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Ligand Tuning in Asymmetric Hydrovinylation of 1,3-Dienes: A Stereoselective Route to Either Steroid-C_{20} (*S*) or -C_{20} (*R*) Derivatives

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Abstract: 1,3-Dienes derived from steroidal D-ring C_{17}-ketones undergo Ni(II)-catalyzed hydrovinylation to give 1,2- or 1,4-addition of ethylene. Using finely tuned phosphoramidite ligands, it is possible to synthesize either the C_{20} (*R*)- or (*S*)-derivatives without mutual contamination. The proportion of the 1,4-adduct, which is also formed stereoselectively, can be minimized by optimizing the reaction conditions. Because the two alkenes in the resultant dienes have differing steric demands for many potential reactions, and are ideally juxtaposed for further D-ring functionalization, these intermediates could be useful for the preparation of biologically important compounds such as vitamin D analogs and various antitumor steroidal glycosides.

Introduction

A chiral side chain carrying a methyl group is a very common structural motif in many terpenoids, and this side chain is often attached at a stereogenic center of a ring. Examples can be found in simple sesquiterpenes such as juvenile hormone juvabione,[1] or in more complex structures such as pseudopterosins,[2] elisabethin A,[3] ophiobolin C,[4] steroid hormone calcitriol (1-α-2,5-dihydroxyvitamin D_3) and its analogs,[5] antitumor agents cephalostatins,[6] and various cytotoxic steroidal glycosides[7] (Figure 1). Several creative solutions to the problem of installation of these stereogenic centers have been developed over the years, even though no broadly applicable method that uses readily available precursors has emerged.[8] The problem is especially acute for the synthesis of the unnatural 20(*S*)-epimers. Consider, for example, precursors (e.g., **1**) for calcitriol analogs with exocyclic C_{20} (*S*)-configuration, which have been shown to have significant biological activity.[9] These molecules are currently prepared by circuitous routes that involve the equilibration of the aldehyde **2**, obtained from vitamin D_2 and subsequent reactions of the minor isomer isolated from the mixture.[10]

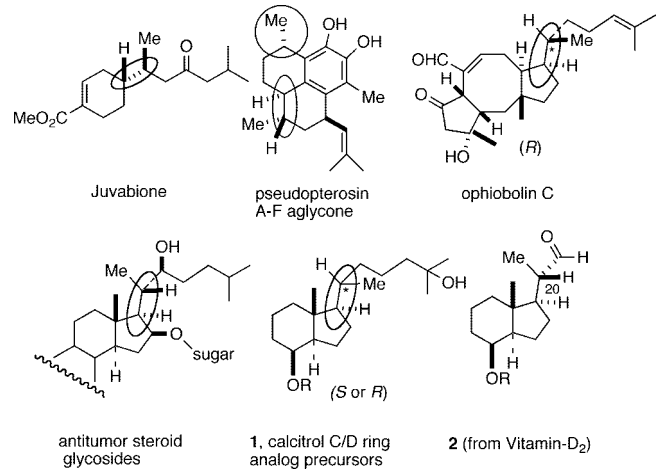

Figure 1. Important classes of natural products with exocyclic chirality carrying a methyl-bearing carbon.

We recently showed[11] that the asymmetric hydrovinylation of readily available 1-vinylcycloalkene offers a potential general

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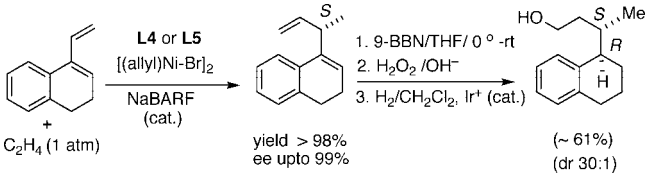
Scheme 1. Exocyclic Stereocenters via Asymmetric Hydrovinylation

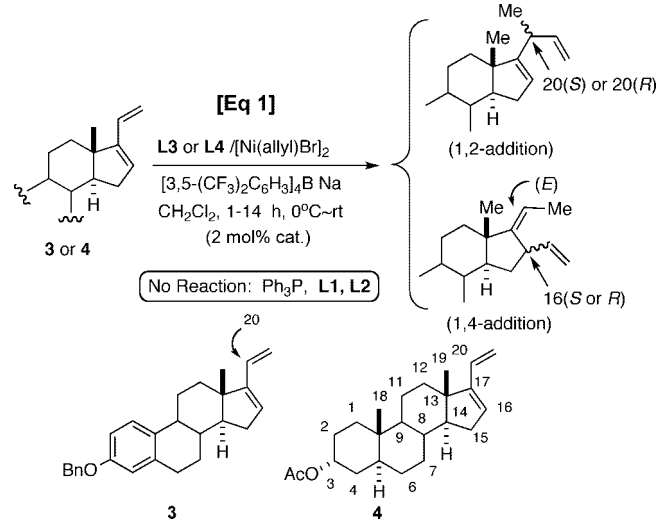


solution to this exocyclic stereochemistry problem (Scheme 1). Both achiral and chiral ligands (Figure 2) carrying suitable hemilabile groups such as *o*-benzyloxyphenyldiphenylphosphine (**L3**), phospholanes (e.g., **L4**), and phosphoramidites (e.g., **L5**) gave nearly quantitative yields of the hydrovinylation products, which could be subjected to further functionalization via diastereoselective reactions.

While attempting to apply the diene hydrovinylation for the functionalization of a steroid D-ring (eq 1), it was observed, that several excellent ligands we had initially employed either did not react (Figure 2: Ph_3P, **L1**, **L2**) or gave mixtures (**L3**, **L4**) of stereo- and regioisomers. We anticipate this lack of selectivity to be a recurring problem in the context of this and other future synthetic objectives in which hydrovinylations of key *chiral* intermediates will be involved. It is entirely conceivable that the inherent diastereoselectivity in such intermediates could be low or even opposite to what would be desired. Thus, from a synthetic perspective, either enhancing the inherent selectivity or overriding such an outcome with the use of a tunable asymmetric catalyst will be a highly desirable goal. Looking for a general solution to this problem, we decided to examine the effect of ligands on the selectivity of the hydrovinylation reactions of 1,3-dienes **3** and **4**, derived from two prototypical steroids, estrone and 3-epiandrosterone. In this paper, we report the results of these studies, which demonstrate that in these steroids it is possible to install, *with complete stereoselectivity*, either C_{20} (*R*) or C_{20} (*S*) configuration by proper choice of ligands and reaction conditions. A limited study of the Ru-catalyzed hydrovinylation of **3** published earlier[12] did not address the key issue of control of stereoselectivity at this stereogenic center.

Results and Discussion

Our initial studies were conducted with the diene **3**, readily prepared from estrone as described previously.[13] Nickel-catalyzed hydrovinylation of **3** under our initially reported



conditions[14] using either [(allyl)NiBr]$_2$/Ph_3P/AgOTf or [(allyl)NiBr]$_2$/(**L**)/(NaBARF) [**L** = **L1**, **L2**; BARF = *tetrakis*-(3,5-*bis*-trifluoromethylphenyl)borate] at temperatures between −55 and 25 °C under 1 atm of ethylene gave no products. This lack of reactivity is quite surprising in this otherwise broadly applicable hydrovinylation protocol. Upon further examination of the reaction using other ligands **L3**−**L12**, most notably the phosphoramidites,[15] under a variety of conditions, it was found that synthetically useful levels of selectivity could be achieved (eqs 1–3). The results are listed in Table 1.

Hydrovinylation using an achiral ligand **L3** (*o*-benzyloxyphenyldiphenylphosphine) gives a mixture of C_{20} (*S*) [**5**] and C_{20} (*R*) [**7**] epimers in a ratio of 1.0:2.5 (entry 1) along with 1,4-adducts **6** and **8** (see the following paragraphs and Supporting Information for details of structural assignments).[16] This inherent selectivity for the formation of the C_{20} (*R*) adduct can be reversed, albeit modestly, with the use of a chiral ligand, the phospholane **L4**, which yields a ratio of 3:1 for **5**:**7** (entry 2). In addition to the formation of the byproducts, **6** and **8** (the 1,4-adducts), these reactions are also complicated by minor isomerization of the primary products giving what appears to be conjugated dienes. The first indication that this unwanted isomerization can be completely blocked and exclusive selectivity for the 20(S) compound can be achieved came from ligands **L5** (*RaScSc*) and **L10** (*ScSc*), which gave a clean mixture of **5** and **6**, with no trace of the 20(*R*)-epimer **7**, the 1,4-adduct **8**, or isomerization products (eq 2, entries 3 and 5−8). Typically, the reaction is done as follows:[15h] a solution of 0.0025 mmol of [(allyl)$_2$NiBr]$_2$ in 0.5 mL of solvent (usually CH_2Cl_2) and a solution of the ligand in 0.5 mL solvent are mixed in a drybox. This solution is added to a suspension of NaBARF (1 equiv

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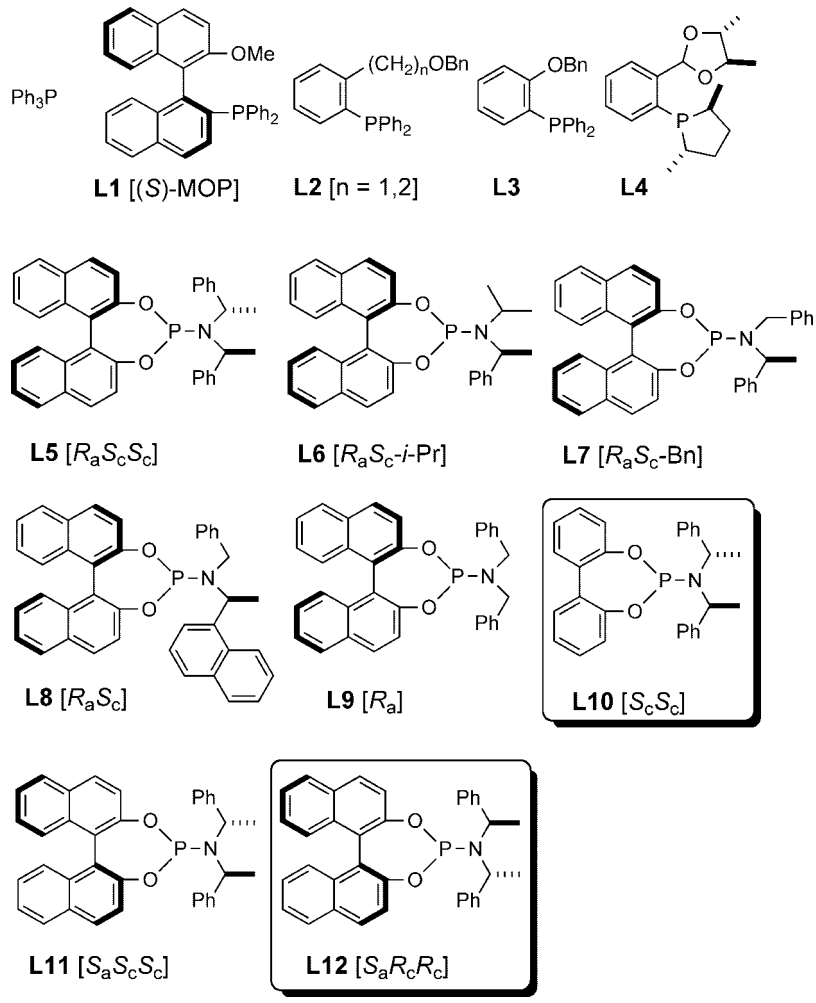


Figure 2. Ligands for hydrovinylation of steroidal 1,3-dienes.

Table 1. Ni-Catalyzed Hydrovinylation of the Steroidal Diene **3**[a]

no.	ligand/conditions	yield (%)	**5**(20*S*):**6**:**7**(20*R*):**8**[b]
1.	**L3** 22 °C, 14 h	76	18:16:45:5[c]
2.	**L4** 22 °C, 14 h	76	45:18:15:14[c]
3.	**L5** (*RaScSc*) 22 °C, 14 h	64	30:70:0:0
4.	**L6** (*RaSc-i-Pr*) 0−22 °C, 14 h	86	∼7:80:0:0[c]
5.	**L10 (*ScSc*) −10 °C, 14 h**	**78**	**83:15:0:0**
6.	**L10** (*ScSc*)		
	(a) CH_2Cl_2, 0−22 °C, 4 h	85	71:38:0:0
	(b) tol.,[d] 0−22 °C, 14 h	66	88:12:0:0
7.	**L10** (*ScSc*) 0−10 °C, 1 h	84[e]	90:10:0:0
8.	**L10** (*ScSc*), 0 °C, 10 min, then warmed to 20 °C, 14 h	82	22:72:0:0
9.	**L11** (*SaScSc*) 22 °C, 14 h	83	trace:trace:75:8[c]
10.	**L12 (*SaRcRc*) 22 °C, 14 h**	**84**	**trace:0:70:30**

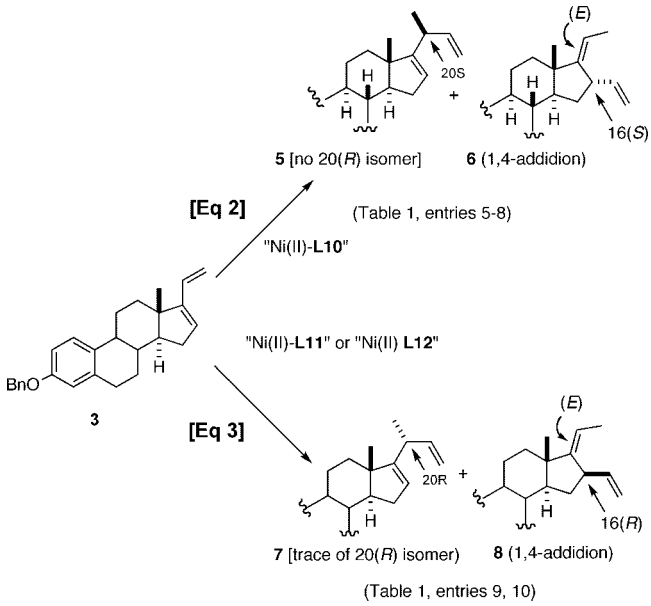
[a] See eqs 1–3. See text for details of the experiments. For entries 1−7, 9, and 10, the reaction was started at the indicated temperature and was warmed to the final temperature with the cold bath in place. [b] Ratio as %; no isomerization products unless indicated. [c] Rest isomerization products (δ 5.60−5.85). [d] No reaction in EtOAc, C_6F_6. [e] Yield based on recovered starting material (40% conversion).

Table 2. Ni-Catalyzed Hydrovinylation of the Steroidal Diene **4**[a]

no.	ligand/conditions	yield (%)	**9** (20*S*):**10**:**11**(20*R*):**12**[b]
1.	**L3** 0−22 °C, 14 h	73	28:15:42:<5[c]
2.	**L5** (*RaScSc*) 22 °C, 14 h	74	75:25:0:0
3.	**L6** (*RaSc-i*-Pr) 22 °C, 14 h	86	12:80:0:0[c]
4.	**L10 (*ScSc*) 0−10 °C, 2 h**	**83**	**80:20:0:0**
5.	**L10** (*ScSc*) 0−22 °C, 4 h	87	68:30:0:0
6.	**L10** (*ScSc*) 0 °C, 10 min, then warmed to 20 °C, 14 h	82	20:80:0:0
7.	**L11** (*SaScSc*) 22 °C, 14 h	81	0:<5:66:10[c]
8.	**L12 (*SaRcRc*) 22 °C, 14 h**	**69**	**0:0:65:35**

[a] See eqs 1, 4, and 5. [b] Ratio as %; no isomerization unless indicated. [c] Contains other olefins (δ 5.60−5.75).

with respect to Ni). After stirring for 1.5 h, the mixture is filtered through a small plug of Celite into a Schlenk flask, which is taken out of the drybox. The catalyst is brought to the appropriate temperature, and under 1 atm of ethylene the substrate is added in 1.2 mL of solution. The mixture is stirred for the times indicated in Tables 1 and 2 and then quenched with saturated ammonium chloride before work up. In the preparatively useful runs (e.g., entry 5 in Table 1 and entry 4 in Table 2), the reaction mixture is maintained at the temperatures and times indicated. Under these conditions the highest proportion of the 1,2-adduct is obtained. For example, in 14 h at −10 °C, 83% of the 20(*S*)-compound was formed from **3** using ligand **L10** (entry 5, Table 1). Attempts to shorten the reaction time by running the reaction at 0−10 °C for 1 h gave a slightly higher proportion (90%) of the desired product, but the conversion remained low (∼40%, entry 7, Table 1). One useful variable was the solvent. Reactions done in toluene (entry 6, Table 1) gave 88% of the desired product in 14 h. Ethyl acetate and hexaflurobenzene gave no products. Mixing the reagents at low temperature (0 °C) and immediately warming the solution to room temperature in 10 min resulted in the



formation of mostly the 1,4-adduct (entry 8). The ratio of the 1,2- vs 1,4-adducts is also dependent on the structure of the ligands. For example, the ligand **L6** with an *N*-*i*-Pr group (or the corresponding *N*-benzyl derivative **L7**) instead of the *N*-α-methylbenzyl substituent of **L5** gave a good yield of the 1,4-adduct **6** (entry 4). Surprisingly, a ligand without α-methylbenzyl substituents (**L9**) gave no product. Ligands derived from (*S*)-binaphthol (**L11** and **L12**) gave 20(*R*)-adduct in moderate yields (eq 3, Table 1, entries 9 and 10), *with only traces (2−3%) of the 20(S)-epimer.*[16] These experimental observations are based on multiple trials, and this lack of reactivity of **L9** complexes is highly reproducible in the hydrovinylation of dienes and as well as in vinyarenes.[15g] One possible explanation for the lack of reactivity of **L9** (vis-à-vis **L10** or **L12**) might be the absence of the Me substitution at the benzylic position, which is essential to limit the degrees of freedom for the *N*-substituent facilitating hemilabile coordination of the Ph-unit as conjectured by Leitner.[17] This would be somewhat akin to the "Thorpe-Ingold" effect, which operates in certain cyclization reactions.

Preparatively, the most useful reactions involve the use of ligands **L10** and **L12**, which give the 20(*R*) or the 20(*S*) compound, respectively, along with minor amounts of a 1,4-adduct (eqs 2 and 3). The highly stereoselective formation of the otherwise scarce C_{20} (*S*)-isomer uncontaminated with the corresponding (*R*)-epimer is particularly noteworthy. Thus, the diene **3** reacts with ethylene (1 atm) in the presence of a catalyst[14,15g,h] prepared from [(allyl)NiBr]$_2$/**L10**/NaBARF (2 mol%) at −10 °C giving 78% yield of hydrovinylation products **5** and **6** (Table 1, entry 5). The hydrovinylation product **5** is identified as the 20(*S*)-derivative by comparison of ^{1}H and ^{13}C NMR spectra with those of a compound described in the literature.[12] The connectivity of atoms in the minor 1,4-adduct **6** is ascertained from the ^{1}H NMR features. The ^{1}H NMR spectrum (500 MHz, $CDCl_3$) shows the most discernible peaks at δ 5.843 (ddd, J = 18, 10, and 8 Hz, 1 H, vinyl, $C_{16}-CH{=}CH_2$), 5.309 (dq, J = 7, 2 Hz, 1 H, vinyl, $C_{20}-H$), 5.062 (s, 2 H, OCH_2Ph), 5.044 (d, J = 18 Hz, 1 H, vinyl, $C_{16}-CH{=}CH^t$ H^c), 4.994 (d br, J = 10 Hz, 1 H, vinyl, $C_{16}-CH{=}CH^t$ H^c), 3.423 (dd, J = 8, 8 Hz, 1 H, $C_{16}-$H), 2.80−3.00 (m, 3 H, benzyl H's), 1.607 (dd, 7 Hz, 1 Hz, 3 H, $C_{20}-CH_3$), 0.860 (s, 3 H, C_{18}). The doublet of quartert at δ 5.309 ($C_{20}-$H), the dd at δ 3.423 for the $C_{16}-$H, and the doublet of doublet at δ 1.607 for the $C_{20}-CH_3$ are especially valuable in identifying this product. The NOESY spectrum indicates proximity of the bisallylic hydrogen ($C_{16}-$H) on the D-ring to the $C_{20}-$Me suggesting an *E*-configuration for the alkene. This is further supported by NOE contact between the vinylic $C_{20}-H$ and C-ring hydrogens rather than the D-ring hydrogens. The stereochemistry (α-vinyl appendage at C_{16}) is deduced from the fact that **6** is *the only other product formed* with the 20(*S*) compound **5** and, thus, must originate from the same allyl-Ni intermediate arising from the α-face addition of the cationic Ni−H to the starting diene (Scheme 2).[18a–c] Further support for this rationale comes from the corresponding *exclusive formation* of the C_{16}-β-vinyl side product (**8**) concomitant with the formation of the C_{20} (*R*)-epimer (**7**) [vide infra]. The most stable conformation for the 1,3-diene is assumed in the construction of the models shown in Scheme 2. It is premature to propose models for these reactions, especially considering the two possible orientations of the square planar complex [**L**∼**X** Ni-(olefin)H]$^+$ are possible (**L** = phosphorus; **X** = hemilabile group: a dioxalane O in **L4** or the **Ph** group attached to the N-benzyl substituent[17]). Clearly each of the two ligands **L10** or **L12** that give respectively the 20(*S*) and the 20(*R*) product, must form a complex which matches the chirality of the starting material, only when the appropriate face of the diene is coordinated, resulting in the high selectivity observed. Support for the aryl group acting as a hemilabile ligand comes from Leitner's DFT-based computational studies on the Ni-phosphoramidite-catalyzed hydrovinylation.[17]

The 20(*R*) epimer **7** is similarly prepared using the ligand **L12** (Table 1, entry 10). The corresponding 1,4-addition product **8** was formed in 25% as the sole side product. Adduct **7** has ^{1}H and ^{13}C spectra closely resembling **5** except for characteristic differences listed below: the C_{20}-methyl in **7** appears as a doublet δ 1.199 (d, J = 7 Hz), 0.029 ppm upfield compared to that for the 20(*S*)-compound **5** (δ 1.228, J = 7 Hz). Similar differences in chemical shifts of 20(*S*)- and 20(*R*)-methyl compounds have been reported in the literature for structurally related compounds with $C_{16}-C_{17}$ unsaturation.[19] We also note that the ^{13}C NMR signal for $C_{20}-CH_3$ for the *R*-derivative also appear at higher field (20*S*: 20.74; 20*R*: 20.28). The chemical shift of C_{16}–*H* in the two compounds also distinguishes the two isomers (**5**: 5.446; **7**: 5.432). The minor product **8** shown in eq 2 is very similar to **6**, yet distinctly different, showing the following diagnostic peaks in the NMR. The C_{20}-vinyl hydrogen in **8** appears at δ 5.259 as a dq compared to the corresponding peak at δ 5.309 (dq, J = 7, 2 Hz, 1 H, vinyl, $C_{20}-H$) in **6**. The other major differences are in the chemical shifts of the allylic hydrogen $C_{16}-$H (**8**: 3.320 ddd, 8 Hz, 8 Hz, 8 Hz; **6**, 3.423, dd, 8 Hz, 8 Hz) and $C_{18}-H_3$'s (**8**:0.844; **6**: 0.860). The almost identical chemical shift of the vinyl $C_{20}-$Me signals (**6**: 1.607; **8**: 1.604) and the significant differences in chemical shifts (δ **6**: 3.423 and **8**: 3.320) and coupling patterns of $C_{16}-$H's in the two compounds (**6**: dd; **8**: ddd) also provide indirect support for these two structures in which the *only difference* is the configuration

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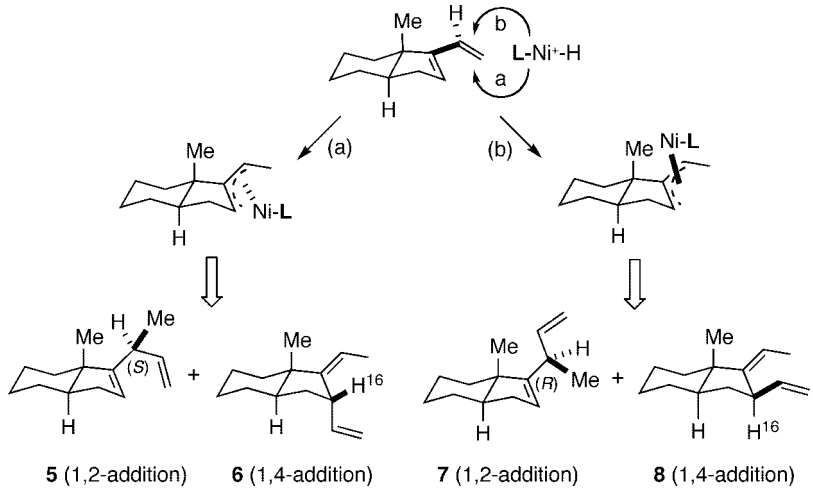
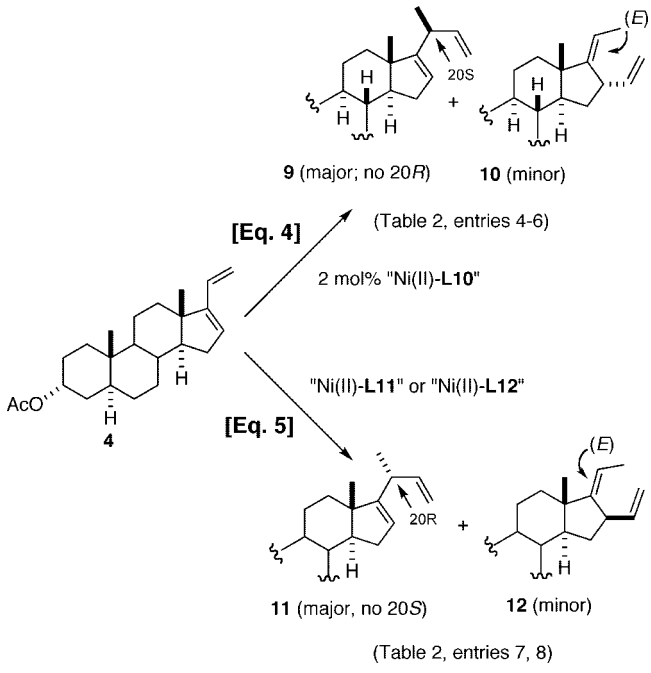
Scheme 2. Origin of 1,2- and 1,4-Adducts in the Hydovinylation Reactions

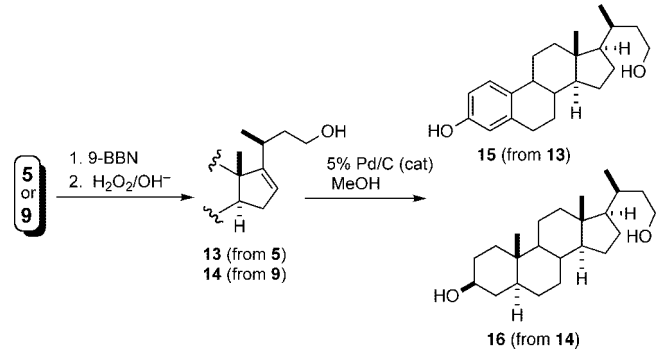


of C_{16}. The upfield shift for $C_{18}H_3$ in the ^{13}C NMR of **8** with a C_{16}-β-substituent compared to the $C_{18}H_3$ in **6** (C_{16}-α-substituent) is also consistent with the γ-effect observed in *cis*- dialkyl substituted cycloalkanes.[20]



Functional group compatibility of the Ni(II)-catalyzed hydrovinylation allows the functionalization of diene **4**, derived from 3-acetylepiandrosterone (eqs 4 and 5). The observed ligand effects parallel the results obtained with the diene **3**. These are listed in Table 2. The C_{20} (*S*) compound **9** and the corresponding C_{20} (*R*) compound **11** are produced *without any mutual contamination* using ligands **L10** and **L12** respectively (entries 4 and 8). As with the estrone derivatives, the C_{20} (*S*) compounds are characterized by the downfield chemical shifts of the C_{20}-CH_3 signals in both the ^1H (**9**: 1.177; **11**: 1.096) and ^{13}C NMR (**9**: 20.66; **11**: 20.22).[16] Among other distinguishing features is the diagnostic chemical shift difference of the C_{16}−H in the

Scheme 3. D-Ring Functionalization via Hydrovinylation Adducts



two epimeric compounds (**9**: 5.376; **11**: 5.360). The NMR features that distinguish the minor products **10** and **12** mirror what is seen for the byproducts, **6** and **8**, from the estrone-derived system. Thus the C_{20}−Me groups appear at δ 1.554 and 1.557 (almost identical) whereas the C_{16}−H's appear at δ 3.335 (dd) and 3.228 (ddd) [significantly different]. The mechanistic rationale outlined in Scheme 2 for the formation of the two sets of compounds applies here as well.

The steroid D-ring can be elaborated in myriad ways using the diene functionality in **5** and **9**. For example, selective hydroboration of the monosubstituted olefin gives an alcohol (**13** or **14**), which could serve as a precursor for more advanced intermediates. Catalytic hydrogenation of each of these alcohols gives a single product, (**15** or **16**), whose structure is inferred as arising from α-face addition of hydrogen from well-precedented steroid examples.[19,21] The endocyclic π-bond (C_{16}−C_{17}) will also be a useful handle for oxygenation of the D-ring, a key feature in many important steroidal glycosides,[7] including potent anticancer agent OSW-1.[8k]

Conclusions

In summary, here we disclose a new highly stereoselective, ligand-dependent protocol for the installation of exocyclic stereocenters in a steroid D-ring via asymmetric hydrovinylation. Phosphoramidites derived from enantiopure (*S*)-1,1′-bisphosphinoxynaphthyl ligands containing (−)-bis[(*R*)-1-phenylethyl]amine (**L12**) gives exclusively 20(*R*)-hydrovinylation adduct, where as enantiomeric ligand (*RaScSc,* **L5**) gives the

(20) Lambert, J. B.; Shurvell, H. F.; Lightner, D. A.; Cooks, R. G. *Organic Structural Spectroscopy*; Printice-Hall: Upper Saddle River, NJ, 1998; p 49.

(21) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435.

20(*S*) product. In the case of the corresponding ligand with the biphenyl scaffolding, **L10**, bis[(*S*)-1-phenylethyl]amine substituent induces 20(*S*)-selectivity. This result is consistent with the observation that the chiral amine component dictates the atropisomeric nature of the fluxional biphenyl unit when the (*SS*)-amine is resident, leading to (*R*) axial chirality at the biphenyl[22] and the attendant 20(*S*)-selectivity in the hydrovinylation reaction. The two alkenes in the resultant diene have differing steric demands for several potential reactions and are ideally juxtaposed for further D-ring functionalization for elaboration along the chain. Such studies are in progress. A slight modification of the reaction also allows the stereoselective preparation of C_{16}-vinyl derivatives.

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Supporting Information Available: Full experimental details for the preparation of the substrates and protocols for the hydrovinylation reactions; ^{1}H and ^{13}C NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA711475F

(22) For a related result in Cu-catalyzed conjugate addition of diethylzinc reagents to enones, see ref 15c.