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Tetrahedron 62 (2006) 7598–7610
Tetrahedron

Directing effects of tethered alkenes in nickel-catalyzed coupling reactions of 1,6-enynes and aldehydes

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Received 7 December 2005; revised 1 March 2006; accepted 1 March 2006
Available online 15 June 2006

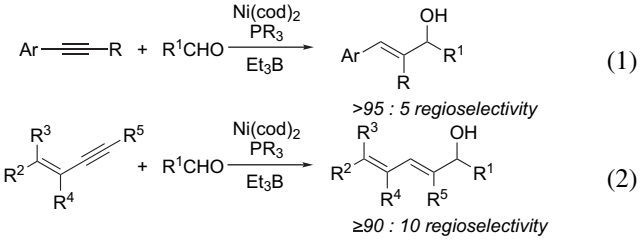
Dedicated to Professor Günther Wilke in honor of his groundbreaking contributions to organonickel chemistry

Abstract—Nickel-catalyzed reductive coupling reactions of aldehydes and 1,6-enynes proceed in excellent regioselectivity in the absence of a phosphine, and the use of a monodentate phosphine additive leads to the formation of the opposite regioisomer with equally high selectivity. Both products are the result of the same fundamental mechanism, with the inversion of regioselectivity being the result of stereospecific ligand substitution at the metal center.

1. Introduction

Substrate-directable reactions are an important class of selective organic transformations, and understanding their mechanism of direction is paramount to their utility.[1] Recently, we reported a substrate-directed, nickel-catalyzed reductive coupling of 1,6-enynes and aldehydes in which the regioselectivity of the reaction was controlled by a tethered olefin.[2] Herein we report a full account of this class of coupling reactions, as well as a description of the likely mechanism by which regioselectivity is controlled.

The nickel-catalyzed coupling of alkynes and aldehydes has emerged as a powerful method for the efficient and selective preparation of allylic alcohols.[3,4] In most cases, the regioselectivity of these coupling reactions is determined by a steric or electronic difference in the alkyne substituents. For example, previous investigations in our laboratory have shown that alkynes conjugated to either an aryl or alkenyl substituent undergo nickel-catalyzed reductive coupling with aldehydes in high regioselectivity (Scheme 1, Eqs. 1 and 2).[4b,d,f]



Scheme 1.

The high degree of regioselectivity observed with certain classes of 1,3-enynes led us to hypothesize that an interaction between the alkene and the metal center has an influence on selectivity (Fig. 1).[4f] Assuming that the reaction proceeds through an oxametallacyclopentene intermediate, interaction of the conjugated alkene with the metal center could result in a stabilizing interaction, thus favoring formation of the regioisomer shown.[5] These results led us to conduct a thorough investigation of the directing effects of tethered alkenes in reductive coupling reactions of alkynes and aldehydes.[6]

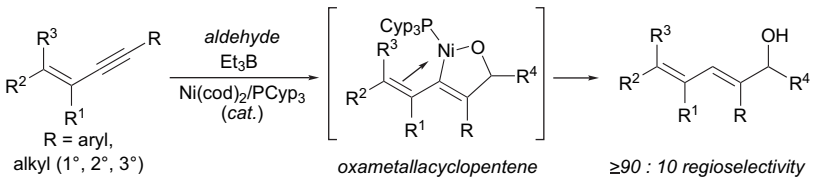


Figure 1.

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doi:10.1016/j.tet.2006.03.122

2. Results and discussion

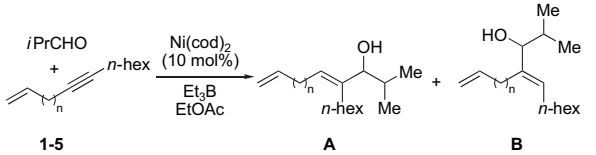
2.1. Discovery of ligand-switchable nickel-catalyzed couplings of aldehydes and 1,6-enynes

A study of nickel-catalyzed reductive coupling reactions of isobutraldehyde with enynes of different tether lengths revealed a marked difference in reactivity and selectivity when the alkyne and alkene were separated by three methylene units (Table 1, entry 4). As it is very unlikely that **4** is significantly different sterically or electronically than alkynes **2**, **3**, or **5**, it seems that involvement of the olefin in the reaction occurs uniquely in the case of the 1,6-enyne. Also interesting is that conjugated enynes do not couple effectively in the absence of a phosphine additive (entry 1), suggesting that the origin of the high regioselectivity observed with 1,3-enynes is different than that observed with 1,6-enynes.

Reductive coupling reactions of 1,6-enynes and aldehydes in the absence of phosphine additive proved remarkably general, considering that previous systems had all required the addition of a phosphine (Table 2).[2,4,7] Also noteworthy is that the presence of an olefin tether is sufficient to overcome an inherent steric preference for the **B** regioisomer (entry 4).[4c] Heteroatoms, which could conceivably compete with the olefin for binding, are well tolerated and augment the versatility of the directed transformation (entries 6–8).

The effect of different phosphine additives on the regioselectivity of reductive coupling reactions of enyne **4** and isobutyraldehyde was also investigated and provided valuable insight into the mechanism of these transformations (Table 3).[8] Electron-rich phosphines afforded superior yields and, remarkably, with very large phosphines (cone angle >160°), the sense of regioselectivity was completely reversed, giving >95:5 of regioisomer **B** (Table 3, entries 1–3).[9] The use of smaller phosphines, even those marginally so ferrocenyldiphenylphosphine ($PFcPh_2$) (cone angle ~155°),[10] resulted in a significant loss of regioselectivity (entries 4–6, Table 3). Since no regioselectivity was observed when 1,2-dihydro-**4** was coupled to isobutyraldehyde in the presence of tricyclopentylphosphine ($PCyp_3$) (77%, 50:50 regioselectivity) it is likely that the tethered olefin is responsible for the regioselectivity both in the presence and absence of a phosphine additive.

Table 1. Directing effects of tethered alkenes[a]



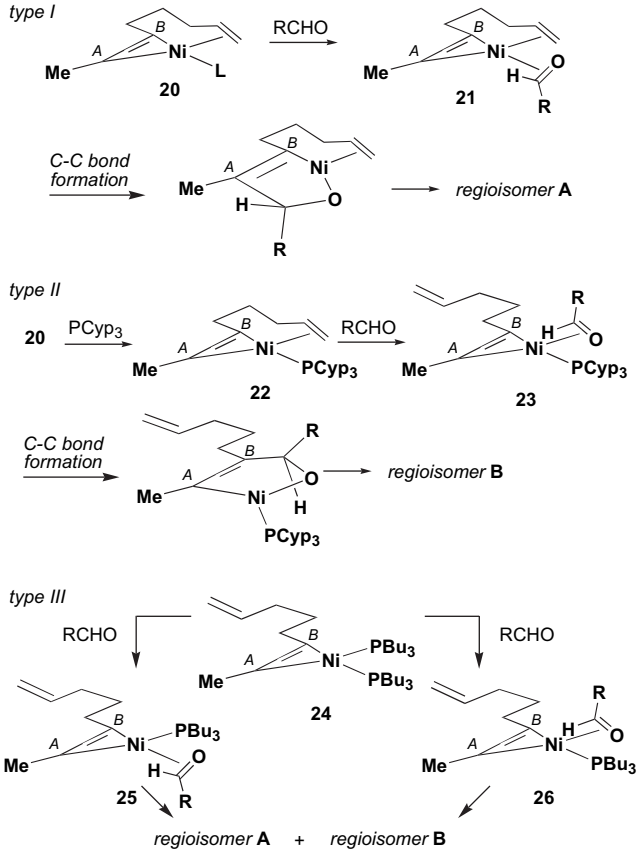
	Alkyne	*n*	Yield	Regioselectivity[b]
1	**1**	0	<5	n.d.
2	**2**	1	<5	n.d.
3	**3**	2	<5	n.d.
4	**4**	3	53[c]	>95:5
5	**5**	4	<5	n.d.
6	*n*-Pentyl–C≡C–*n*-hexyl	n.a.	28[c]	50:50

[a] Standard procedure: The alkyne (0.50 mmol) was added to a 0 °C solution of $Ni(cod)_2$ (0.05 mmol), *i*-PrCHO (1.00 mmol), and Et_3B (1.00 mmol) in EtOAc (0.5 mL), and the solution was allowed to stir 15 h at room temperature.
[b] Determined by ^1H NMR and/or GC.
[c] Some alkylative coupling (transfer of Et from Et_3B) also observed.

Although directing effects of tethered alkenes have been demonstrated in other metal-mediated reactions,[11] the only other examples in which the sense of the effect was reversed by an additive are Pd-catalyzed enyne isomerizations reported by Trost.[12] However, in this case high regioselectivity was observed in only one direction (≥15:1 vs 1:2.5), while we observe equal and opposite regioselectivity in the presence or absence of an additive.

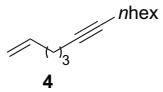
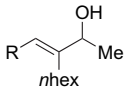
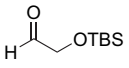
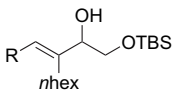
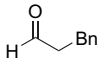
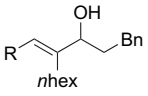
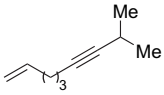
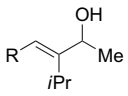
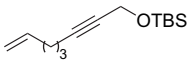
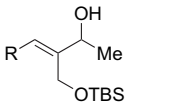
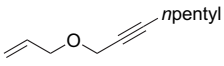
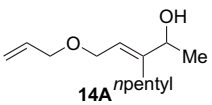
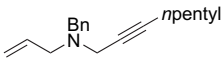
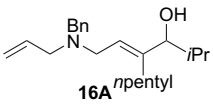
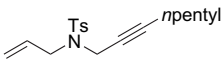
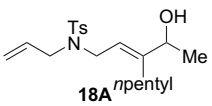
2.2. Origin of regioselectivity in the nickel-catalyzed reductive coupling of aldehydes and 1,6-enynes

Our investigation of additive effects (Table 3) led us to propose that three different pathways could be operating in these reactions depending upon which phosphine is used: one that exclusively forms **A** (Scheme 2, type I), one that exclusively forms **B** (type II), and one that gives a mixture of regioisomers **A** and **B** (type III). We propose a mechanistic rationale for each of the observed regiochemical outcomes, each of which is based on the assumption that the active catalyst involves a trisubstituted, planar, d^8 metal center undergoing stereospecific ligand substitution.[13]



Scheme 2.

Table 2. Highly regioselective, catalytic reductive coupling reactions directed by a remote alkene[a]

Entry	Enyne	Aldehyde	Product	Yield, regioselectivity (**A**:**B**)
1	 **4**		 **6A**	69% (>95:5)
2	**4**		 **7A**	58% (>95:5)
3	**4**		 **8A**	60% (>95:5)
4	 **9**		 **10A**	64% (>95:5)
5	 **11**		 **12A**	62% (>95:5)
6	 **13**		 **14A**	60% (>95:5)
7	 **15**		 **16A**	62% (>95:5)
8	 **17**		 **18A**	68% (>95:5)

[a] See Eq. 3, Table 1. R=$(CH_2)_3CH{=}CH_2$. Regioselectivity determined by ^{1}H NMR and/or GC.

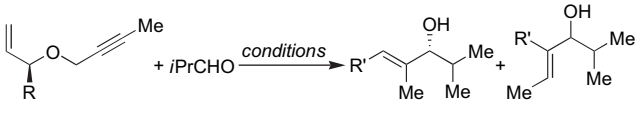
In all cases, C–C bond formation is believed to occur through an oxanickellacyclopentene.[2,4] Also, in all cases the third ligand (L) is assumed to be an olefin[14] and, as it is not part of a bidentate chelate, is considered to be the most weakly bound ligand. Therefore, in substitution reactions of **20**, L is the ligand that is preferentially displaced from the metal center.

Table 3. Effect of phosphine ligand on regioselectivity in reductive couplings of **4** and isobutyraldehyde[a,b]

Entry	PR_3	PR_3 cone angle	**19A**	**19B**	Yield[c]
1	$PCyp_3$	ND[d]	5	>95	50
2	PCy_3	170	5	>95	30
3	$PiPr_3$	161	5	>95	25
4	$PFcPh_2$	155[e]	40	60	20
5	$PCyPh_2$	152	42	58	30
6	PBu_3	132	42	58	75
7	None	—	>95	5	50

[a] Conditions (see Eq. 3): 0.5 mmol scale, 10 mol % $Ni(cod)_2$, 20 mol % ligand, 100 mol % alkyne, 200 mol % *i*-PrCHO, 200 mol % Et_3B, EtOAc, 0 °C to rt, 15 h. Regioselectivity determined by GC analysis.
[b] Ref. 8.
[c] 10–15% reductive cyclization product observed in all cases (cf. 2.4); yields are approximated based on ^{1}H NMR integration of the mixture.
[d] A value for the cone angle of $PCyp_3$ has not been reported.
[e] Ref. 9.

Table 4. Coupling reactions of chiral 1,6-enynes



27 R = Et
28 R = *t*Bu

29A, **30A** **29B**, **30B**

Entry	Enyne	Reaction conditions[a]	Products	**A**:**B**[b]	dr **A**[c]	dr **B**[c]
1	**27** (R=Et)	I	**29A**, **B**	>95:5	95:5	—
2		II		<5:95	—	45:55
3		III		55:45	50:50	45:55
4	**28** (R=*t*Bu)	I	**30A**, **B**	>95:5	>95:5	—
5		II		<5:95	—	42:58
6		III		51:49	45:55	42:58

[a] I: $Ni(cod)_2$ (10 mol %), Et_3B (200 mol %). II: Reaction conditions I+$PCyp_3$ (20 mol %). III: Reaction conditions I+PBu_3 (20 mol %).
[b] Based on isolated yields.
[c] Determined by ^{1}H NMR.

In the absence of a phosphine ligand (Scheme 2, type I), ligand substitution places the aldehyde cis to the alkyne carbon that is distal to the alkene (C(*A*)) and cis to the bound olefin, giving **21**. C–C bond formation occurs at C(*A*) while the olefin tether is coordinated to the nickel, resulting in exclusive formation of regioisomer **A**. In the presence of a large, electron-rich phosphine (e.g., $PCyp_3$), L is again displaced, but in this case by the phosphine, giving complex **22** (Scheme 2, type II). As the phosphine is coordinated more strongly to the metal center than the tethered alkene, the latter is preferentially displaced by the aldehyde in a stereospecific fashion, ultimately leading to regioisomer **B** by way of **23**. Thus, despite not being bound during the C–C bond formation, the olefin nevertheless determines regioselectivity. When the smaller tri-*n*-butylphosphine (PBu_3) is employed (type III), two equivalents of phosphine are bound to the metal center, displacing both the olefin tether and L to give **24**. In this case, regioselectivity is not determined by the olefin, and a non-selective displacement of either phosphine by the aldehyde leads to a mixture of **25** and **26**, which in turn affords a mixture of regioisomers **A** and **B**.

In order to test these mechanistic hypotheses and the overriding assumption of a planar, three-coordinate nickel complex, we evaluated the effect of a stereogenic center in the olefin tether. We hypothesized that in the absence of a phosphine (type I), coordination of the olefin to the metal center should enhance diastereoselection, while conditions employing achiral phosphines (types II and III) should lead to lower diastereoselectivity since the olefin would be dissociated during the C–C bond-forming step.

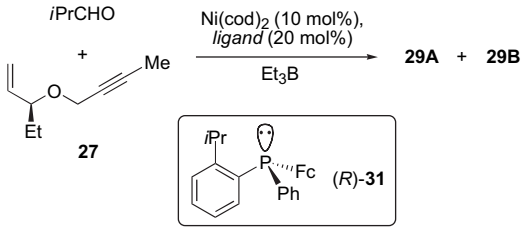
Thus, chiral 1,6-enynes **27** and **28** were synthesized and coupled with isobutyraldehyde under three distinct sets of catalytic conditions (Table 4): (I) $Ni(cod)_2$ with no additive; (II) $Ni(cod)_2$+$PCyp_3$; and (III) $Ni(cod)_2$+PBu_3.

As predicted, under type I reaction conditions (no phosphine) both enynes gave exclusively regioisomer **A** (Table 4, entries 1 and 4). In addition, both allylic alcohols were formed in excellent diastereoselectivity, indicating a strong influence of the stereogenic center in the tether, despite being separated from the site of C–C bond formation by five atoms (1,6-induction).

Conversely, under type II reaction conditions, regioisomer **B** is formed exclusively, but diastereoselection is negligible (entries 2 and 5). Type III reaction conditions are neither regioselective nor diastereoselective (entries 3 and 6).

Taken together, these experiments strongly support the notion that, in the absence of phosphine (type I), the alkene is coordinated to Ni during the C–C bond-forming step and that, in the presence of phosphine (type II or III), the alkene is not coordinated to Ni during the C–C bond-forming step. In other words, the critical aspect of the type II and type III mechanisms is that the phosphine is bound to the Ni during the C–C bond-forming step. We reasoned that since the influence of the chiral center in the tether in these cases is minimal, any diastereoselectivity induced by a chiral phosphine could be attributed to the phosphine alone, a result that would be consistent with phosphine being bound to Ni as the C–C bond is formed.

Table 5. Coupling reactions of chiral, enantiomerically enriched 1,6-enynes[a] with ferrocenyl-containing phosphines



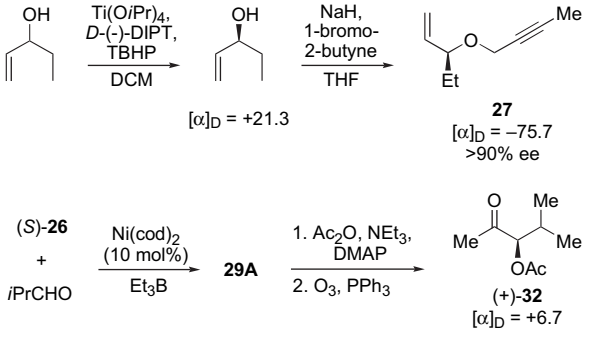
Ligand	**A**:**B**[b]	dr **29A** (*R*:*S*)[c]	dr **29B**[d]
(*R*)-**31**	48:52	30:70	28:72
(*S*)-**31**	55:45	66:34	68:32
$FcPPh_2$	54:46	56:44	48:52

[a] Enantiomerically enriched (>90% ee) **27** was used (Scheme 3).
[b] Based on isolated yields.
[c] Configuration of allylic alcohol stereogenic center.
[d] Relative stereochemistry not determined.

To this end, we subjected enyne **27** and isobutyraldehyde to reductive coupling conditions in the presence of an achiral or chiral ferrocenyl-containing phosphine (Table 5).[4c,15] Nearly equimolar amounts of regioisomers **A** and **B** were obtained in all cases, suggesting that the reaction occurs via a type III mechanistic pathway (cf. Scheme 2). Both the *R* and *S* phosphine ligands afforded modest diastereoinduction. These results demonstrate that the enyne stereocenter exerts little to no influence on the diastereoselectivity and clearly indicate that phosphine is bound to nickel during the C–C bond-forming step.

2.3. Origin of diastereoselectivity in the coupling of chiral 1,6-enynes

The high levels of diastereoselectivity afforded by enynes **27** and **28** in the absence of phosphine (Table 4, entries 1 and 4), prompted us to investigate coupling reactions of these chiral enynes further. In order to determine the sense of induction in the formation of regioisomer **A**, enantiomerically enriched enyne **27** was prepared (Scheme 3). 1-Penten-3-ol was resolved using a Sharpless asymmetric epoxidation,[16,17] and Williamson ether synthesis using the (*S*) enantiomer afforded enyne **27**.



Scheme 3.

Nickel-catalyzed reductive coupling of (*S*)-**27** and *i*-PrCHO in the absence of a phosphine (type I reaction conditions) afforded **29A** in >95:5 regioselectivity and 95:5 diastereoselectivity. Conversion to the corresponding acetate followed

by ozonolysis afforded ketone (+)-**32**. The sign of the specific rotation of this compound was opposite that of (−)-**32** prepared from commercially available (*S*)-2-hydroxy-3-methylbutyric acid,[18] thus establishing the allylic alcohol configuration in **29A** as *R*.

One possible explanation for the high diastereoselectivity was that the oxygen in the ethereal tether was binding to the aldehyde via the boron (Fig. 2), thus directing the aldehyde to the top face due to the conformation of the ring chelate.

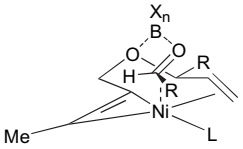
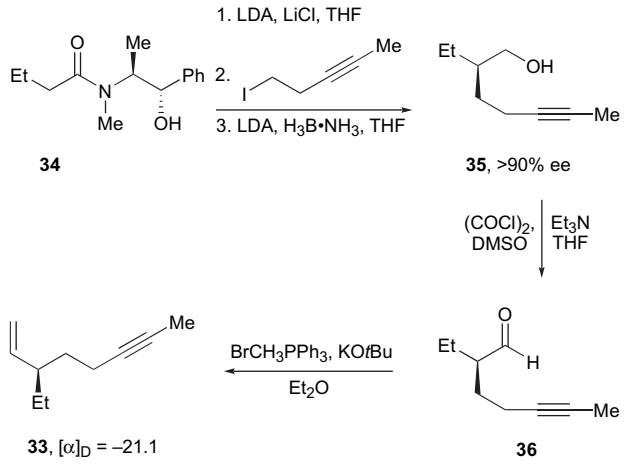


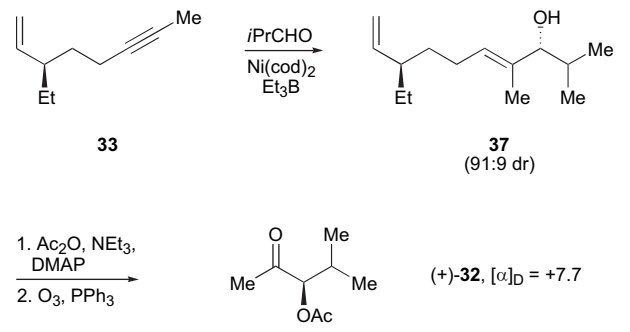
Figure 2.

To evaluate whether the oxygen atom of the tether plays a significant role in the reaction, we synthesized a 1,6-enyne (**33**) in which the oxygen was replaced with a methylene group, by way of a highly diastereoselective Myers alkylation, followed by Swern oxidation and Wittig olefination (Scheme 4)[19].



Scheme 4.

Under type I coupling conditions, enyne **33** gave results similar to those obtained with the enynes possessing an ethereal tether between the alkene and the alkyne. Nickel-catalyzed reductive coupling of **33** and *i*-PrCHO afforded allylic alcohol **37** in very high regioselectivity and in slightly reduced but nevertheless high diastereoselectivity (Scheme 5). The



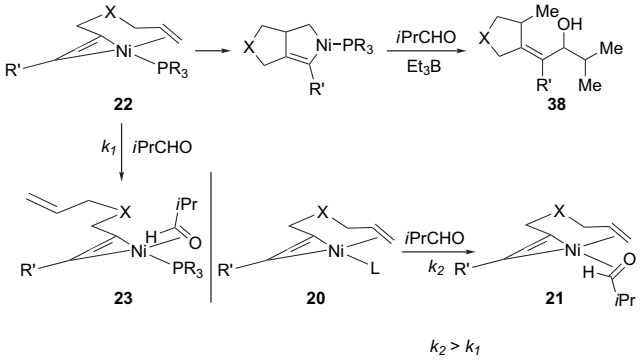
Scheme 5.

sense of induction, determined to be *R* using the same sequence of operations shown in Scheme 3, was also the same as that observed with enynes **27** and **28**. Thus, an oxygen atom and a CH_2 group at this position in the tether have similar (albeit measurably different) effects in type I coupling reactions.

The exact mode of diastereoinduction is unknown. However, since the size of the alkyl substituent of the chiral center has very little effect on the diastereoinduction (Table 4, entries 1 and 4), and since the oxygen of the ethereal tether does not appear to be involved, therefore, it is likely that the alkyl substituent controls the conformation of the ring chelate and it is the conformation of the ring chelate rather than the chiral center itself that interacts with the aldehyde and determines the stereochemical outcome of the reaction.

2.4. Carbocyclization

In the presence of a phosphine additive, **38** is observed as a minor product of nickel-catalyzed couplings of 1,6-enynes and aldehydes (Scheme 6).[2] This compound is thought to arise from complex **22** in a manner analogous to the nickel(0)-promoted enyne cyclizations previously reported by Tamao et al.[20] We propose that this side reaction is seen only in the presence of a phosphine additive because the formation of **23** (from **22**) will be slow relative to the formation of **21** (from **20**), since L is presumed to be more weakly bound than the tethered olefin.



Scheme 6.

3. Conclusion

In summary, alkene-directed, nickel-catalyzed reductive coupling of 1,6-enynes and aldehydes is a versatile tool for organic synthesis. The chelation-controlled, highly diastereoselective transformations possible in the absence of a phosphine additive have clear synthetic utility, while in the presence of a well-suited chiral phosphine, an enantioselective method for the production of regioisomer **B** might also be achieved.

Three distinct mechanistic pathways and their associated reaction conditions have been described, and our observations support the hypothesis that nickel-catalyzed reductive coupling reactions of alkynes and aldehydes proceed through an approximately planar, three-coordinate d^8 nickel complex. The mechanistic insight gained through this investigation should facilitate the development of other selective, nickel-catalyzed transformations.

4. Experimental

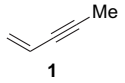
4.1. General methods

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of argon using standard Schlenk-line techniques. Bis(cyclooctadienyl)nickel(0) ($Ni(cod)_2$) and tricyclopentylphosphine ($PCyp_3$) were purchased from Strem Chemicals, Inc. and used without further purification. Triethylborane (Et_3B), triethylamine, methylsulfoxide, tributylphosphine (PBu_3), and penten-3-ol were purchased from Aldrich Chemical Co. and, unless otherwise stated, used as received. Isobutyraldehyde (Alfa Aeser) was distilled from anhydrous magnesium sulfate ($MgSO_4$) prior to use. (±)-4,4-Dimethyl-penten-3-ol was synthesized according to the literature procedure, and distilled prior to use.[21] Tetrahydrofuran (THF) and diethyl ether were freshly distilled over sodium/benzophenone ketyl, and dichloromethane (DCM) was freshly distilled from calcium hydride. Toluene was distilled from sodium metal, ethyl acetate was distilled from anhydrous magnesium sulfate, both toluene and ethyl acetate were sparged for 10 min with argon prior to use in coupling experiments.

4.2. Preparation of starting materials

The synthesis of 6-tridecyne, **2**–**5**, **9**, **11**, **13**, **15**, and **17** have been reported previously.[2]

4.2.1. 1-Decen-3-yne[22] (1).



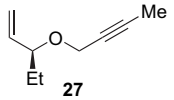
1

1-Octyne (2.21 mL, 15 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. Then *n*-BuLi (15 mmol, 6 mL of 2.5 M solution in hexanes) was added dropwise, and the mixture was stirred at 0 °C for 30 min. A solution of dry $ZnCl_2$ (2.04 g, 15 mmol) in THF (10 mL) was added via cannula and the mixture was allowed to warm to room temperature. In a 250 mL round-bottom flask, vinyl bromide (25 mmol, 25 mL of a 1 M solution in THF) and $Pd(PPh_3)_4$ (0.69 g, 0.6 mmol) were combined. The alkynyl zinc solution was transferred to the palladium solution via cannula. The bright yellow solution was stirred for 2 h, and then quenched with 1 M HCl (75 mL). The organics were extracted with pentanes (2×75 mL), washed with saturated NaCl, dried over $MgSO_4$, and filtered. Pentanes were removed via distillation, and the residue was then distilled under reduced pressure to provide **1** (0.95 g, 7.0 mmol, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddt, J=17.4, 10.8, 2.1 Hz, 1H); 5.54 (dd, J=17.4, 2.3 Hz, 1H); 5.37 (dd, J=10.8, 2.3 Hz, 1H); 2.29 (dt, J=10.2, 2.1 Hz, 2H); 1.48–1.57 (m, 2H); 1.25–1.44 (m, 6H); 0.89 (t, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 125.6, 117.9, 91.5, 76.5, 31.6, 28.9, 28.8, 22.8, 19.6, 14.3.

4.2.2. (+)-Penten-3-ol.

Synthesized according to a literature procedure.[23] Flame-dried molecular sieves 4 Å (ca. 5 g) were loaded into a 100 mL round-bottomed flask filled with DCM (25 mL). To this suspension was added diisopropyl D-tartrate (352 μL, 2.1 mmol) and racemic penten-3-ol (3 g, 34 mmol). The suspension was cooled to −5 °C and $Ti(OiPr)_4$ (414 μL, 1.4 mmol) was added. The reaction was stirred for 30 min, and then *t*-BuOOH (5.5 M in decanes, 6 mL, 33 mmol) was added. The reaction was warmed to 0 °C and stirred for 7 h. The slurry was added to a solution of iron(II) sulfate (11 g) and citric acid (3.5 g) in water (30 mL) and diluted with ether (80 mL). The layers were separated and the aqueous layer extracted once with diethyl ether. The combined organics were washed with brine, dried over magnesium sulfate, and filtered. Solvent was removed under atmospheric pressure via distillation through a Vigereux column (10 cm). Fractional distillation (20 Torr, 50 °C) of the residue then provided (+)-penten-3-ol as a clear oil (1 g, 33% yield). $[\alpha]_D^{22}$ +21.6 (*c* 0.37, $CHCl_3$). The optical rotation was compared to literature values,[17] and the stereocenter was determined to be (*S*).

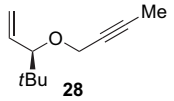
4.2.3. (−)-3-But-2-ynyloxy-pent-1-ene (27).



27

Sodium hydride (7.5 g, ~58%, ~180 mmol) was loaded into a round-bottom flask and rinsed with anhydrous pentanes (3×50 mL) and dried in vacuo. THF (200 mL) was added followed by addition of (+)-penten-3-ol (3.08 mL, 30 mmol), and the mixture was stirred for 3 h at room temperature prior to addition of 1-bromo-2-butyne (5.25 mL, 60 mmol). After stirring overnight, the reaction was quenched by careful addition of saturated aqueous ammonium chloride. The organics were extracted with diethyl ether (3×150 mL), washed with brine, dried over magnesium sulfate, filtered, and concentrated (0 °C, 50 Torr). The product (as a solution in THF) was loaded directly onto silica (7 cm×5 cm) and chromatographed (10:1 pentanes/diethyl ether). Removal of the solvent (0 °C, 50 Torr) followed by distillation through a short-path apparatus (35 °C, 1 Torr) yielded (−)-**27** as a clear oil (3.83 g, 92%, >90% ee). Compound (−)-**27**: $[\alpha]_D^{22}$ −75.7 (*c* 3.09, $CHCl_3$); chiral GC analysis (Varian CP-3800, G-TA column, 50 °C, 0.7 mL/min H_2 carrier) t_R (*S*) 14.4 min, t_R (*R*) 14.9 min; IR 2964 (m), 2924 (s), 2856 (m), 2248 (w), 1457 (b, w), 1057 (s), 910 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (ddd, J=17.0, 11.0, 8.5 Hz, 1H), 5.23 (dd, J=8.5, 2.0 Hz, 1H), 5.22 (dd, J=17.0, 2.0 Hz, 1H), 4.15 (dq, J_d=15.0 Hz, J_q=2.0 Hz, 1H), 3.97 (dq, J_d=15.0 Hz, J_q=2.0 Hz, 1H), 3.73 (q, J=7.0 Hz, 1H), 1.86 (t, J=2.0 Hz, 3H), 1.66 (apparent septet, J=7.0 Hz, 1H), 1.52 (apparent septet, J=7.0 Hz, 1H), 0.91 (t, J=7.5 Hz, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.3, 118.1, 81.9, 81.8, 75.8, 56.1, 28.3, 9.9, 3.9.

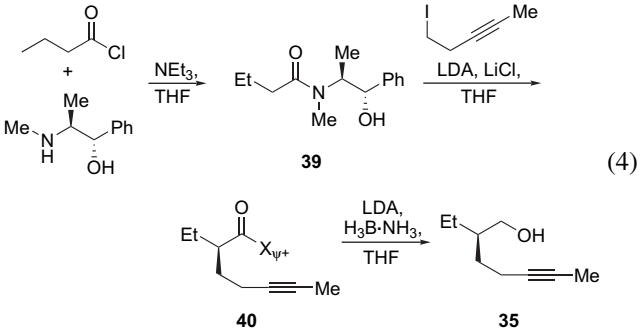
4.2.4. (±)-3-But-2-ynyloxy-4,4-pent-1-ene (28).



28

According to the procedure for **27**, (±)-4,4-dimethyl-penten-3-ol (1.71 g, 15 mmol) was reacted with 600 mol % NaH and 300 mol % 1-bromo-2-butyne to give 2 g (80%)

of a clear oil after chromatography (25:1 pentanes/diethyl ether) and distillation (65 °C, 1 Torr). Compound **28**: IR 2956 (s), 2870 (m), 2361 (w), 1464 (b, w), 1363 (m), 1136 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, J=17.0, 10.5, 8.5 Hz, 1H), 5.27 (dd, J=10.5, 1.5 Hz, 1H), 5.19 (dd, J=17.0, 1.5 Hz, 1H), 4.14 (dq, J_d=15.0 Hz, J_q=2.0 Hz, 1H), 3.92 (dq, J_d=15.0 Hz, J_q=2.0 Hz, 1H), 3.42 (d, J=8.5 Hz, 1H), 1.86 (t, J=2.0 Hz, 3H), 0.91 (s, 9H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 135.4, 119.2, 88.0, 81.5, 76.1, 56.4, 34.4, 26.3, 3.9; HRMS m/z (ESI, M+Na^+) calcd 189.1250 found 189.1256.



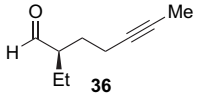
(4)

4.2.5. 2-Ethyl-hept-5-yn-1-ol (35). The synthesis of **35** was accomplished following the work of Myers and co-workers.[19] Butyryl chloride (3.1 mL, 30 mmol) was added dropwise to a chilled (0 °C) solution of (+)-(*S*, *S*)-pseudoephedrine (4.95 g, 30 mmol) and NEt_3 (5.4 mL, 39 mmol) in THF (10 mL). The reaction was stirred for 30 min and then quenched by the addition of water. The product mixture was partitioned between ethyl acetate and brine, the organic layer was separated, washed two times with brine, and then dried over sodium sulfate. The solvent was removed in vacuo and the crude solid recrystallized from toluene (20 mL) to give **39** as white crystals (5.15 g, 74%). NMR matched known values.[24]

n-Butyllithium (2.5 M in hexanes, 9.8 mL, 24.5 mmol) was added dropwise to a cold (−78 °C) slurry of *i*-Pr_2NH (3.7 mL, 26 mmol) and LiCl (flame dried under vacuum prior to use) (3.23 g, 77 mmol) in THF (17 mL). The suspension was warmed to 0 °C for 5 min then cooled to −78 °C. Compound **39** (2.96 g, 12.6 mmol) was added dropwise as a solution in cold (0 °C) THF (37 mL) and the reaction stirred at −78 °C for 1 h, 0 °C for 15 min and then room temperature for 5 min before being re-cooled to 0 °C. 5-Iodo-2-pentyne (1.16 g, 6.0 mmol), available in two steps from the corresponding alcohol,[25] was added in a single portion and the reaction was stirred at 0 °C for 2 h before being allowed to gradually warm to room temperature overnight. The reaction was quenched via the addition of saturated aqueous ammonium chloride and the product extracted with ethyl acetate. The combined organics were dried over sodium sulfate, filtered, concentrated, and then chromatographed (3:2 hexanes/ethyl acetate) to give **40** as a viscous pale yellow oil (1.34 g, 73%). The relative stereochemistry of **40** was assigned by analogy to Myers' work.[19]

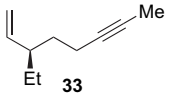
Compound **40** was reduced using LDA and $H_3B\cdot NH_3$ (LAB) prepared as follows: *n*-Butyllithium (2.5 M in hexanes, 5.3 mL, 13.2 mmol) was added dropwise to a cold (−78 °C) solution of *i*-Pr_2NH (2.0 mL, 13.9 mmol) in THF (14 mL). The solution was warmed to 0 °C and stirred for 10 min, then $H_3B\cdot NH_3$ (407 mg, 13.2 mmol) was added in a single portion. The reaction was stirred at 0 °C for an additional 15 min and then warmed to room temperature for 15 min. The reaction was re-cooled (0 °C) for the dropwise addition of **40** (1.0 g, 3.3 mmol) in THF (8.3 mL), and then warmed back up to room temperature until the reaction was determined to be complete by TLC (2 h). The system was cooled to 0 °C and 33 mL of 3 N HCl was added carefully. The slurry was stirred for 30 min at 0 °C, the product was extracted with ether, and the combined organics washed with 1 N HCl, 1 N NaOH, and brine. The crude product was dried over magnesium sulfate, filtered, concentrated, and chromatographed (5:2 hexanes/diethyl ether) to give **35** as a clear oil (267 mg, 81%). The enantiomeric excess was approximated by formation of the Mosher ester of this sample and of racemic material[26] and then comparing their respective ^1H NMR spectra. $[\alpha]_D^{22}$ −4.6, (*c* 3.37, $CHCl_3$); IR 3348 (b, m), 2961 (s), 2921 (s), 2876 (s), 2361 (m), 2341 (m), 1461 (m), 1380 (w), 1043 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.60 (m, 2H), 2.19 (m, 2H), 1.79 (t, J=2.5 Hz, 3H), 1.55 (m, 2H), 1.39 (m, 3H), 0.92 (t, J=7.5 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 79.5, 75.9, 64.9, 41.3, 30.1, 23.4, 16.6, 11.3, 3.7.

4.2.6. 2-Ethyl-hept-5-ynal (36).



DMSO (298 μL, 4.2 mmol) was added to oxalyl chloride (262 μL, 3 mmol) in cold (−78 °C) dichloromethane (20 mL), and the mixture was stirred for 10 min before **35** (280 mg, 2 mmol) was added. After stirring for an additional 20 min, NEt_3 (836 μL, 6 mmol) was added in a single portion, and the cold bath subsequently removed. The reaction was allowed to warm for 30 min before being quenched via the addition of water. The product was extracted with ether and the combined organics dried over magnesium sulfate. The solvent was removed under reduced pressure (80 Torr, 0 °C, rotary evaporator), and the crude mixture was flushed through a silica plug eluting with 10:1 pentanes/diethyl ether and then concentrated to give a clear oil (274 mg, 99%). IR 2964 (m), 2923 (m), 2361 (s), 2341 (s), 1726 (m), 1380 (b, m), 1261 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.64 (d, J=2.5 Hz, 1H), 2.39 (dtt, J_d=2.5, J_t=7.5, 5.5 Hz, 1H), 2.18 (m, 2H), 1.87 (m, 1H), 1.77 (t, J=2.5 Hz, 3H), 1.70 (m, 1H), 1.66–1.52 (m, 4H), 0.94 (t, J=7.5 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.2, 78.3, 76.9, 52.4, 27.7, 21.7, 16.8, 11.5, 3.6; HRMS m/z (ESI, M+Na^+) calcd 161.0937 found 161.0944.

4.2.7. 3-Ethyl-oct-1-en-6-yne (33).



Freshly dried methyltriphenylphosphonium bromide (1.02 g, 2.86 mmol) was added in one portion to a cooled (0 °C) suspension of KO*t*Bu (355 mg, 2.86 mmol) in ether (4 mL), resulting in the suspension turning bright yellow. The suspension was warmed to room temperature and stirred

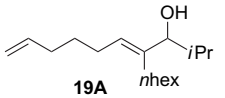
for 40 min, **36** (274 mg, 2 mmol) was added from a 10 mL pear-shaped flask, rinsing with ether (total volume 2 mL). Stirring was continued for 45 min at room temperature and then the reaction was quenched with water (200 μL). The suspension was stirred until all of the precipitate collected at the bottom of the flask (5 min) leaving a clear liquid phase. The flask was equipped with a short-path distillation apparatus and heated to 50 °C to remove most of the diethyl ether. The receiving flask was then cooled to −78 °C and the system was placed under vacuum resulting in the instantaneous transfer of all remaining liquid materials (a mixture of diethyl ether, *t*-BuOH, water, and **33**) to the cooled receiving flask. Sodium sulfate was added to the biphasic mixture and then the material was passed through a plug of silica eluting with pentanes. The solvent was removed (0 °C, 140 Torr) to give **33** as a clear oil (175 mg, 64%). $[\alpha]_D^{22}$ −21.1 (*c* 0.41, DCM); IR 3077 (w), 2964 (s), 2921 (s), 2875 (m), 2361 (w), 1640 (w), 1455 (m), 997 (m), 914 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.48 (ddd, J=17.0, 10.0, 9.5 Hz, 1H), 5.00 (m, 2H), 2.16 (m, 1H), 2.06 (m, 1H), 1.98 (m, 1H), 1.79 (t, J=2.5 Hz, 3H), 1.60 (m, 1H), 1.40 (m, 2H), 1.26 (m, 1H), 0.86 (t, J=7.5 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 142.3, 115.3, 79.5, 75.5, 45.2, 34.1, 27.7, 16.8, 11.8, 3.7; HRMS *m/z* (EI, M^+) calcd 136.1248 found 136.1247.

4.3. Alkene-directed reductive coupling of alkynes and aldehydes

4.3.1. General procedure A. In a glove box, $Ni(cod)_2$ (14 mg, 0.05 mmol) was placed into an oven-dried, single-necked round-bottom flask, and the flask was then sealed with a rubber septum. The flask was removed from the glove box, placed under argon, and degassed ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The reaction could also be run in the absence of any additional solvent with no detrimental effect. The resulting solution was then cooled to 0 °C, and isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring for 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to gradually warm to room temperature and stirred for 15 h. The septa was then removed and the reaction opened to air for 30 min to promote quenching of the catalyst. Reactions, which were run neat, were first diluted with 2 mL of reagent grade ethyl acetate prior to being opened to the air. The crude mixture was concentrated and purified by flash chromatography.

4.3.2. General procedure B (with phosphine additive). In a glove box, $Ni(cod)_2$ (14 mg, 0.05 mmol) and PR_3 (0.1 mmol) were placed into an oven-dried, single-necked round-bottom flask, and the flask was then sealed with a rubber septum. The flask was removed from the glove box, placed under argon, and degassed ethyl acetate (0.5 mL) was added via syringe, followed immediately by Et_3B (0.15 mL, 1.0 mmol). The reaction could also be run in the absence of any additional solvent with no detrimental effect. The resulting solution was then cooled to 0 °C, and isobutyraldehyde (90 μL, 1.0 mmol) was added dropwise via microsyringe. After stirring for 5 min, the enyne (0.5 mmol) was added. The reaction was allowed to gradually warm to room temperature and stirred for 15 h. The septa was then removed and the reaction opened to air for 30 min to promote quenching of the catalyst. Reactions, which were run neat, were first diluted with 2 mL of reagent grade ethyl acetate prior to being opened to the air. The crude mixture was concentrated and purified by flash chromatography.

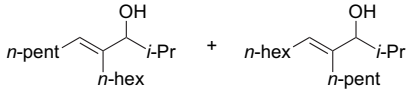
4.3.2.1. 4-Hexyl-2-methyl-deca-4,9-dien-3-ol (19A).



19A

Procedure A (no additive) (half-scale): Reaction of isobutyraldehyde (45 μL, 0.5 mmol) and **4** (45 mg, 0.25 mmol) in the presence of $Ni(cod)_2$ (7 mg, 0.025 mmol) and Et_3B (75 μL, 0.5 mmol) in EtOAc (0.25 mL) afforded an 85:15 mixture of the title compound and the corresponding alkylative coupling product (transfer of an ethyl group instead of a hydrogen from Et_3B) (34 mg, 53% yield (46% reductive), >95:5 regioselectivity). An analytically pure sample of **19A** was obtained via flash chromatography on silica gel impregnated with 5% silver nitrate. R_f=0.40 (10:1 hexanes/ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$) δ 5.78–5.87 (m, 1H); 5.35 (t, J=7.5 Hz, 1H); 4.99–5.04 (m, 1H); 4.95–4.98 (m, 1H); 3.66 (d, J=7.5 Hz, 1H); 1.92–2.10 (m, 6H); 1.78 (oct., J=7 Hz, 1H); 1.44–1.51 (m, 2H); 1.24–1.43 (m, 8H); 0.96 (d, J=7 Hz, 3H); 0.89 (t, J=7 Hz, 3H); 0.84 (d, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 139.0, 127.4, 114.7, 82.9, 33.7, 31.9, 31.9, 31.8, 30.3, 30.2, 29.3, 28.2, 27.2, 22.9, 20.1, 18.3, 14.3. IR (thin film NaCl): 3623, 3428, 3078, 2956, 2929, 2871, 2859, 1823, 1641, 1468, 1379, 1365, 1295, 1246, 1169, 1130, 1116, 1007. HRMS (ESI) *m/z* 275.235 [$(M+Na)^+$; calcd for $C_{17}H_{32}O$: 275.235]. Regioselectivity confirmed by GC analysis (chiral B-PH, 125 °C, 2.5 mL/min): 21.30, 22.06 min.

4.3.2.2. 4-Hexyl-2-methyl-dec-4-en-3-ol (41A) and 2-methyl-4-pentyl-undec-4-en-3-ol (41B).



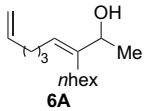
41A **41B**

Procedure A (no additive): Reaction of isobutyraldehyde and 6-tridecyne (90 mg, 0.5 mmol) afforded an 85:15 mixture of the title compounds and the corresponding alkylative coupling products (transfer of an ethyl group instead of a hydrogen from Et_3B) as a clear oil (36 mg, 28% yield (24% reductive), 51:49 mixture of regioisomers **41A** and **41B**).

Procedure B ($PCyp_3$): Reaction of isobutyraldehyde and 6-tridecyne (90 mg, 0.5 mmol) afforded a 51:49 mixture of regioisomers **41A** and **41B** as a clear oil (98 mg, 77% yield). R_f=0.39 (10:1 hexanes/ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (t, J=7 Hz, 1H); 3.65 (d, J=7.5 Hz, 1H); 1.92–2.07 (m, 4H); 1.78 (oct., J=7 Hz, 1H); 1.24–1.44 (m, 14H); 0.96 (d, J=6 Hz, 3H); 0.87–0.92 (m, 6H); 0.84 (d, J=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 128.0, 83.0, 83.0, 32.7, 32.0, 31.9, 31.8, 31.8, 30.3, 30.2, 30.0, 30.0, 29.7, 29.3, 28.2, 28.1, 27.8, 27.7, 22.9, 22.9, 22.8, 22.7, 20.1, 18.3, 14.3, 14.3, 14.3,

14.3. IR (thin film NaCl): 3624, 3423, 2957, 2927, 2872, 2859, 1713, 1661, 1467, 1379, 1366, 1297, 1244, 1169, 1105, 1008. HRMS (ESI) *m/z* 277.251 [(M+Na)$^+$; calcd for $C_{17}H_{34}O$: 277.250]. Regioselectivity determined by GC analysis (chiral B-PH, 110 °C, 2.0 mL/min): 51.08, 52.04 min.

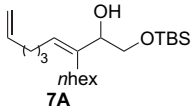
4.3.2.3. 3-Hexyl-nona-3,8-dien-2-ol (6A).



6A

Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of acetaldehyde (100 μL, 2 mmol) and **4** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (77 mg, 69% yield, >95:5 regioselectivity). R_f=0.19 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78–5.86 (m, 1H); 5.41 (t, *J*=7 Hz, 1H); 4.99–5.05 (m, 1H); 4.94–4.98 (m, 1H); 4.23 (q, *J*=6.5 Hz, 1H); 1.95–2.12 (m, 6H); 1.46 (quin., *J*=7.5 Hz, 2H); 1.28–1.42 (m, 8H); 1.27 (d, *J*=6.5 Hz, 3H); 0.90 (t, *J*=6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 139.0, 125.2, 114.7, 72.3, 33.6, 31.9, 30.1, 30.0, 29.2, 27.8, 27.1, 22.9, 22.6, 14.3. IR (thin film NaCl): 3349, 3078, 2957, 2928, 2858, 1641, 1458, 1415, 1378, 1366, 1283, 1116, 1062. HRMS (ESI) *m/z* 247.203 [(M+Na)$^+$; calcd for $C_{15}H_{28}O$: 247.203].

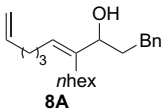
4.3.2.4. 1-(*tert*-Butyl-dimethyl-silanyloxy)-3-hexyl-nona-3,8-dien-2-ol (7A).



7A

Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of (*tert*-butyldimethylsilyloxy)acetaldehyde (190 μL, 1 mmol) and **4** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (102 mg, 58% yield, >95:5 regioselectivity). R_f=0.42 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.86 (m, 1H); 5.48 (t, *J*=7 Hz, 1H); 5.10 (dd, *J*=17, 1 Hz, 1H); 4.96 (dt, *J*=10, 1 Hz, 1H); 4.08 (dd, *J*=8.5, 3 Hz, 1H); 3.64 (dd, *J*=10, 3 Hz, 1H); 3.42 (dd, *J*=10, 8.5 Hz, 1H); 2.03–2.12 (m, 5H); 1.87–1.94 (m, 1H); 1.47 (quin., *J*=7.5 Hz, 2H); 1.24–1.40 (m, 8H); 0.91 (s, 9H); 0.89 (t, *J*=7 Hz, 3H); 0.09 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 138.4, 127.2, 114.7, 75.7, 67.3, 33.7, 31.9, 29.9, 29.8, 29.2, 28.6, 27.2, 26.1, 22.9, 18.5, 14.3, −5.1, −5.1. IR (thin film NaCl): 3572, 3472, 3078, 2956, 2929, 2858, 1824, 1730, 1641, 1471, 1464, 1390, 1362, 1316, 1255, 1223, 1099, 1057, 1006, 992. HRMS (ESI) *m/z* 377.284 [(M+Na)$^+$; calcd for $C_{21}H_{42}O_2Si$: 377.285].

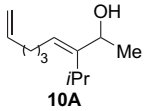
4.3.2.5. 4-Hexyl-1-phenyl-deca-4,9-dien-3-ol (8A).



8A

Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of 3-phenylpropionaldehyde (132 μL, 1 mmol) and **4** (89 mg, 0.5 mmol) afforded the title compound as a clear oil (95 mg, 60% yield, >95:5 regioselectivity). R_f=0.23 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.31 (m, 2H); 7.17–7.22 (m, 3H); 5.78–5.87 (m, 1H); 5.41 (t, *J*=7 Hz, 1H); 5.00–5.04 (m, 1H); 4.95–4.98 (m, 1H); 4.05 (t, *J*=6.5 Hz, 1H); 2.70–2.76 (m, 1H); 2.60–2.66 (m, 1H); 1.96–2.11 (m, 6H); 1.84–1.89 (m, 2H); 1.47 (quin., *J*=7.5 Hz, 2H); 1.24–1.42 (m, 8H); 0.89 (t, *J*=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 142.4, 138.9, 128.6, 128.6, 126.8, 126.0, 114.8, 76.3, 37.6, 33.6, 32.5, 31.9, 30.2, 30.1, 29.9, 27.8, 27.2, 22.9, 14.3. IR (thin film NaCl): 3360, 3077, 3064, 3027, 2954, 2928, 2858, 1940, 1821, 1727, 1641, 1604, 1496, 1455, 1415, 1378, 1301, 1154, 1048, 1031, 992. HRMS (ESI) *m/z* 337.250 [(M+Na)$^+$; calcd for $C_{22}H_{34}O$: 337.250].

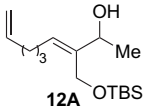
4.3.2.6. 3-Isopropyl-nona-3,8-dien-2-ol (10A).



10A

Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **9** (68 mg, 0.5 mmol) afforded the title compound as a clear oil (58 mg, 64% yield, >95:5 regioselectivity). R_f=0.20 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78–5.86 (m, 1H); 5.47 (t, *J*=7 Hz, 1H); 4.99–5.04 (m, 1H); 4.95–4.98 (m, 1H); 4.30 (q, *J*=6.5 Hz, 1H); 2.76 (septet, *J*=7 Hz, 1H); 2.05–2.13 (m, 4H); 1.47 (quin., *J*=7 Hz, 2H); 1.29 (d, *J*=6.5 Hz, 3H); 1.11 (d, *J*=7 Hz, 3H); 1.05 (d, *J*=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.4, 139.0, 124.2, 114.7, 68.4, 33.6, 29.4, 28.2, 27.0, 24.2, 22.0, 21.7. IR (thin film NaCl): 3361, 3078, 2962, 2929, 2872, 1824, 1641, 1460, 1415, 1365, 1304, 1282, 1217, 1150, 1111, 1060. HRMS (ESI) *m/z* 205.156 [(M+Na)$^+$; calcd for $C_{12}H_{22}O$: 205.156].

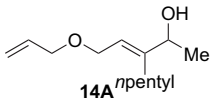
4.3.2.7. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-nona-3,8-dien-2-ol (12A).



12A

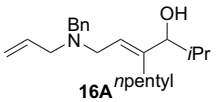
Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **11** (119 mg, 0.5 mmol) afforded the title compound as a clear oil (88 mg, 62% yield, >95:5 regioselectivity). R_f=0.40 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76–5.85 (m, 1H); 5.49 (t, *J*=7.5 Hz, 1H); 4.99–5.04 (m, 1H); 4.95–4.98 (m, 1H); 4.31–4.40 (m, 3H); 2.00–2.10 (m, 4H); 1.48 (quin., *J*=7.5 Hz, 2H); 1.34 (d, *J*=6 Hz, 3H); 0.92 (s, 9H); 0.12 (s, 3H); 0.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 138.7, 127.7, 114.9, 72.4, 60.2, 33.4, 28.9, 26.9, 26.1, 22.2, 18.4, −5.3. IR (thin film NaCl): 3421, 3078, 2956, 2929, 2886, 2858, 1668, 1641, 1472, 1463, 1442, 1406, 1390, 1362, 1255, 1072. HRMS (ESI) *m/z* 307.206 [(M+Na)$^+$; calcd for $C_{16}H_{32}O_2Si$: 307.206].

4.3.2.8. 5-Allyloxy-3-pentyl-pent-3-en-2-ol (14A).



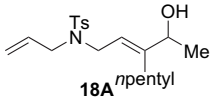
Procedure A (no additive) (modifications: toluene used in place of EtOAc as the reaction solvent, and slow addition of the enyne over 3 h via syringe pump): reductive coupling of acetaldehyde (100 μL, 1.8 mmol) and **13** (83 mg, 0.5 mmol) afforded the title compound as a clear oil (64 mg, 60% yield, >95:5 regioselectivity). R_f=0.17 (5:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90–5.97 (m, 1H); 5.64 (t, J=6.5 Hz, 1H); 5.27–5.32 (m, 1H); 5.19–5.22 (m, 1H); 4.27 (q, J=6.5 Hz, 1H); 4.05 (d, J=6.5 Hz, 2H); 3.99 (dt, J=6, 1.5 Hz, 2H); 2.09–2.16 (m, 1H); 1.98–2.04 (m, 1H); 1.20–1.42 (m, 11H); 0.90 (t, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 135.0, 121.2, 117.4, 71.6, 71.6, 66.5, 32.4, 30.0, 28.2, 22.7, 22.4, 14.2. IR (thin film NaCl): 3392, 2957, 2932, 2861, 1647, 1459, 1367, 1212, 1065. HRMS (ESI) m/z 235.166 [(M+Na)$^+$; calcd for $C_{13}H_{24}O_2$: 235.167].

4.3.2.9. 6-(Allyl-benzyl-amino)-2-methyl-4-pentyl-hex-4-en-3-ol (16A).



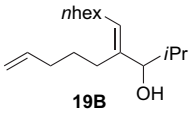
Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of isobutyraldehyde (90 μL, 1.0 mmol) and **15** (128 mg, 0.5 mmol) afforded the title compound as a clear oil (102 mg, 62% yield, >95:5 regioselectivity). R_f=0.22 (5:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.36 (m, 4H); 5.86–5.95 (m, 1H); 5.52 (t, J=6.5 Hz, 1H); 5.20 (dd, J=17.5, 2 Hz, 1H); 5.16 (d, J=10 Hz, 1H); 3.69 (d, J=7 Hz, 1H); 3.57 (s, 2H); 3.12 (d, J=7 Hz, 2H); 3.09 (d, J=6.5 Hz, 2H); 1.97–2.04 (m, 1H); 1.89–1.95 (m, 1H); 1.79 (octet, J=7 Hz, 1H); 1.22–1.38 (m, 6H); 0.95 (d, J=6.5 Hz, 3H); 0.88 (t, J=7 Hz, 3H); 0.86 (d, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 139.7, 136.2, 129.2, 128.4, 127.0, 124.7, 117.7, 82.4, 58.3, 57.1, 50.9, 32.6, 31.7, 29.9, 28.4, 22.7, 20.1, 18.1, 14.3. IR (thin film NaCl): 3423, 3065, 3028, 2956, 2930, 2870, 1643, 1495, 1455, 1366, 1255, 1118, 1073, 1012. HRMS (ESI) m/z 330.279 [(M+Na)$^+$; calcd for $C_{22}H_{35}NO$: 330.279].

4.3.2.10. *N*-allyl-*N*-[3-(1-hydroxyethyl)-oct-2-enyl]-benzenesulfonamide (18A).



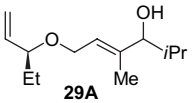
Procedure A (no additive) (modification: toluene used in place of EtOAc as the reaction solvent): reductive coupling of acetaldehyde (200 μL, 3.6 mmol) and **17** (160 mg, 0.5 mmol) afforded the title compound as a clear oil (125 mg, 68% yield, >95:5 regioselectivity). R_f=0.29 (3:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J=8.5 Hz, 2H); 7.30 (d, J=8.5 Hz, 2H); 5.64–5.73 (m, 1H); 5.26 (t, J=7 Hz, 1H); 5.14–5.18 (m, 2H); 4.16 (q, J=6.5 Hz, 1H); 3.86 (d, J=6.5 Hz, 2H); 3.79–3.81 (m, 2H); 2.44 (s, 3H); 2.02–2.08 (m, 1H); 1.89–1.96 (m, 1H); 1.22–1.36 (m, 6H); 1.20 (d, J=6.5 Hz, 3H); 0.89 (t, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 143.4, 137.7, 133.4, 129.8, 127.4, 119.0, 118.9, 71.3, 49.9, 44.2, 32.4, 29.7, 28.0, 22.6, 22.4, 21.7, 14.2. IR (thin film NaCl): 3521, 2957, 2931, 2870, 1644, 1598, 1495, 1446, 1418, 1402, 1343, 1305, 1289, 1264, 1213, 1159, 1119, 1092, 1059. HRMS (ESI) m/z 388.192 [(M+Na)$^+$; calcd for $C_{20}H_{31}NO_3S$: 388.192].

4.3.2.11. 2-Methyl-4-pent-4-enyl-undec-4-en-3-ol (19B).



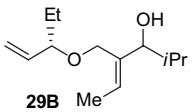
Procedure B (general for all phosphines listed in Table 3) (modification: aldehyde added over 3 h via syringe pump): Reaction of isobutyraldehyde and **4** (89 mg, 0.5 mmol) provided **19B** as a clear oil (57 mg, 45% yield). Following initial purification, flash chromatography on silica gel impregnated with 5% silver nitrate was required to remove minor impurities. R_f=0.40 (10:1 hexanes/ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79–5.87 (m, 1H); 5.36 (t, J=7 Hz, 1H); 5.01–5.05 (m, 1H); 4.96–4.99 (m, 1H); 3.65 (d, J=7 Hz, 1H); 1.95–2.13 (m, 6H); 1.78 (oct., J=7 Hz, 1H); 1.46–1.56 (m, 2H); 1.24–1.40 (m, 8H); 0.96 (d, J=7 Hz, 3H); 0.89 (t, J=7 Hz, 3H); 0.83 (d, J=7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0, 138.9, 128.4, 114.9, 83.0, 34.6, 32.0, 31.8, 30.0, 29.5, 29.3, 27.8, 27.5, 22.8, 20.08, 18.4, 14.3. IR (thin film NaCl): 3415, 3077, 2956, 2928, 2858, 1823, 1722, 1641, 1467, 1379, 1366, 1297, 1249, 1168, 1113, 1010. HRMS (ESI) m/z 275.235 [(M+Na)$^+$; calcd for $C_{17}H_{32}O$: 275.235]. Regioselectivity confirmed by GC analysis (chiral B-PH, 125 °C, 2.5 mL/min): 21.30, 22.06 min.

4.3.2.12. 6-(1-Ethyl-allyloxy)-2,4-dimethyl-hex-4-en-3-ol (29A).



Procedure A (no additive) (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether → 7:1 hexanes/ethyl acetate to give 59 mg (56%) of **29A** as a clear oil. R_f=0.30 (6:1 hexanes/EtOAc, $KMnO_4$) (single regioisomer, 95:5 mixture of *S*, *R* and *S*, *S*).

4.3.2.13. 4-(1-Ethyl-allyloxymethyl)-2-methyl-hex-4-en-3-ol (29B).



Procedure B ($PCyp_3$) (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of

$Ni(cod)_2$ (14 mg, 0.05 mmol), $PCyp_3$ (28 μL, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 25 mg (24%) of **29B** as a clear oil R_f=0.46 (6:1 hexanes/EtOAc, $KMnO_4$) (single regioisomer, 55:45 mixture of diastereomers).

Compounds **29A+29B**. Procedure B (PBu_3) (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol), PBu_3 (25 μL, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 19.3 mg (18%) of **29A** and 16 mg (15%) of **29B** as clear oils (**29A**: 50:50 mixture of diastereomers; **29B**: 55:45 mixture of diastereomers).

Compounds **29A+29B**. Procedure B ((*R*)-**31**)[27] (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) (*R*)-**31** (41 mg, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 9 mg (8%) of **29A** and 10 mg (9%) of **29B** as clear oils (**29A**: 30:70 mixture of *S*, *R*:*S*, *S*; **29B**: 72:28 mixture of diastereomers).

Compounds **29A+29B**. Procedure B ((*S*)-**31**)[27] (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) (*S*)-**31** (41 mg, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 10.6 mg (10%) of **29A** and 8.9 mg (9%) of **29B** as clear oils (**29A**: 66:34 mixture of *S*, *R*:*S*, *S*; **29B**: 32:68 mixture of diastereomers).

Compounds **29A+29B**. Procedure B ($FcPPh_2$) (no EtOAc): **27** (69 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol), $FcPPh_2$ (37 mg, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 8.2 mg (7%) of **29A** and 7.2 mg (6%) of **29B** as clear oils (**29A**: 56:44 mixture of *S*, *R*:*S*, *S*; **29B**: 52:48 mixture of diastereomers).

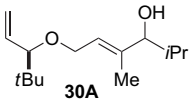
Compound **29A**: $[\alpha]_D^{22}$ −23.4 (*c* 0.86, $CHCl_3$); IR 3429 (b, m), 2962 (s), 2934 (s), 2872 (s), 1465 (m), 1094 (s), 1017 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)—data are for (*S*,*R*) diastereomer—δ 5.68 (ddd, *J*=17.0, 10.5, 8.0 Hz, 1H), 5.55 (t, *J*=6.0 Hz, 1H), 5.20 (dd, *J*=10.5, 1.0 Hz, 1H), 5.18 (dd, *J*=17.0, 1.0 Hz, 1H), 4.10 (dd, *J*=12.0, 6.5 Hz, 1H), 3.90 (dd, *J*=12.0 Hz, 6.5 Hz, 1H), 3.64 (dd, *J*=8.0, 3.0 Hz, 1H), 3.56 (q, *J*=6.5 Hz, 1H), 1.78 (apparent hex, *J*=6.5 Hz, 1H), 1.62 (m, 1H), 1.60 (s, 3H), 1.55 (OH) (br s, 1H), 1.49 (apparent sept, *J*=7.0 Hz, 1H), 0.98 (d, *J*=6.5 Hz, 3H), 0.90 (t, *J*=7.5 Hz, 3H), 0.81 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.3, 139.3, 124.5, 117.2, 83.6, 82.4, 64.5, 31.0, 28.5, 19.6, 18.5, 11.9, 10.0; HRMS *m*/*z* (ESI, M+Na^+) calcd 235.1669 found 235.1670.

The (*S*,*S*) diastereomer was not independently synthesized; however, those peaks, which were resolvable from the (*S*,*R*) diastereomer were ^1H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, *J*=12.0, 5.5 Hz, 1H), 3.94 (dd, *J*=12.0, 7.0 Hz, 1H).

Compound **29B**: IR 3454 (b, m), 2962 (s), 2934 (s), 2872 (s), 1669 (w), 1466 (m), 1319 (m), 1056 (s) cm^{-1}; the diastereomers were not separated, peaks belonging to a specific diastereomer are indicated by subscript A or B, those peaks labeled A were favored with achiral phosphines and (*R*)-**31**. ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.64 (m, 1H), 5.24 (m, 2H), 4.30_A (d, *J*=11.0 Hz, 1H), 4.09_B (d, *J*=11.0 Hz, 1H), 4.04_B (d, *J*=11.0 Hz, 1H), 3.80_A (d, *J*=11.0 Hz, 1H), 3.58 (m, 2H), 2.86 (OH) (d, *J*=7.0 Hz, 1H), 1.80 (m, 1H), 1.69 (apparent t, *J*=7.0 Hz, 3H), 1.63 (M, 1H), 1.52 (m, 1H), 1.03_A (d, *J*=6.0 Hz, 3H), 1.03_B (d, *J*=6.0 Hz, 3H), 0.91_A (t, *J*=7.5 Hz, 3H), 0.89_B (t, *J*=7.5 Hz, 3H), 0.77_A (d, *J*=6.0 Hz, 3H), 0.75_B (d, *J*=6.0 Hz, 3H); no attempt was made to specify which carbon signals belonged to each diastereomer, there are exactly double the number of expected signals for a single compound. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 138.7, 138.7, 127.2, 127.0, 118.0, 117.8, 84.3, 84.0, 83.6, 83.3, 64.5, 64.2, 32.6, 32.5, 28.6, 28.5, 19.8, 19.8, 19.3, 19.2, 13.4, 13.4, 10.1, 9.9; HRMS *m*/*z* (ESI, M+Na^+) calcd 235.1669 found 235.1672.

The relative stereochemistry of **30A** was assigned based on analogy to **29A**.

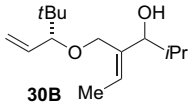
4.3.2.14. 6-(1-*tert*-Butyl-allyloxy)-2,4-dimethyl-hex-4-en-3-ol (30A).



30A

Procedure A (no additive) (no EtOAc): **28** (83 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→8:1 hexanes/ethyl acetate to give 33 mg (28%) of **30A** as a clear oil R_f=0.43 (6:1 hexanes/EtOAc, $KMnO_4$) (single regioisomer, >95:5 (±) *S*,*S*:*S*,*R*).

4.3.2.15. 4-(1-*tert*-Butyl-allyloxymethyl)-2-methyl-hex-4-en-3-ol (30B).



30B

Procedure B ($PCyp_3$) (no EtOAc): **28** (83 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol), $PCyp_3$ (28 μL, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 22 mg (18%) of **30B** as a clear oil R_f=0.55 (6:1 hexanes/EtOAc, $KMnO_4$) (single regioisomer, 42:58 mixture of diastereomers).

Compounds **30A+30B**. Procedure B (PBu_3) (no EtOAc): **28** (83 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL,

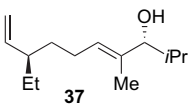
1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol), PBu_3 (25 μL, 0.1 mmol), and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→9:1 hexanes/ethyl acetate to give 15.6 mg (13%) of **30A** and 14.8 mg (12%) of **30B** as clear oils (**30A**: 45:55 mixture of diastereomers; **30B**: 42:58 mixture of diastereomers).

Compound **30A**: IR 3411 (b, m), 2962 (s), 2956 (s), 2872 (s), 2870 (s), 2361 (w), 1465 (m), 1363 (s), 1016 (b, s), 925 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)—data are for (±)-(*R*,*R*) diastereomer—δ 5.72 (ddd, *J*=17.5, 10.0, 8.5 Hz, 1H), 5.52 (t, *J*=6.0 Hz, 1H), 5.25 (dd, *J*=10.0, 1.5 Hz, 1H), 5.14 (dd, *J*=17.5, 1.5 Hz, 1H), 4.08 (dd, *J*=12.5, 6.0 Hz, 1H), 3.86 (dd, *J*=12.5 Hz, 7.0 Hz, 1H), 3.64 (dd, *J*=8.5, 3.0 Hz, 1H), 3.21 (d, *J*=8.5 Hz, 1H), 1.78 (apparent hex, *J*=7.0 Hz, 1H), 1.60 (s, 3H), 1.54 (OH) (d, *J*=3.0 Hz, 1H), 0.99 (d, *J*=7.0 Hz, 3H), 0.88 (s, 9H), 0.82 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 140.3, 139.3, 124.5, 117.2, 83.6, 82.4, 64.5, 31.0, 28.5, 19.6, 18.5, 11.9, 10.0; HRMS *m*/*z* (ESI, M+Na^+) calcd 263.1982 found 263.1982.

The (±)-(*R*,*S*) diastereomer was not independently synthesized; however, those peaks that were resolvable from the (±)-(*R*,*R*) diastereomer were ^1H NMR (500 MHz, $CDCl_3$) δ 4.05 (dd, *J*=12.5, 5.5 Hz, 1H), 3.23 (d, *J*=8.5 Hz, 1H), 0.97 (d, *J*=6.5 Hz, 3H), 0.89 (s, 9H).

Compound **30B**: IR 3462 (b, m), 2956 (s), 2870 (s), 2361 (w), 1670 (b, w), 1465 (m), 1364 (m), 1068 (s) cm^{-1}; the diastereomers were not separated, peaks belonging to a specific diastereomer are indicated by subscript A or B, with achiral phosphines A was the major product. ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (m, 1H), 5.61 (apparent q, *J*=6.5 Hz, 1H), 5.32_A (dd, *J*=10.5, 2.0 Hz, 1H), 5.31_B (dd, *J*=10.5, 2.0 Hz, 1H), 5.21 (d, *J*=17.5 Hz, 1H), 4.29_B (d, *J*=11.0 Hz, 1H), 4.08_A (d, *J*=11.0 Hz, 1H), 3.94_A (d, *J*=11.0 Hz, 1H), 3.74_B (d, *J*=11.0 Hz, 1H), 3.56 (q, *J*=7.0 Hz, 1H), 3.27_B (d, *J*=8.0 Hz, 1H), 3.23_A (d, *J*=8.0 Hz, 1H), 2.85_B (OH) (d, *J*=7.0 Hz, 1H), 2.82_A (OH) (d, *J*=7.0 Hz, 1H), 1.80 (m, 1H), 1.66 (m, 3H), 1.63 (M, 1H), 1.03 (apparent t, *J*=6.5 Hz, 3H), 0.90_B (s, 9H), 0.89_A (s, 9H), 0.76 (apparent t, *J*=6.0 Hz, 3H); no attempt was made to specify which carbon signals belonged to each diastereomer, there are exactly double the number of expected signals for a single compound. ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 137.3, 137.1, 135.9, 135.8, 126.8, 126.7, 119.5, 119.3, 90.6, 90.6, 84.4, 84.3, 65.0, 64.8, 34.6, 34.6, 32.5, 32.4, 26.4, 26.3, 19.9, 19.8, 19.3, 19.3, 13.4, 13.4; HRMS *m*/*z* (ESI, M+Na^+) calcd 263.1982 found 263.1986.

4.3.2.16. 8-Ethyl-2,4-dimethyl-deca-4,9-dien-3-ol (37).

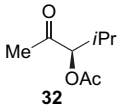


37

Procedure A (no additive) (no EtOAc): **33** (68 mg, 0.5 mmol) was reacted with *i*-PrCHO (90 μL, 1.0 mmol) in the presence of $Ni(cod)_2$ (14 mg, 0.05 mmol) and Et_3B (0.15 mL, 1.0 mmol). Crude material was chromatographed with 15:1 hexanes/diethyl ether→8:1 hexanes/ethyl acetate to give 82 mg (78%) of **37** as a single regioisomer and as a mixture of diastereomers (91:1 *R*, *R*, to *R*, *S*). R_f=0.48 (6:1 hexanes/EtOAc, $KMnO_4$) $[\alpha]_D^{22}$ −0.45 (*c* 0.84, DCM); IR 3391 (b, m), 2959 (s), 2922 (s), 2872 (s), 1640 (w), 1460 (m), 1121 (w), 1010 (s), 911 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)—data are for (*R*,*R*) diastereomer—δ 5.52 (ddd, *J*=17.0, 10.0, 9.0 Hz, 1H), 5.34 (t, *J*=7.0 Hz, 1H), 5.00 (dd, *J*=10.0, 2.0 Hz, 1H), 4.95 (dd, *J*=17.0, 2.0 Hz, 1H), 3.57 (dd, *J*=9.0, 3.0 Hz, 1H), 2.01 (m, 2H), 1.86 (m, 1H), 1.76 (m, 1H), 1.58 (s, 3H), 1.43 (m, 2H), 1.39 (OH) (d, *J*=3.0 Hz, 1H), 1.28 (m, 2H), 0.99 (d, *J*=7.0 Hz, 3H), 0.85 (t, *J*=7.0 Hz, 3H), 0.78 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 143.1, 136.5, 128.2, 114.8, 84.5, 45.7, 34.6, 31.3, 28.0, 25.4, 19.7, 18.9, 11.9, 11.4.

The (*R*,*S*) diastereomer was not independently synthesized; however, those peaks which were resolvable from the (*R*,*R*) diastereomer were ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (ddd, *J*=17.0, 10.0, 9.0 Hz, 1H), 4.10 (dd, *J*=9.0, 3.0 Hz, 1H), 1.07 (d, *J*=6.0 Hz, 3H), 0.72 (d, *J*=6.0 Hz, 3H).

4.3.2.17. (+)-Acetic acid 1-isopropyl-2-oxo-propyl ester ((+)-32).



32

To a cold (0 °C) solution of (−)-**29A** (35 mg, 0.165 mmol) in DCM (1.5 ml) was added NEt_3 (71 μL, 0.51 mmol), Ac_2O (24 μL, 0.25 mmol), and DMAP (2 mg, 0.016 mmol). The mixture was warmed to room temperature and stirred for 1.5 h. At this point it was concentrated in vacuo and filtered through silica eluting with 10:1 hexanes/ethyl acetate. This afforded the crude acetate-protected product, which was carried on to the ozonolysis without purification. The intermediate was dissolved in DCM (3 mL) cooled to −78 °C and exposed to O_3 until the reaction was dark blue. The solution was then degassed with argon and PPh_3 (600 mg) was added. The reaction was allowed to warm to 0 °C over 4 h, and then concentrated in vacuo. The crude material was loaded onto a column (15:1 pentanes/DCM) with a minimal amount of DCM and then eluted with 15:1 pentanes/DCM until separation of PPh_3 and byproducts was complete, then column was flushed with 1:1 pentanes/diethyl ether to give (+)-**32** as a clear oil (15.1 mg, 58% over two steps). $[\alpha]_D^{22}$ +6.7 (*c* 1.01, DCM); ^1H NMR (500 MHz, $CDCl_3$) δ 4.87 (d, *J*=4.0 Hz, 1H), 2.24 (m, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 1.01 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 205.6, 171.0, 83.0, 29.6, 27.2, 20.8, 19.4, 17.0.

Compound (+)-**32**: Following the above procedure, **37** (42 mg, 0.2 mmol) was converted to (+)-**32** (20.5 mg, 66%) over two steps. $[\alpha]_D^{22}$ +7.7 (*c* 1.4, DCM).

Acknowledgements

This work was supported by the National Institute of General Medical Science (GM-063755). We thank Dr. Li Li (MIT Department of Chemistry Instrumentation Facility) for

obtaining mass spectrometry data. The MIT DCIF is supported in part by the NSF (CHE-9809061 and DBI-9729592) and the NIH (1S10RR13886-01).

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