MeOH (1.8 mL) followed by a saturated solution of Rochelle's salt (1.8 mL). The reaction mixture was warmed to room temperature and filtered through a cotton plug. The residue was washed thoroughly with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 20% EtOAc/hexanes.

Table 2
One-pot sequential CM/hydride reduction method for the stereoselective synthesis of primary (*E*)-allylic alcohols with the Hoveyda–Grubbs II catalyst (**2**)



Entry	Olefin	Product	Yield[a] (%) dr > 20:1 (*E*/*Z*)[b]
1	 **16**	 **22**	59
2	 **17**	 **23**	56
3	 **18**	 **24**	54
4	 **19**	 **25**	64
5	 **20**	 **26**	57
6	 **21**	 **27**	74

[a] Yields refer to the average of two runs.
[b] Ratio determined by ^{1}H NMR.

Acknowledgments

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References and notes

1. Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992.
2. (a) Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891; (b) Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 43; (c) Edlin, C.; Faulkner, J.; Quayle, P. *Tetrahedron Lett.* **2006**, *47*, 1145; (d) Mix, S.; Blechert, S. *Adv. Synth. Catal.* **2007**, *349*, 157.
3. (a) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312; (b) Goldberg, S.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807; (c) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900; (d) Virolleaud, M.-A.; Piva, O. *Eur. J. Org. Chem.* **2007**, 1606; (e) Comins, D. L.; Dinsmore, J. M.; Marks, L. R. *Chem. Commun.* **2007**, 4170; (f) Murelli, R. P.; Snapper, M. L. *Org. Lett.* **2007**, *9*, 1749; (g) Paul, T.; Andrade, R. B. *Tetrahedron Lett.* **2007**, *48*, 5367. For a highlight of tandem metathesis/non-metathesis processes, see: (h) Dragutan, V.; Dragutan, I. *J. Organomet. Chem.* **2006**, *691*, 5129.
4. (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. and references cited therein; (b) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
5. For a review of the SAE, see: Johnson, R. A.; Sharpless, K. B. *Catal. Asymmetric Synth.* **2000**, 231 (2nd ed.).
6. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
7. For examples see: Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
8. Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.
9. Spectral data (^{1}H and ^{13}C) were in agreement for the following compounds: Compound **10**: (a) Pospisil, J.; Marko, I. E. . *Org. Lett.* **2006**, *8*, 5983; Compound **11**: (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330; Compound **12**: (c) Francesca, A.; Federico, C.; Paolo, C.; Cristina, G.; Granco, M.; Mauro, P. *Tetrahedron* **1995**, *51*, 10601; Compound **13**: (d) Wang, J.; Hsung, R. P.; Ghosh, S. K. *Org. Lett.* **2004**, *6*, 1939; Compound **14**: (e) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321; Compound **15**: (f) Hayashi, Y.; Kanayama, J.; Yamaguchi, J.; Shoji, M. *J. Org. Chem.* **2002**, *67*, 9443.

10. Enoate intermediates were isolated in separate experiments. Coupling constants obtained from the ^{1}H NMR ($J = 15.6$–16.0 Hz) confirm a *trans* olefin geometry, which is retained in the subsequent reduction (DIBAL-H) step.
11. Spectral data (^{1}H and ^{13}C) were in agreement for the following compounds: Compound **25**: Takano, S.; Sekiguchi, Y.; Shimazaki, Y.; Ogasawara, K. *Heterocycles* **1992**, *33*, 713. Compound **16**: Yadav, J. S.; Rao, E. S.; *Synth. Commun.* **1988**, *18*, 2315. Compound **17**: Hiebel, M.-A.; Pelotier, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874. Compound **19**: Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.
Compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.44 (m, 2H), 7.40–7.37 (m, 2H), 7.32–7.29 (m, 1H), 6.61 (d, $J = 16.0$ Hz, 1H), 6.31 (dd, $J = 16.0$, 6.0 Hz, 1H), 5.99–5.89 (m, 1H), 5.20–5.13 (m, 2H), 4.44–4.39 (m, 1H), 2.51–2.37 (m, 2H), 1.03 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 134.8, 132.8, 129.2, 128.5, 127.3, 126.4, 117.0, 73.3, 43.2, 25.9, 18.3, −4.3, −4.7; IR (neat): 2955, 2930, 2895, 2856, 1472, 1361, 1254, 1071, 966, 910 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{28}OSi$–H^+ 287.1831, found 287.1826.
Compound **20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.21 (m, 5H), 5.88–5.79 (m, 1H), 4.98–4.89 (m, 2H), 4.45 (d, $J = 6.0$ Hz, 2H), 2.43–2.41 (m, 1H), 0.89 (s, 3H), 0.87 (s, 9H), −0.02 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 141.1, 127.6, 126.9, 126.9, 114.4, 79.1, 46.4, 25.8, 18.2, 16.1, −4.6, −5.1; IR (neat): 2957, 2930, 2886, 2858, 1454, 1362, 1254, 1086, 1065, 910 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{28}OSi$–H^+ 275.1831, found 275.1830.
Compound **21**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.51 (m, 2H), 7.47–7.43 (m, 2H), 7.38–7.34 (m, 1H), 6.66 (d, $J = 16.0$ Hz, 1H), 6.33 (dd, $J = 16.0$, 6.5, 16 Hz, 1H), 6.07–5.99 (m, 1H), 5.23–5.18 (m, 2H), 4.19 (t, $J = 5.2$, 1.2 Hz, 1H), 2.53 (m, 1H), 1.20 (d, $J = 6.8$ Hz, 1H), 1.11 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 137.2, 131.4, 130.2, 128.5, 127.3, 126.4, 114.6, 45.1, 25.9, 18.3, 15.4, −4.1, −4.8; IR (neat): 2957, 2929, 2886, 2857, 1252, 1065, 967 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{30}OSi$–H^+ 301.1989, found 301.1996.
Compound **22**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 5.76–5.65 (m, 2H), 4.54, 4.52 (ABq, $J = 12.0$ Hz, 2H), 4.08 (br s, 2H), 3.41–3.35 (m, 1H), 2.33–2.30 (m, 2H) 1.59–1.55 (m, 3H), 0.93 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 131.4, 129.0, 128.3 (2C), 127.7 (2C), 127.5, 79.8, 70.9, 63.6, 36.1, 26.4, 9.6; IR (neat): 3384, 2964, 2932, 2872, 1454, 1349, 1090, 1064, 1027, 1005, 972, 910 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{20}O_2$+Na 243.1361, found 243.1351.
Compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.20 (m, 5H), 5.70–5.58 (m, 2H), 4.68 (dd, $J = 7.0$, 5.0 Hz, 1H), 4.05–4.04 (m, 2H), 2.50–2.35 (m, 2H), 1.39 (br s, 1H), 0.88 (s, 9H), 0.02 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 131.5, 129.4, 128.0 (2C), 127.0, 125.8 (2C), 74.9, 63.7, 43.8, 25.8, 18.2, −4.7, −4.9; IR (neat): 3363, 2953, 2930, 2885, 2857, 1471, 1362, 1255, 1091, 1005, 909, 836 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{28}O_2Si$+Na 315.1756, found 315.1750.
Compound **24**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.30 (m, 4H), 7.26–7.23 (m, 1H), 6.52 (d, $J = 16.0$ Hz, 1H), 6.20 (dd, $J = 16.0$, 6.4 Hz, 1H), 5.74–5.71 (m, 2H), 4.36 (q, $J = 6.0$ Hz, 1H), 4.16–4.12 (m, 2H), 2.38–2.35 (m, 2H), 1.50 (br s, 1H), 0.95 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 132.7, 131.7, 129.3, 128.8, 128.5 (2C), 127.4, 126.4 (2C), 73.3, 63.6, 41.5, 25.9, 18.3, −4.3, −4.7; IR (neat): 3356 cm^{-1}; IR (neat): 3356, 2953, 2929, 2893, 2856, 1471, 1253, 1071, 968 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{30}O_2Si$+Na 341.1913, found 341.1904.
Compound **26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.21 (m, 5H), 5.72–5.50 (m, 2H), 4.43 (d, $J = 6.0$ Hz, 1H), 4.06 (br s, 2H), 2.45–2.40 (m, 1H), 1.16 (br s, 1H), 0.89 (d, $J = 3.6$ Hz, 3H), 0.87 (s, 9H), 0.01 (s, 3H), −0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 135.3, 129.2, 127.6, 127.0, 126.9, 126.8, 79.1, 63.9, 45.1, 25.8, 18.2, 16.5, −4.6, −5.1; IR (neat): 3333, 2955, 2929, 2885, 2856, 1471, 1455, 1253, 1088, 1064 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{30}O_2Si$+Na 329.1913, found 329.1923.
Compound **27**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.34 (m, 4H), 7.30–7.26 (m, 1H), 6.53 (d, $J = 16.0$ Hz, 1H), 6.19 (dd, $J = 16.0$, 6.8 Hz, 1H), 5.80–5.68 (m, 2H), 4.19–4.16 (m, 3H), 2.44–2.38 (m, 1H), 1.43 (br s, 1H), 1.07 (d, $J = 6.8$ Hz, 3H), 0.96 (s, 9H), 0.12 (s, 3H), 0.08(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 135.0, 131.4, 130.3, 129.3, 128.5 (2C), 127.4, 126.4 (2C), 77.3, 63.8, 43.6, 25.9, 18.2, 15.8, −4.2, −4.8; IR (neat): 3357, 2956, 2929, 2884, 2856, 1471, 1461, 1362, 1253, 1070, 969, 909 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{32}O_2Si$+Na 355.2069, found 355.2079.
12. For a review see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **1982**, *21*, 555; (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.
13. Cossy, J.; BouzBouz, S.; Hoveyda, A. *J. Organomet. Chem.* **2001**, *624*, 327.
14. BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465.