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Highly($\geq 98\%$) Stereo- and Regioselective Trisubstituted Alkene Synthesis of Wide Applicability via 1-Halo-1-alkyne Hydroboration–Tandem Negishi-Suzuki Coupling or Organoborate Migratory Insertion Protocol

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Abstract

(*Z*)-1-Halo-1-alkenylboranes (**7**), preparable in 82–90% yields as 98% isomerically pure compounds via hydroboration of 1-halo-1-alkynes, have been converted to a wide range of trisubstituted alkenes via three different routes in the tail-to-head (**T-to-H**) direction, i.e., (i) Palladium-catalyzed Negishi-Suzuki tandem alkenylation, (ii) treatment of **7** with organolithium or Grignard reagents to generate α -bromo-1-alkenylboronate complexes (**10**) that can undergo migratory insertion of a carbon group (R^2) to form (*E*)-alkenylboranes (**11**) with inversion of alkene configuration (98% inversion), followed by fluoride-promoted Suzuki alkenylation, and (iii) Negishi coupling to generate (*Z*)-alkenylboranes (**8**) in 98% retention of configuration, followed by treatment with organolithium or Grignard reagents to produce trisubstituted alkenes with reversed stereo configurations. The synthetic utility of the present methodology has been demonstrated in the highly selective synthesis of side chain (**4**) of scyphostatin in 28% yield over nine steps in the longest linear sequence from allyl alcohol. Thus, this new tandem protocol has been emerged as the most widely applicable and highly selective route to trisubstituted alkenes including those that are otherwise difficult to prepare.

Keywords

alkene synthesis; hydroboration; Palladium-catalyzed cross-coupling; (*Z*)-1-halo-1-alkenylborane; alkenylation

Introduction

Sequential alkyne elementometalation^[1], such as hydrometalation and carbometalation, and Pd-catalyzed alkenylation constitute a powerful route that provides various types of acyclic alkenes in a high level (98%) of stereoselectivity which is often difficult to achieve with carbonyl olefination reactions (e.g., Wittig,^[2a] Horner-Wadsworth-Emmons (HWE),^[2b,2c] Still-Gennari,^[2d] Peterson,^[2e] Julia^[2f] olefination, etc.), because these conventional methods must involve carbonyl addition and β -elimination that often lack high stereoselectivity (Scheme 1).

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Recently, we reported highly selective and widely applicable procedures for synthesizing trisubstituted alkenes via alkyne haloboration–fluoride-promoted Pd-catalyzed tandem alkenylation.^[3] Crucial to the development were the following three breakthroughs: (i) improvement of the stereoselectivity of haloboration of the single-most important case of propyne to 98% *syn*-selectivity, (ii) minimization of undesirable debromoboration in the Pd-catalyzed Negishi coupling of α -bromoalkenylboranes by using highly active catalysts, such as Pd(*t*Bu₃P)₂ or PEPPSITM-IPr, where PEPPSI stands for Pyridine Enhanced Precatalyst Preparation Stabilization and Initiation,^[4] and (iii) improvement of the yields in the generally sluggish Suzuki alkenylation by using fluoride bases.

Notably, the approach described in Scheme 2 represents a head-to-tail (**H**-to-**T**) construction route to stereodefined trisubstituted alkenes. Additionally, a complementary tail-to-head (**T**-to-**H**) route^[5] is also desirable. As an example, the following pair of syntheses of the C7-C16 fragment **4** of the side-chain of scyphostatin^[6] may demonstrate the importance of the direction of building trisubstituted alkenes (Scheme 3). In the **H**-to-**T** construction,^[7a] **1** (Z = TBDPS) was sequentially tosylated, ethynylated, methylaluminated, and subjected to an “S_N2” reaction with (*S*)-EtO₂CCH(Me)OTf to provide **3** in 34% yield in 3 steps, which was then converted to **4** in 54% yield in three steps or in 18% yield in six linear steps from **1**. In the **T**-to-**H** construction,^[7b, 7c] **1** (Z = TBS) was iodinated and cross-coupled with **6a** to give **4** just in two steps in 82% yield after desilylation, while the key intermediate **6a** was prepared from allyl alcohol in 30% yield over 7 steps.

Herein, we report the development of a few additional **T**-to-**H** procedures, via (*Z*)-1-halo-1-alkenylboranes **7** as key intermediates, prepared via hydroboration of 1-halo-1-alkynes, providing widely applicable and highly selective routes to trisubstituted alkenes.

Results and Discussion

Whereas hydroboration of internal alkynes often suffers from low regioselectivity levels, that of 1-halo-1-alkynes is nearly 100% regioselective to give 98% isomerically pure (*Z*)-1-halo-1-alkenylboranes (**7**).^[9] If both halogen (X) and boryl groups (BY₂) can selectively and sequentially be substituted with a wide range of carbon groups by Pd-catalyzed alkenylation, (*Z*)-1-halo-1-alkenylboranes (**7**) would serve as useful intermediates for preparing various types of trisubstituted alkenes as shown in Scheme 4.^[10]

1-Halo-1-alkynes, prepared by iodination of the corresponding lithium acetylides or by bromination of the corresponding terminal alkynes catalyzed by silver nitrate,^[11] can be converted regioselectively and stereoselectively (> 98%) to (*Z*)-1-halo-1-alkenyl(pinacol)boranes (**7**) by hydroboration with HBBR₂ followed by quenching with pinacol.^[9] During the course of this investigation, we also noticed that the hydroboration of 1-iodo-1-alkynes with diisopinocampheylborane,^[12] followed by treatment with acetaldehyde and subsequent esterification with pinacol, provided the desired 1-iodo-1-alkenylboranes in similarly high regioselectivity and stereoselectivity (> 98%), but in higher yields (83–90%).

For substitution of iodine or bromide with a carbon group, Pd-catalyzed cross-coupling of **7** with organozincs is by far the most satisfactory method that has uniformly provided satisfactory results based on our recent studies,^[3, 13] although organoindium and organozirconium reagents were also satisfactory in some cases, as reported in our brief survey.^[13c] As shown in Table 1, Pd(PPh₃)₄ is an effective catalyst in some cases (entries 3, 4, and 12). However, when alkyl- or alkenylzincs were used as coupling partners, Pd(PPh₃)₄ led to the formation of **8** in low yields and regenerated the original terminal alkynes as major side products as a result of unwanted deiodoboration. Pd(*t*Bu₃P)₂ facilitated the cross-

coupling reaction of (*Z*)-1-halo-1-alkenylboranes (**7**) with a variety of organozincs, including alkyl, benzyl, alkenyl, and aryl groups, leading to the formation of (*Z*)-alkenylboranes (**8**) in good yields and, most importantly, with full (98%) retention of configuration. The subsequent Pd-catalyzed cross-coupling of α,β -disubstituted alkenylboranes **8** with aryl or alkenyl iodides, proceeded smoothly by using $\text{PdCl}_2(\text{DPEphos})$ as a catalyst and TBAF as a promoter.^[3] Trisubstituted alkenes **9** were thus obtained in high yields and high isomeric purities. The geometrical configurations and isomeric purities of all products, i.e., **7**, **8**, and **9**, were confirmed by ^1H and ^{13}C NMR spectroscopy including NOE measurements. It should be clearly noted that, even in cases where R^1 and R^2 groups were similar (entries 1, 2, 5, 9, and 12 in Table 1), the desired trisubstituted alkenes can be obtained in 98% stereoselectivity.

As previously reported,^[14] treatment of (*Z*)-1-halo-1-alkenylboranes (**7**) with organolithium or Grignard reagents would form α -bromo-1-alkenylboronate complexes (**10**) which would then undergo migratory insertion of R^2 to give (*E*)-alkenylboranes (**11**) via 98% stereo-inversion. As shown in Table 2, use of the $\text{O}(\text{CH}_2)_3\text{O}$ group (entries 1–3) led to satisfactory yields of substitution product **11** (72–87%), whereas use of $\text{O}[\text{C}(\text{CH}_3)_2]_2\text{O}$ group (entries 4–6) led to disappointingly low yields (40–64%) due to a competitive pathway for formation of a mixture of **11** and the dissociation product **13**. The subsequent fluoride-promoted Suzuki alkenylation of **11** led to 98% stereoisomerically pure trisubstituted alkenes **12** in good yields.

Alternatively, treatment of **8** with an organometal (R^3M) containing Li or Mg to generate the corresponding borate complex, followed by addition of I_2 to induce migratory insertion of R^3 , and then treatment with aqueous NaOH to induce deiodoboration produces **14** of 98% isomeric purity in good yields (72–84%) as shown in Table 3.^[15] It should be noted that the protocol in Table 3 offers some advantageous features that are not readily available in those shown in Tables 1 and 2, involving Suzuki coupling of alkenylboranes for introduction of the R^3 group. In these protocols, it would not be readily feasible to prepare trisubstituted alkenes containing an alkyl group as R^3 . As exemplified by entry 3 in Table 3, no difficulty was encountered in the introduction of Me as R^3 . To further demonstrate this potentially significant advantage, an all-alkyl substituted trisubstituted alkene **4**, used as the C7-C16 side chain fragment of (+)-scyphostatin, was performed and achieved as shown in Scheme 5. Although the overall yield of **4** in 28% over 9 steps in this longest linear sequence is roughly comparable to that reported recently by us (25% yield in 9 steps),^[7c] the previous route involved generation of a 85/15 regioisomeric mixtures of **6a** and **6b**, which were purified by chromatographies separation. Even though further comparison are needed, the highly (98%) selective synthesis without the need for isomeric separation (Scheme 5) promises to reveal advantages in cases where the formation of isomeric mixtures should prove to be more cumbersome.

Conclusions

A highly stereo- and regioselective and widely applicable route to trisubstituted alkenes in the **T**-to-**H** direction has been developed. Its synthetic utility has been demonstrated in a highly selective synthesis of scyphostatin side chain (**4**) by using one of these protocols shown in Scheme 5. In two other protocols, hydroboration of 1-halo-1-alkynes followed by either Pd-catalyzed Negishi-Suzuki tandem alkenylation or nucleophilic substitutions of alkenylboranes with organometallic reagents containing Li or Mg to induce migratory induction of R^2 with configurational inversion. A wide range of trisubstituted alkenes were obtained in 98% isomeric purity and in synthetically useful yields (45–73%) in three steps starting from 1-halo-1-alkynes. This practical and satisfactory approach also nicely complements their **H**-to-**T** construction reported by us recently.^[3]

Experimental Section

General

All reactions were run under a dry Ar atmosphere. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) or by GC analysis of reaction aliquots. GC analysis was performed on an HP 6890 Gas Chromatograph using an HP-5 capillary column (30 m $\times$ 0.32 mm, 0.5 μ M film) packed with SE-30 on Chromosorb W. Column chromatography was carried out on 230–400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on Varian-Inova-300. ZnBr_2 was flame-dried *in vacuo*. THF was dried by distillation under Ar from sodium/benzophenone. CH_2Cl_2 was dried by distillation under Ar from CaH_2 . Other commercially available solvents and reagents were of reagent grade and used without further purification, unless otherwise indicated.

Representative procedure I for the hydroboration of 1-bromo-1-alkynes with $\text{HBBr}_2\cdot\text{SMe}_2$

(Z)-2-(1-bromooct-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7-entry 4 in Table 1)—To a solution of 1-bromo-1-octyne (1.9 g, 10 mmol) in CH_2Cl_2 (10 mL) was added $\text{HBBr}_2\cdot\text{SMe}_2$ (1 M in CH_2Cl_2 , 11 mL, 11 mmol) at 0 $^\circ\text{C}$. The solution was allowed to stir at 23 $^\circ\text{C}$ for overnight and then quenched with ice water. The aqueous layer was extracted with ether (3 $\times$ 15 mL). The combined organic layers were dried over anhydrous MgSO_4 and concentrated to give crude alkenylboronic acid. The resulting boronic acid was then dissolved in CH_2Cl_2 and pinacol (1.3 g, 11 mmol) was added, stirring for 1 h, dried over MgSO_4 , filtered and concentrated. The crude product was purified via flash chromatography (R_f = 0.28; 20% ethyl acetate/hexane) to give a clear oil (2.76 g, 87%). ^1H NMR (300 MHz, CDCl_3) δ 6.79 (t, J = 6.9 Hz, 1 H), 2.24 (m, 2 H), 1.2–1.4 (m, 20 H), 0.83 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 149.3, 84.4, 32.3, 31.5, 28.9, 27.6, 24.6, 22.4, 13.9.

Representative procedure II for the hydroboration of 1-iodo-1-alkynes with $(\text{Ipc})_2\text{BH}$

(Z)-2-(5-chloro-1-iodopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (7-entry 5 in Table 1)— $(\text{Ipc})_2\text{BH}$ was prepared by treating borane-methyl sulfide complex (0.8 mL, 8.4 mmol) in THF (5 mL) at 0 $^\circ\text{C}$, and followed by adding α -pinene (3.0 mL, 18.6 mmol). The reaction mixture was stirred at 0 $^\circ\text{C}$ for 1 h, and 23 $^\circ\text{C}$ for 2 h. The reaction mixture was then cooled to -35 $^\circ\text{C}$, 5-chloro-1-iodopent-1-yne (1.8 g, 7.9 mmol) was added slowly. The resulting solution was allowed to stir for 1.5 h at -35 $^\circ\text{C}$ and 5 h at 23 $^\circ\text{C}$, and then cooled down to 0 $^\circ\text{C}$ before acetaldehyde (6.4 mL) was added. The solution was refluxed for 12 h and then concentrated *in vacuo* (10 mmHg for 1 h) to remove excess acetaldehyde and volatiles. Then, a solution of pinacol (1.0 g, 8.7 mmol) in THF (2 mL) was added. After 3 h stirring at 23 $^\circ\text{C}$, the pure 1-iodo-1-alkenylboronic ester was obtained via flash chromatography (R_f = 0.32; 20% ethyl acetate/hexane) to give a clear oil (2.45 g, 87%). ^1H NMR (300 MHz, CDCl_3) δ 6.77 (t, J = 6.6 Hz, 1 H), 3.55 (t, J = 6.3 Hz, 2 H), 2.40 (dd, J = 7.8, 6.6 Hz, 2 H), 1.94 (dt, J = 7.5, 6.9 Hz, 2 H), 1.28 (s, 12 H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.14, 84.8, 44.3, 35.7, 30.5, 24.7; HRMS calcd for $\text{C}_{11}\text{H}_{19}\text{O}_2\text{BICl} [\text{M}]^+$: 356.0211; Found: 356.0212.

Representative procedure III for the Negishi cross-coupling

(Z)-2-(dodec-5-en-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8-entry 2 in Table 1)—A flame-dried, 25-mL, round-bottomed flask, equipped a magnetic stirring bar, a rubber septum, and an argon inlet, was charged with $\text{Pd}(\text{tBu}_3\text{P})_2$ (15.6 mg, 0.03 mmol), 1-bromo-1-hexenyl(pinacol)borane (864 mg, 3.0 mmol), and THF (6 mL). A solution of *n*-hexylzinc bromide (3.6 mmol), [prepared by treating ZnBr_2 (810 mg, 3.6 mmol)] in THF (6

mL) at $-78\text{ }^{\circ}\text{C}$, followed by adding hexyllithium (1.6 mL, 3.6 mmol) for 30 min at $0\text{ }^{\circ}\text{C}$] was added. The mixture was allowed to stir at $23\text{ }^{\circ}\text{C}$ and monitored by TLC. The reaction mixture was then quenched with aq. NH_4Cl . The aqueous layer was separated and extracted with ether ($3\times 10\text{ mL}$). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporator ($30\text{ }^{\circ}\text{C}$, 20 mmHg). The crude product was purified via flash chromatography ($R_f = 0.35$; 5% ethyl acetate/hexane) to give a clear oil (776 mg, 88%). ^1H NMR (300 MHz, CDCl_3) δ 6.27 (t, $J = 6.9\text{ Hz}$, 1 H), 2.15–2.08 (m, 4 H), 1.25–1.38 (m, 24 H), 0.85–0.91 (m, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.8, 132.1, 82.8, 31.8, 31.4, 30.1, 29.2, 28.4, 28.1, 24.6, 22.6, 22.5, 14.0, 13.9; HRMS calcd for $\text{C}_{18}\text{H}_{35}\text{O}_2\text{B}$ $[\text{M}]^+$: 294.2730; Found: 294.2730.

Representative procedure IV for the Suzuki cross-coupling

(E)-dodec-5-en-6-ylbenzene (9-entry 2 in Table 1).—A flame-dried, 25-mL, round-bottomed flask, equipped a magnetic stirring bar, a rubber septum, and an argon inlet, was charged with $\text{PdCl}_2(\text{DPEphos})$ (3.5 mg, 0.0051 mmol), (*Z*)-2-(dodec-5-en-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (150 mg, 0.51 mmol), iodobenzene (124 mg, 0.61 mmol), and THF (2 mL) under an atmosphere of argon. TBAF (0.76 mL, 0.76 mmol) was added. The mixture was heated to $65\text{ }^{\circ}\text{C}$ and monitored by TLC. The reaction mixture was then quenched with aq. NH_4Cl . The aqueous layer was separated and extracted with ether ($3\times 10\text{ mL}$). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporator ($30\text{ }^{\circ}\text{C}$, 20 mmHg) to give the crude product. The crude product was purified via flash chromatography ($R_f = 0.38$; 1% ethyl acetate/hexane) to give a clear oil (114 mg, 92%). ^1H NMR (300 MHz, CDCl_3) δ 7.20–7.35 (m, 5 H), 5.63 (t, $J = 7.5\text{ Hz}$, 1 H), 2.47 (t, $J = 7.5\text{ Hz}$, 2 H), 2.18 (dd, $J = 7.5, 6.9\text{ Hz}$, 2 H), 1.20–1.44 (m, 12 H), 0.92 (t, $J = 7.2\text{ Hz}$, 3 H), 0.85 (t, $J = 6.9\text{ Hz}$, 3 H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.5, 140.1, 129.1, 128.1, 126.3, 32.2, 31.7, 29.7, 29.3, 28.7, 28.3, 24.8, 22.7, 22.5, 14.1; HRMS calcd for $\text{C}_{18}\text{H}_{28}$ $[\text{M}]^+$: 244.2191; Found: 244.2190.

Representative procedure V for the preparation of 11

(*R,E*)-2-(3-methyl-1-phenylnon-1-enyl)-1,3,2-dioxaborinane (11-entry 1 in Table 2)—A flame-dried, 25-mL, round-bottomed flask, equipped a magnetic stirring bar, a rubber septum, was charged with **7** (100 mg, 0.29 mmol), and ether (2 mL) in a dry ice-acetone bath under an atmosphere of argon. Phenyllithium (0.17 mL, 0.3 mmol) was added against the inside wall of the flask. The solution was allowed to stir for 30 min at $-78\text{ }^{\circ}\text{C}$, another 30 min at $23\text{ }^{\circ}\text{C}$, and then cooled down to $-78\text{ }^{\circ}\text{C}$ before the addition of MeOH (0.6 mL) and KOH (0.3 mL, 3M, 0.9 mmol). The reaction mixture was then warmed up to $23\text{ }^{\circ}\text{C}$, stirred for overnight, and quenched with aq. NH_4Cl . The aqueous layer was separated and extracted with ether ($3\times 10\text{ mL}$). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporator ($30\text{ }^{\circ}\text{C}$, 20 mmHg) to give the boronic acid. The resulting boronic acid was reesterified with 1,3-propanediol (23 mg, 0.3 mmol) in pentane (2 mL). The reaction mixture was then stirred for 2 h at $23\text{ }^{\circ}\text{C}$, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporator ($40\text{ }^{\circ}\text{C}$, 20 mmHg) to give the crude product. The crude product (NMR yield 87%) was used without further purification for subsequent Suzuki coupling.

Representative procedure VI for the preparation of 14

(Z)-dodec-5-en-6-ylbenzene (14-entry 2 in Table 3)—A flame-dried, 25-mL, round-bottomed flask, equipped a magnetic stirring bar, a rubber septum, and an argon inlet, was charged with (*Z*)-2-(dodec-5-en-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (147 mg, 0.5 mmol), and ether (2 mL) in a dry ice-acetone bath under an atmosphere of argon. Phenyllithium (0.32 mL, 0.55 mmol) was added against the inside wall of the flask. The

solution was allowed to stir for 30 min at -78°C , and 1 h at 0°C . The solvents were pumped off and MeOH (1.0 mL) was added at 0°C . Then the solution was cooled down to -78°C before the addition of I_2 (127 mg, 0.5 mmol) in MeOH (1 mL). After 3 h stirring at -78°C , it was allowed to warm up to 23°C and NaOH (0.5 mL, 3M, 1.5 mmol) was added. Stirred for 15 min, the reaction was diluted with water and extracted with *n*-hexane. The aqueous layer was separated and extracted with *n*-hexane (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporator (30°C , 20 mmHg) to give the crude product. The product was purified by flash chromatography ($R_f = 0.36$; 1% ethyl acetate/hexane) to give a clear oil (102 mg, 84%). ^1H NMR (300 MHz, CDCl_3) δ 7.1–7.35 (m, 5 H), 5.41 (t, $J = 7.5$ Hz, 1 H), 2.21–2.47 (m, 2 H), 1.91 (dt, $J = 7.5, 6.6$ Hz, 2 H), 1.21–1.37 (m, 12 H), 0.73–0.87 (m, 6 H); ^{13}C NMR (75 MHz, CDCl_3) δ 140.2, 140.1, 128.5, 127.9, 127.2, 126.2, 39.3, 32.4, 31.7, 28.9, 28.6, 28.1, 22.7, 22.3, 14.2, 14.1; HRMS calcd for $\text{C}_{18}\text{H}_{28} [\text{M}]^+$: 244.2191; Found: 244.2190.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
 Carbonyl olefination and alkyne elementometalation-Pd-catalyzed alkenylation

$R^1 = \text{Me, Ph}$; $R^2 = R^3 = \text{carbon groups}$; Bpin = pinacolboryl.

Scheme 2.

H-to-T construction route to stereodefined trisubstituted alkenes.

H-to-T construction^[7a] **T-to-H construction**^[7b, 7c] **Scheme 3.**

Syntheses of the C7-C16 fragment **4** of the side-chain of scyphostatin.

Scheme 4.**T-to-H** construction route to stereodefined trisubstituted alkenes.

Scheme 5.

An enantioselective **T**-to-**H** route to the C7-C16 fragment **4** of the side-chain of (+)-scyphostatin

Table 1

			7			8			9		
Entry	X	R ¹	Yield (%) ^f	R ² ZnBr	Yield (%) ^f	R ³ X	Yield (%) ^f	R ⁴ X	Yield (%) ^f	g	
1 ^a	Br		87	<i>n</i> BnZnBr	86	PhI	86	PhI	82 (61)		
2 ^b	I	<i>n</i> Bu	90	<i>n</i> HexZnBr	88	PhI	88	PhI	92 (73)		
3 ^c	Br		82 ^e	PhZnBr	81 ^{d,e}		81 ^{d,e}		75 (50)		
4 ^a	Br	<i>n</i> Hex	87	PhZnBr	87 ^d		87 ^d		91 (69)		
5 ^b	I	Cl(CH ₂) ₃	87	<i>n</i> BnZnBr	69		69		75 (45)		
6 ^b	I	Ph	85	<i>n</i> HexZnBr	85		85		80 (58)		
7 ^b	I	Ph	85	<i>n</i> HexZnBr	85	<i>p</i> MeC ₆ H ₄ I	85	<i>p</i> MeC ₆ H ₄ I	82 (59)		
8 ^b	I	Ph	85	<i>n</i> HexZnBr	85	<i>p</i> ClC ₆ H ₄ I	85	<i>p</i> ClC ₆ H ₄ I	86 (62)		
9 ^b	I	Ph	85	<i>p</i> MeOC ₆ H ₄ ZnBr	88	<i>p</i> ClC ₆ H ₄ I	88	<i>p</i> ClC ₆ H ₄ I	85 (63)		
10 ^b	I	PhCH ₂	83	<i>n</i> BuZnBr	72	PhI	72	PhI	82 (49)		
11 ^b	I	PhCH ₂	83	<i>n</i> Hex	71	PhI	71	PhI	81 (48)		
12 ^b	I	PhCH ₂	83	PhZnBr	83 ^d		83 ^d		86 (59)		

^a (i) HBrBr₂ (1.1 eq), CH₂Cl₂ (ii) pinacol (1.1 eq).

^b (i) (Ipc)₂BH (1.2 eq), THF (ii) acetaldehyde (10 eq) (iii) pinacol (1.1 eq).

^c (i) HBBT₂ (1.1 eq), CH₂Cl₂ (ii) 1,3-propanediol (1.1 eq).

^d 5% Pd(PPh₃)₄ was used.

^e NMR yield. The product decomposed during chromatography.

^f Isolated yields.

^g Yield in parentheses is overall yield from R¹CX in three steps.

Table 2

Entry	(OR) ₂	R ¹	R ² M	Yield (%) ^b	R ³ X	Yield (%) ^{c,d}
1	O(CH ₂) ₃ O	<i>n</i> Hex	PhLi	87	HO-CH=CH-I	(54)
2	O(CH ₂) ₃ O	<i>n</i> Hex ^a	PhLi	82	<i>n</i> Bu-CH=CH-I	(63)
3	O(CH ₂) ₃ O	<i>n</i> Hex ^a	MeOC ₆ H ₄ MgBr	72	<i>n</i> Bu-CH=CH-I	(55)
4	O[C(CH ₃) ₂] ₂ O	<i>n</i> Hex	PhLi	64	<i>n</i> Bu-CH=CH-I	90 (50)
5	O[C(CH ₃) ₂] ₂ O	<i>n</i> Hex	MeOC ₆ H ₄ MgBr	40	<i>n</i> Bu-CH=CH-I	90 (31)
6	O[C(CH ₃) ₂] ₂ O	<i>n</i> Hex	MeOC ₆ H ₄ MgBr	40	PhI	87 (30)

^aNMR yield is 90% from 1-bromooct-1-yne.

^bNMR yield.

^cIsolated yields

^dYield in parentheses is overall yield from R¹C-CX in three steps.

Table 3

Entry	R ¹	R ²	R ³ M	Yield(%) ^{a, b}
1		<i>n</i> Bu	PhLi	80 (60)
2	<i>n</i> Bu	<i>n</i> Hex	PhLi	84 (66)
3	<i>n</i> Bu	<i>n</i> Hex	MeLi	72 (57)
4	Ph	<i>n</i> Hex	<i>p</i> ClC ₆ H ₄ MgBr	76 (55)

^a Isolated yields from **8**.

^b Yield in parentheses is overall yield from R¹C–CX in three steps.