Pergamon

Tetrahedron 54 (1998) 1117–1130

TETRAHEDRON

PHOSPHINE-DIRECTED STEREO- & REGIOSELECTIVE Ni-CATALYZED REACTIONS OF GRIGNARD REAGENTS WITH ALLYLIC ETHERS

Mary T. Didiuk, James P. Morken[1] and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center

Boston College, Chestnut Hill, Massachusetts 02167

Received 18 August 1997; accepted 26 September 1997

Abstract: Studies on the directed regio- and stereoselective Ni-catalyzed allylic substitution reactions involving methyl- and phenylmagnesium bromides and various acyclic and cyclic allylic ethers are reported. In the presence of a properly positioned internal Lewis base, C-C bonds can be formed catalytically and with excellent levels of selectivity. Internal chelation allows Ni-catalyzed C-C bond forming reactions that are otherwise non-selective, sluggish, or do not occur at all, to proceed to completion readily, in excellent yields, at ambient temperature and with high regio- and stereocontrol. Directed alkene isomerization highlights an especially attractive feature of the metal-catalyzed alkylation strategy: because the initial product contains a prostereogenic site that remains within reach of the internal Lewis base, it can be subjected to additional directed stereoselective manipulations.

I. Introduction

In recent years, the development of catalytic, regio- and stereoselective additions of Grignard reagents to alkenes has been one of the major research goals in these laboratories. Our work in the area of zirconocene-catalyzed alkylations has resulted in the development of useful and complementary ethylmagnesation of acyclic allylic and homoallylic alcohols and ethers,[2] and the diastereo- and enantioselective addition of Et-, Pr-, and BuMgCl to unsaturated heterocycles.[3] The utility of these catalytic enantioselective protocols was recently demonstrated in the context of the first total synthesis of the antifungal agent Sch 38516 (also known as fluvirucin B_1).[4] Zr-catalyzed enantioselective reactions with EtMgCl were later utilized in the catalytic kinetic resolution of unsaturated furans,[5] pyrans,[6] oxepins, oxocenes,[3b] and six-, seven- and eight-membered ring allylic ethers.[7] The Zr-catalyzed reactions present their greatest utility in the resolution arena: it is here that there is notable product generality. As far as this class of catalytic addition reactions are concerned, however, only a narrow range of alkyl groups can be used (*i.e.*, Et-, Pr- and BuMgCl).[8] Furthermore, reactions with the latter two longer chain alkylmetals afford the derived branched adduct: *n*-Pr- and *n*-PrMgCl give rise to the *iso*- and *sec*-alkyl addition product predominantly.

A drawback of Zr-catalyzed carbomagnesations is that only alkylmagnesium halides that carry an "active" β-hydride may be used, since the catalyst is the derived metallacyclopropane.[2c] Consequently, Me-, Ph- or vinylmagnesium halides cannot be utilized in reactions catalyzed by chiral zirconocenes.

As a result, we have been in search of alternative strategies that allow reactions of Grignard reagents with various olefin systems, where a wider range of alkylmetals can be used. We reasoned that Ni-catalyzed alkylations of allylic ethers offer an attractive option, since dialkylnickel complexes readily undergo reductive elimination to afford a C-C bond - such transformations do not require the presence of a β-hydride.[9]

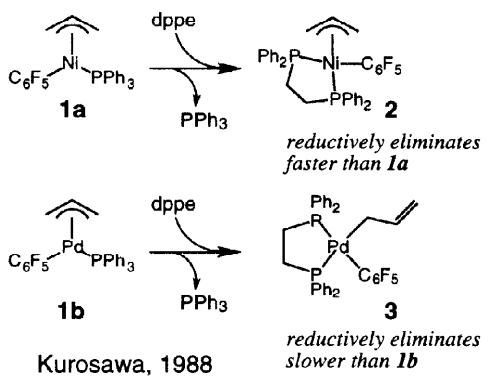
0040-4020/98/$19.00
PII: S0040-4020(97)10212-5

To gain further mechanistic appreciation of this latter class of transformations, first we decided to examine starting materials that would allow us to obtain insight into various subtle interactions that exist between the transition metal and the allylic ether adducts. We decided to increase the conformational rigidity of the Ni-olefin complexes by arming the olefinic substrates with an efficient Lewis basic phosphine. We surmised that the additional substrate-catalyst interaction would lead to enhanced structural organization to afford selectivity or reactivity patterns that would be readily interpretable.[10] In this article, we present details of our studies in connection to regio- and diasteroselective P-directed Ni-catalyzed alkylations of allylic ethers with Grignard reagents.[11]

Previous related mechanistic studies. The experiments outlined herein were inspired by a number of extant mechanistic investigations:

(1) Kurosawa and coworkers reported in 1988 that addition of dppe to **1a** (Scheme 1) leads to the formation of 18-electron η^3-Ni complex **2**, which undergoes dialkyl reductive elimination ~10^8 times faster than **1a**.[12] A similar procedure with the corresponding Pd complex **1b** was shown to lead to the formation of **3**; η^1 complex **3** is more stable than **1b**, indicating that η^3-Pd systems are likely more reactive than the corresponding η^1 complexes.

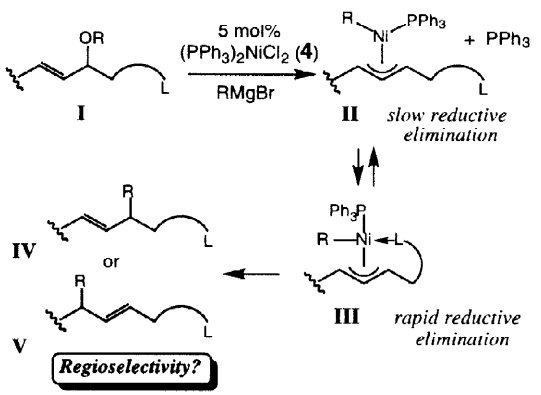
Scheme 1



(2) We were aware of the mechanistic work of Komiya, Yamamoto and Yamamoto,[13] who demonstrated that reductive elimination of dialkylnickel systems proceeds preferentially through pentacoordinate complexes. Specifically, these workers demonstrated that formation of toluene from $Me(Ph)NiL_2$ is facilitated by the presence of excess phosphine.

Initial considerations. As depicted in Scheme 2, we conjectured that an allylic ether that bears an appropriately positioned donor ligand (*e.g.*, a phosphine), in the presence of catalytic amounts of $(PPh_3)_2NiCl_2$ (**4**; 5-10 mol %) and a Grignard reagent should undergo directed - and perhaps regioselective - alkylation. In accord with the higher reactivity of the 18-electron pentavalent intermediates (*vide supra*), C-C bond formation through reductive elimination would be expected to occur preferably through **III**. We therefore set out to establish whether such internal coordination would give rise to high alkylation regioselectivity (**IV** versus **V**). If so, which product isomer would be prevalent? We reasoned that the latter selectivity issue would be particularly informative, since in the absence of a directing unit, catalytic processes are usually not selective.

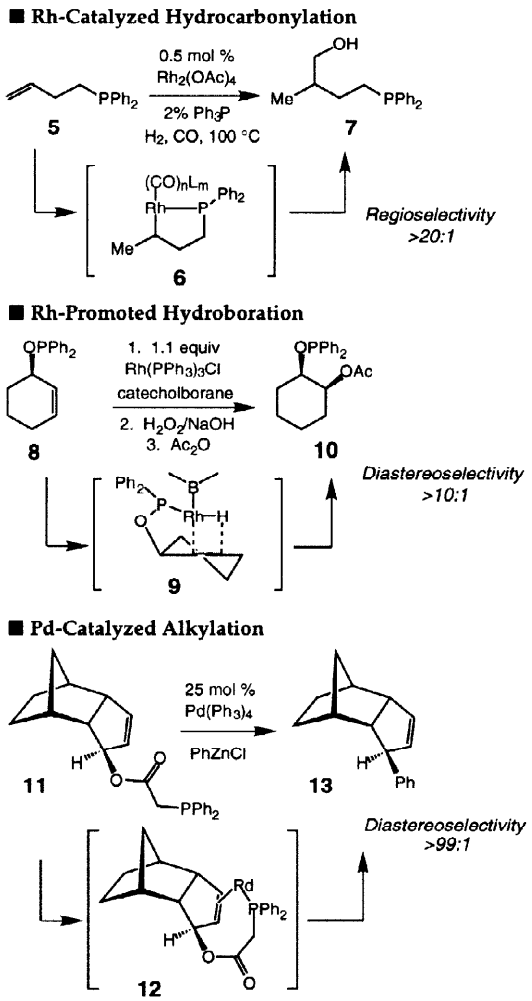
Scheme 2



Our choice of the electron donor (directing) group in this investigation was a phosphine unit, since this class of Lewis basic functions have served admirably in other examinations of directed metal-catalyzed or -mediated processes. Three examples are illustrated in Scheme 3. Perlmutter and coworkers have reported P-directed Rh-catalyzed hydroformylation reactions,[14] where excellent levels of regioselectivity are observed in favor of the branched compound. In the absence of the directing unit, or with substrates that bear the derived non-Lewis basic phosphine oxide, the unbranched adduct is obtained preferentially. Another example has been reported by Evans,[15] where the regio- and stereochemical course of

the Rh-mediated hydroboration reaction is controlled through a suitably disposed chelating group; the derived *tert*-butyl(dimethyl)silyl ether affords, in contrast, a mixture of regio- and stereoisomers. Finally, a paper by Kocovsky illustrates the use of similar principles to control the stereochemical course of a Pd-catalyzed allylic substitution reaction.[16]

Scheme 3



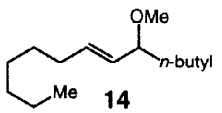
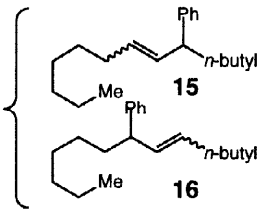
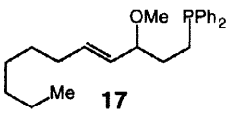
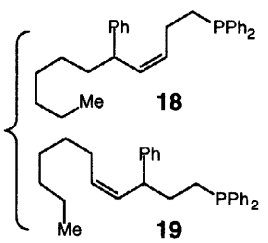
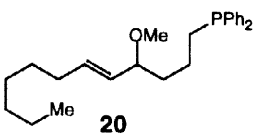
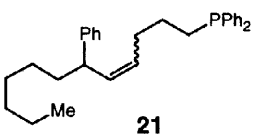
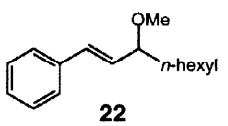
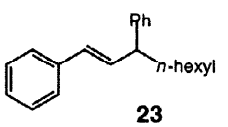
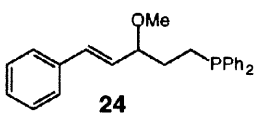
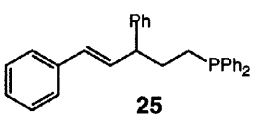
II. Results & Discussion

Directed catalytic regioselective allylic substitutions. As illustrated in Table 1, when allylic ether **14** is treated with 5 mol % $(PPh_3)_2NiCl_2$ (**4**) and 5 equiv PhMgBr for 3 hours (THF, 22 °C), only a 10% total yield of products **15** and **16** is obtained; reaction regioselectivity is non-existent (1:1 mixture of **15** and **16**)[17] and product olefins are a 3:1 *trans*:*cis* mixture. In contrast, when phosphine-containing allylic ether **17** is used (entry 2, Table 1), under identical conditions, **18** is formed regioselectively (**18**:**19**=8:1). Within 3 hours, whereas ether **14** provides **15** and **16** in 10% yield, allylic substitution products from **17** (**18** and **19**) are obtained in 70-75% isolated yield. When the tether length is increased by one methylene unit (entry 3; **20** as substrate), C-C bond formation is more sluggish (24 hours for **20** vs 3 hours with **17**), but somewhat unexpectedly, regioselectivity is *enhanced* to >99:1. With conjugated allylic ether **22**, catalytic alkylation is regioselective in the absence of the internal coordinating group (entry 4); allylic substitution is nonetheless accelerated in the presence of a neighboring phosphine (entry 5; 73% yield with **24** versus 22% yield with **22**).

The influence of the resident Lewis basic phosphine is especially evident in reactions where MeMgBr is used as the alkylating agent. As depicted in Table 2, with substrate **14**, <2% product is detected after 18 hours of reaction time. In contrast, when **17** is subjected to 5 equiv MeMgBr and 5 mol % **4** (THF, 22 °C), **26** is obtained in 74% isolated yield. Moreover, C-C bond formation occurs with complete control of regiochemistry and the product alkene is exclusively *cis* (compare to entry 2 of Table 1 for related reaction of PhMgBr).

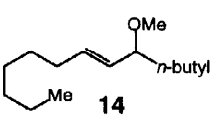
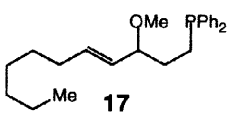
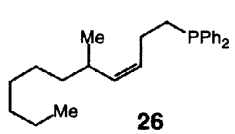
It is worthy of note that $(PPh_3)_2NiCl_2$ (**4**) was selected as precatalyst, since the aforementioned mechanistic considerations dictate that the choice of the Ni catalyst is critical if a directed process is desired. A precatalyst bearing a tethered bidentate ligand (*e.g.*, $(dppe)NiCl_2$) would not require internal chelation: alkylation in such a case would proceed readily through a pentavalent intermediate similar to **2** (Scheme 1) to afford alkylation products, albeit non-selectively. Indeed, treatment of **14** with PhMgBr and 5 mol % $(dppe)NiCl_2$ leads to the facile formation of an equal mixture of product regioisomers **15** and **16** in >80% yield; the bidentate ligand presumably preempts chelation of the internal directing unit. Interestingly, when **17** is treated to identical conditions, <10% of the desired allylic substitution products are isolated (12 h).

Table 1. Ni-Catalyzed Allylic Substitution of Acyclic Ethers with PhMgBr. [a]

entry	substrate	product	regioselec. [b]	c:t [c]	yield (%),[d] time
1	 **14**	 **15** **16**	**15:16** = 1:1	1:3	10, 3 hrs
2	 **17**	 **18** **19**	**18:19** = 8:1	5:1	70, 3 hrs
3	 **20**	 **21**	>99:1	1:1	70, 24 hrs
4	 **22**	 **23**	>95:5	>95:5	22, 2 hrs
5	 **24**	 **25**	>95:5	>95:5	73, 2 hrs

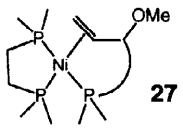
a. Conditions: 5 mol % $(Ph_3P)_2NiCl_2$, 5 equiv arylMgBr, THF, 22 °C. *b.* Regioselectivity determined by GLC or ^1H NMR analysis, in comparison with authentic materials. *c.* Olefin isomer ratios determined through analysis of 300 MHz ^1H NMR spectra. *d.* Isolated yield after purification through silica gel chromatography.

Table 2. Ni-Catalyzed Allylic Substitution of Acyclic Ethers with MeMgBr. [a]

entry	substrate	product	regioselec. [b]	c:t [c]	yield (%),[d] time
1	 **14**	NO REACTION			-- 18 hrs
2	 **17**	 **26**	>99:1	<5:>95	73, 18 hrs

a.-d. See Table 1.

The reason for this unexpected lack of reactivity when (dppe)$NiCl_2$ is used with a substrate that bears an internal phosphine **17** may be due to formation of a complex such as **27**, which is expected to render the transition metal significantly less reactive. Oxidative insertion of Ni to afford the derived η^3 π-allyl complex would involve an unstable 20-electron system, and the corresponding η^1 16-electron complex is predicted to be less reactive.



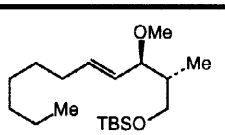
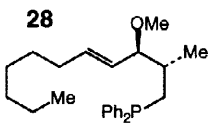
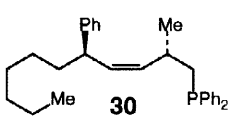
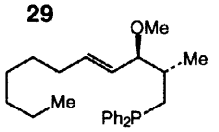
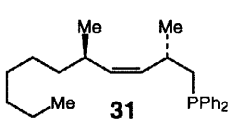
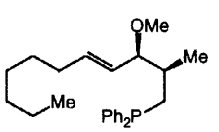
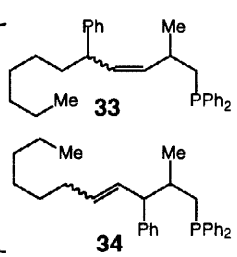
27

Effect of local chirality on catalytic substitution reactions. The data in Tables 1 and 2 demonstrate that the presence of a Lewis basic group within the substrate structure plays a critical role in determining both the reactivity and selectivity of the catalytic substitution reactions. A tell-tale sign of the purported P-Ni association is that local chirality plays a crucial role in the outcome of this class of reactions.[2b-c] Results of our studies on the Ni-catalyzed reactions of allylic ethers **28**, **29** and **32** are summarized in Table 3.

As expected, and as illustrated in entry 1 of Table 3, silyl ether **28** is recovered unchanged after treatment with 5 mol % **4** and five equiv PhMgBr (12 h). Phosphine-containing allylic ether **29**, on the other hand, reacts smoothly to afford **30** in 85% isolated yield and with excellent control of regio-, diastereo-, and olefin stereochemistry (entry 2). Similarly, catalytic reaction of **29** with MeMgBr proceeds with complete control of selectivity. When allylic ether isomer **32** is treated to Ni-catalyzed reaction conditions with PhMgBr, an equal mixture of regio- and diastereoisomers is obtained in 85% yield after chromatography. As the data in Table 3 show, in spite of the low levels of selectivity observed with **32**, this reaction occurs at a rate superior to those of **29**, suggesting that lack of phosphine-Ni association may not be responsible for the diminished levels of regio- and stereochemical control.

Proof of stereochemistry. The stereochemical identity of unsaturated phosphines **30** and **31** was determined through comparison with authentic materials that were synthesized by independent routes.

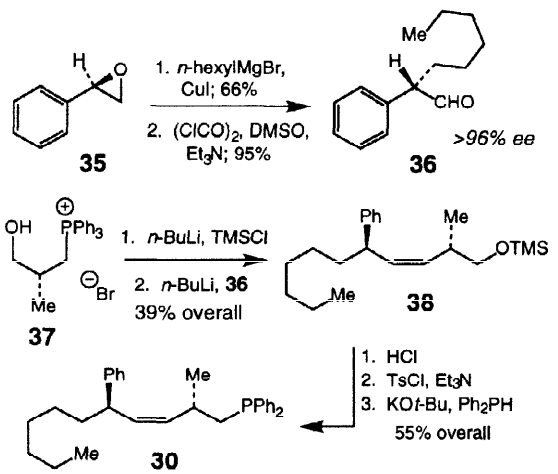
Table 3. Ni-Catalyzed Reactions of Functionalized Allylic Ethers with Ph- and MeMgBr. Effect of Local Chirality on Selectivity.[a]

entry	substrate	Grignard reagent	product	regioselect.	c:t[b]	ds[c]	yield (%)[d] time
1	 **28**	PhMgBr	NO REACTION				-- 12 hrs
2	 **29**	PhMgBr	 **30**	>99:1	>49:1	10:1	85 6 hrs
3	 **29**	MeMgBr	 **31**	>99:1	>49:1	>49:1	75 12 hrs
4	 **32**	PhMgBr	 **33** **34**	1:1		1:1	85 3 hrs

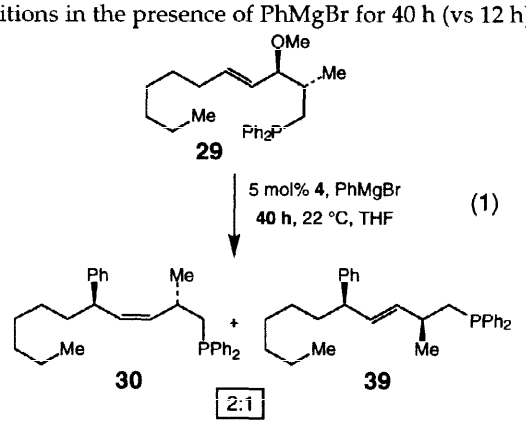
a.-d. See Table 1.

The example shown below for **30** (entry 2, Table 3) is illustrative (for additional examples see the Experimental section). Syntheses of authentic materials typically involved commercially available non-racemic compounds, such as epoxide **35** and phosphonium salt **37**.[18] Derivatization and coupling through a Wittig olefination readily afforded the desired *cis*-alkene **30**. Authentic isomeric adducts were thus prepared and used to establish degrees of selectivity in the Ni-catalyzed processes.

Scheme 4



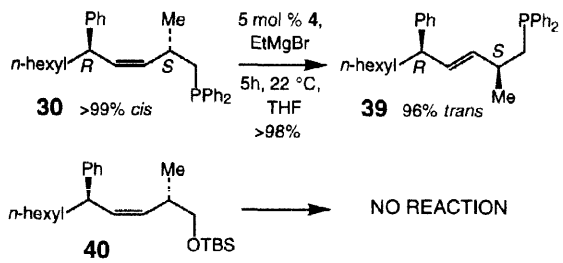
Directed Ni-catalyzed alkene isomerization. The data illustrated in Table 3 indicate that Ni-catalyzed allylic substitutions with Ph- and MeMgBr afford *cis*-olefin products exclusively or with high selectivity. We find, however, that prolonged reaction times lead to alkene isomerization and gradual formation of the corresponding *trans*-alkenes. For example, as shown in eq 1, treatment of **29** to the aforementioned reaction conditions in the presence of PhMgBr for 40 h (vs 12 h)



affords a 2:1 mixture of **30** and **39**. Identical results are obtained with MeMgBr as the alkylating agent.

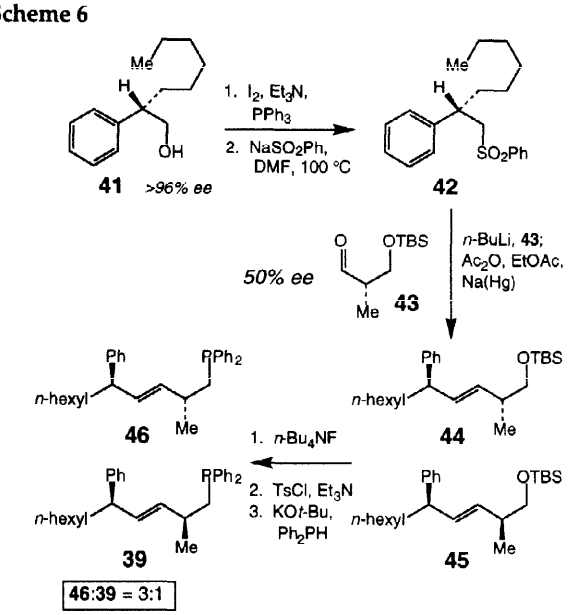
The olefin isomerization shown in eq 1 is Ni-catalyzed; it is facilitated by the presence of an appropriately-positioned directing group, and can afford *trans*-alkenes readily and with excellent selectivity. The example shown in Scheme 5 is illustrative. When **30** is subjected to 5 mol % **4** in the presence of five equiv EtMgCl at 22 °C, **39** is obtained with 96:4 *trans*:*cis* selectivity in >98% yield after five hours. In contrast, when silyl ether **40** is subjected to these reaction conditions, the starting material is recovered unchanged as a *cis*-olefin.

Scheme 5



Proof of stereochemistry. The stereochemical identity of *trans*-alkene **39** was determined through synthesis of an authentic mixture of **39** and its corresponding anti diastereomer **46**.Conversion of non-

Scheme 6

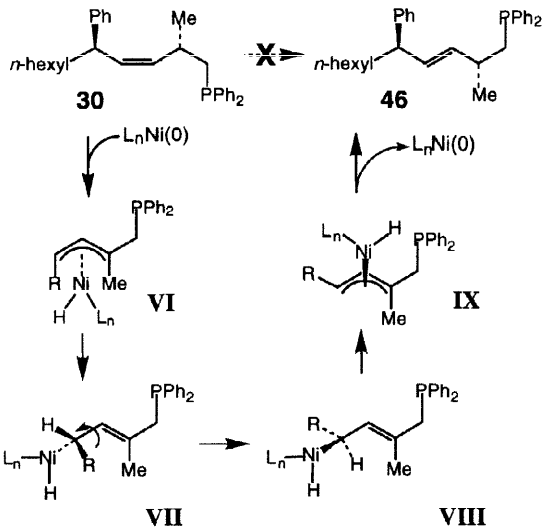


racemic alcohol **41** (see Scheme 6) to sulphone **42** was followed by coupling with non-racemic **43** (50% ee)

leading to the formation of a 3:1 mixture of **44**:**45**, which was then converted to the same isomeric mixture of **46** and **39**.

A critical observation in connection to the Ni-catalyzed directed olefin isomerizations shown in eq 1 and Scheme 5 is that in the final product *neither of the stereogenic centers is inverted.* This observation indicates that hydrido-metal-allylic complexes are probably not involved as intermediates in the olefin isomerization process. That is, if formation of *trans*-alkene occured as depicted in Scheme 7 (through abstraction of an allylic hydride, rotation around a C-C σ bond in the η^1 complex, reformation of the η^3 system and repositioning of the allylic hydride), phosphine **46** - and *not* **39** - would be the predominant diastereomer.[19]

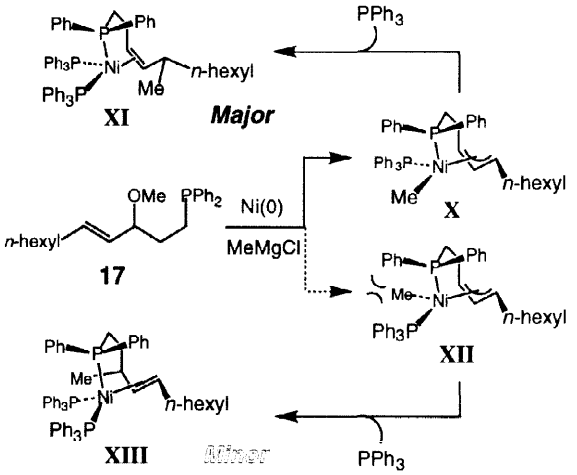
Scheme 7



Catalytic allylic substitutions with C_6D_5MgBr (5 mol % **4**) or alkene isomerization of **30** to **39** with C_2D_5MgBr results in <2% deuterium incorporation; even with 30 or 100 mol % **4**, and in the presence of the above labeled Grignard reagents, <2% labeling is detected. Furthermore, in addition to EtMgBr, Ph- and MeMgBr can effect the aforementioned alkene isomerization. It is therefore unlikely that Ni-H addition followed by β-hydride elimination represents the major pathway for directed Ni-catalyzed conversion of *cis*- to *trans*-alkenes.

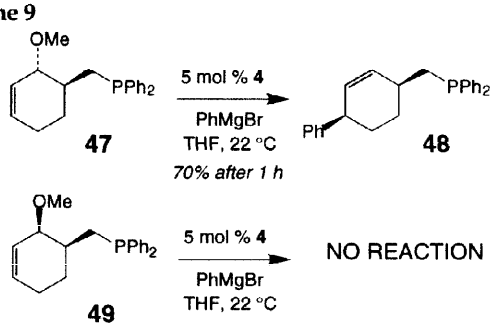
Proposed mechanism for directed catalytic allylic substitutions. It is plausible that directed Ni-catalyzed alkylation reactions described herein proceed through a metal-π-allyl complex, such as **X** or **XII** (Scheme 8). The stereochemical principles on which this proposal is based on, are: (i) anti insertion of the transition metal into the allylic C-O bond, (ii) syn reductive elimination of the resulting π-allyl-Ni-alkyl complex.[20]

Scheme 8



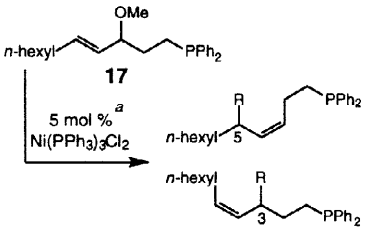
The stereochemical preferences suggested above are supported by Ni-catalyzed allylic substitution reactions of cyclic ethers **47** and **49** (Scheme 9). Whereas reaction of **47** affords **48** in 70% yield in one hour with >95% diastereo- and regioselectivity (5 mol % **4**, 22 °C, THF), subjection of **49** to the same conditions results in the complete recovery of the starting material.

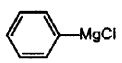
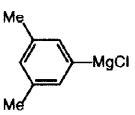
Scheme 9



Intermediates **X** and **XII** in Scheme 8 are proposed, since positioning of the internal phosphine in the apical site of the square pyramidal complex, where the PPh_3 is *trans* to an alkyl group, is in accord with the previously suggested mechanistic paradigms.[19] It is tenable that the observed trends in regioselectivity, as suggested by molecular models, are due to unfavorable steric interactions in complex **XII** between phenyl groups of the tethered diphenylphosphine and the bound PPh_3 group;

Table 4. Regiochemical Control In Directed Ni-Catalyzed Allylic Substitutions.[a]



entry	RMgCl	C5 : C3[b] (yield)[c]
1	MeMgCl	>99:1 (70%)
2		8:1 (70%)
3		4:1 (78%)

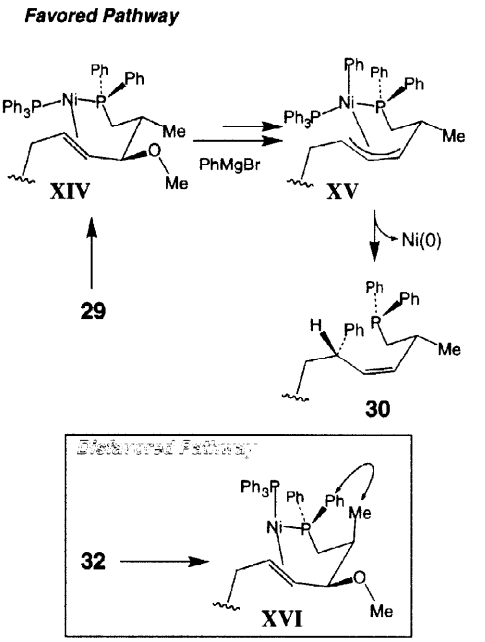
a-c. See Table 1

such interactions exist to a lesser extent in **X**. The hypotheses proposed within Scheme 8 imply that the minor allylic substitution pathway affords the *trans*-alkene product. Consistent with this contention, reaction of PhMgBr with **17** proceeds with lower levels of regio- *and* olefin stereocontrol compared to processes where MeMgBr is used (compare entries 2 of Tables 1 and 2). Lack of control of alkene stereochemistry in the reaction of **20** with PhMgBr may be due to the longer reaction times required for the completion of reaction (entry 3, Table 1).

In support of the aforementioned mechanistic picture, we find that regiocontrol in the Ni-catalyzed allylic substitution varies as a function of the steric bulk of the alkylmagnesium halide. Thus, as illustrated in Table 4, whereas with MeMgBr complete control of regiochemistry is achieved, with meta-xylyl system (entry 3), only modest levels of regiochemical control are achieved. As the size of the alkyl group is increased, preference for complex **X** over **XII** is reduced and regioselectivity suffers. It merits mention that observations in connection to directed Ni-catalyzed hydride addition to allylic ethers can be readily explained by the present mechanism schemes as well.[21]

The reaction pathway described allows us to propose a rational explanation for the observations made in connection to *stereoselective* Ni-catalyzed allylic substitutions of **29** and **32** (cf. Table 3). As illustrated in Scheme 10, substrate isomer **29** can easily form the corresponding π-allyl-Ni complex **XV**; subsequent reductive elimination affords final product **30** with excellent selectivity. In contrast, intramolecular Ni complex derived from diastereomer **32**, **XVI**, would suffer from destabilizing steric interactions. As a result, with the latter substrate, other metal-alkene complexes that lead to the formation of alternative regio- and stereoisomers, become energetically accessible, causing a notable diminution in selectivity. Reactions of diastereomer **32** likely still involve the resident phosphine, as the reaction proceeds readily, albeit non-selectively.

Scheme 10



III. Conclusions

The studies detailed in this article demonstrate that, with an appropriately-positioned directing group, Ni-catalyzed allylic substitution reactions involving Grignard reagents and acyclic allylic ethers can occur with excellent regio- and stereoselectivity. The structural organization that is gained from the additional point of association between the transition metal and the substrate structure is undoubtedly responsible for the effective control of various selectivity issues in this C-C bond forming process. The principles gleaned from the present studies are at present being exploited in the design and development of new *enantioselective* and catalytic C-C bond forming reactions.

Experimental Section

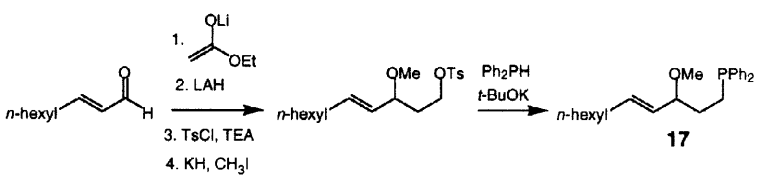
General. Infrared (IR) spectra were recorded on a Perkin Elmer 781 spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on either a Varian Unity 300 (300 MHz), Varian GN-400 (400 MHz) or Varian Unity 500 (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on either a Varian Unity 300 (75 MHz), Varian GN-400 (100 MHz) or Varian Unity 500 (125 MHz) with complete proton decoupling. Where appropriate, the ^{13}C-^{31}P coupling is reported in parentheses following the chemical shift. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.0 ppm). Combustion microanalyses were performed by Robertson Microlit Laboratories (Madison, New Jersey). High resolution mass spectral analysis were performed by the Mass Spectra Laboratory at University of Illinois.

All reactions were conducted in oven (135 °C) and flame-dried glassware under an inert atmosphere of dry argon or nitrogen. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl. Ethyl- and phenylmagnesium bromide were prepared from the distilled bromoalkanes and unpurified Mg (turnings purchased from Aldrich). In order to minimize the amount of haloalkanes remaining in solution, a two-fold excess of magnesium was used in these preparations. Methylmagnesium bromide was purchased from Aldrich chemical company as a 1.0 M solution in THF/toluene and was titrated immediately before use. $(Ph_3P)_2NiCl_2$ and (dppe)$NiCl_2$ were purchased from Strem Co. and handled in a glovebox under an argon atmosphere; (dppb)$NiCl_2$ was prepared according to published procedures[22] and stored in the drybox. Styrene oxide **35** and phosphonium salt **37** were purchased from Aldrich Chemical Co. and were used without further purification.

Representative experimental procedure for the directed nickel-catalyzed allylic substitution of allylic ethers. In a glovebox, 8.8 mg (13 mmol) of $(Ph_3P)_2NiCl_2$ was transferred to a 10 mL flame-dried round-bottom flask. The flask was then sealed with a rubber septum, removed from the glovebox and was kept under an argon atmosphere. 1-Diphenylphosphino-3-methoxy-trans-4-undecene (**17**, 100 mg, 0.27 mmol) was dissolved in 1.7 mL of anhydrous THF. This solution was added by cannula to the original flask containing the catalyst; the solution was allowed to cool to 0 °C (ice). MeMgBr (1.0 mL, 1.3 mmol) was added in a dropwise fashion, and the mixture allowed to stir at 22 °C for 18 h under argon atmosphere. The resulting solution was cooled to 0 °C and quenched by the addition of 1.0 mL of H_2O. After addition of another 15 mL of H_2O, the mixture was washed with 3x35 mL of CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$. Removal of the drying agent through filtration, followed by solvent evaporation *in vacuo*, afforded a yellow oil. Silica gel chromatography with 15:1 hexanes:EtOAc as eluent afforded 69 mg of **26** as a colorless oil (0.19 mmol; 73% yield).

5-Phenyl-*trans*-6-tridecene and 7-phenyl-*trans*-5-tridecene (15 and 16). IR (KBr): 2957 (s), 2926 (s), 2872 (s), 1453 (m), 966 (m), 698 (s) cm^{-1}; ^1H NMR (**15+16**): δ 7.35-7.20 (5H, m, aromatic C**H**), 5.57 (1H, dd, J=15.0, 7.3 Hz, vinylic CCHC**H**) 5.45 (1H, dt, J=15.0, 6.1 Hz, vinylic CH_2CH), 3.20 (1H, q, J=7.3, benzylic C**H**), 2.03 (2H, q, J=5.9 Hz, allylic CH_2), 1.69 (2H, q, J=7.3 Hz, allylic CH_2), 1.45-1.24 (12H, m, aliphatic CH_2), 0.91 (3H, t, J=7.3 Hz, CH_3), 0.90 (3H, t, J=7.1 Hz, CH_3); ^{13}C NMR (major isomer): δ 145.7, 134.0, 131.0, 128.3, 127.5, 125.8, 48.9, 35.9, 32.6, 31.7, 29.8, 29.3, 28.8, 27.5, 22.6, 14.0 (2C). HRMS Calcd for $C_{19}H_{30}$ requires 258.2347, found 258.2348.

Preparation of starting material 17. As illustrated below, aldol reaction on *trans*-nonenal followed by reduction, tosylation, methylation and displacement of the tosyl group with diphenylphosphinopotassium[23] provides the desired starting material **17**.



1-Diphenylphosphino-5-phenyl-*cis*-3-undecene (18). IR (KBr): 3070 (m), 2925 (br m), 2854 (m), 1433 (m), 738 (m), 695 (m) cm^{-1}; ^1H NMR: δ 7.65-7.12 (15H, m, aromatic CH), 5.60-5.44 (2H, m, vinylic CH), 3.4 (1H major alkene isomer, q, J=8.3 Hz, benzylic CH), 3.35 (1H minor alkene isomer, q, J=7.0 Hz, benzylic CH), 2.30-2.10 (4H, m, allylic CH_2 and CH_2P), 1.40-1.20 (10H, broad m, aliphatic CH_2), 0.91 (3H, t, J=6.6 Hz, CH_3); ^{13}C NMR (major): δ 126-134 (20C), 43.4, 37.0, 31.7, 29.2, 28.2 (d, J_{PC}=12.4 Hz), 27.5, 24.0 (d, J_{PC}=16.8 Hz), 22.6, 14.0. HRMS Calcd for $C_{29}H_{35}P$ requires 414.2476, found 414.2475.

Proof of structure for 18. The ^1H NMR spectrum of the derived phosphine oxide (3.0 eq H_2O_2 in CH_2Cl_2) was examined, since the vinylic protons of the reaction product (**18** and **19**) exhibit overlapping peaks in the proton spectrum (400 MHz, C_6D_6). Irradiation of the major benzylic proton (phosphine oxide) results in the collapse of one of the vinylic protons from a triplet to a doublet (J=10.5 Hz); this observation indicates that the major compound bears an alkene with *cis* stereochemistry. The regiochemistry of alkylation was determined by GLC analysis of the alcohols obtained from ozonolysis/reduction of the reaction product. In this case, only the alcohols arising from non-phosphine-containing fragments are recovered. Presumably, ozone oxidizes the diphenylphosphine group to its corresponding oxide which cannot be analyzed by GLC.

1-Diphenylphosphino-6-phenyl-4-dodecene (21). IR (KBr): 3070 (m), 2926 (m), 1480 (m), 1433 (s), 739 (s), 696 (s) cm^{-1}; ^1H NMR (C_6D_6): δ 7.50-7.34 (5H, m, aromatic CH), 7.25-7.05 (10H, m, aromatic CH), 5.62 (1H, dd, J=15.2, 7.7 Hz, vinylic CHCH), 5.37 (1H, dt, J=15.6, 7.0 Hz, vinylic CH_2CH), 3.20 (1H, q, J=7.7 Hz, benzylic CH), 2.09 (2H, q, J=6.6 Hz, allylic CH_2), 2.00-1.90 (2H, m, CH_2P), 1.4-1.8 (2H, m, CH_2CH_2P), 1.40-1.20 (10H, broad m, aliphatic CH_2), 0.91 (3H, t, J=6.7 Hz, CH_3); ^{13}C NMR (reported for the derived phosphine-oxide): δ 136.0, 131.5 (J_{PC}=2.0 Hz), 130.7 (J_{PC}=2.9 Hz), 130.6 (J_{PC}=2.9 Hz), 128.6 (J_{PC}=11.6 Hz), 128.4, 128.3, 128.2, 127.3, 125.9, 48.9, 35.9, 33.4 (J_{PC}=15.5 Hz), 31.7, 29.3, 29.2, 27.6, 22.6, 21.0 ($J_{P\text{-}C}$=3.9 Hz), 14.0. HRMS Calcd for $C_{30}H_{37}P$ requires 428.2632, found 428.2633.

1-Diphenylphosphino-5-methyl-*cis*-3-undecene (26). IR (KBr): 2955 (m), 2924 (s), 2854 (m), 1434 (m), 737 (m), 695 (s) cm^{-1}; ^1H NMR: δ 7.40-7.25 (10H, m, aromatic CH), 5.37 (1H, dt, J=10.7, 6.6 Hz, vinylic CH_2CH), 5.10 (1H, t, J=10.2 Hz, vinylic CHCH), 2.40-2.00 (5H, m, allylic CH_2, allylic CH and CH_2P), 1.30-1.00 (10H, broad m, aliphatic CH_2), 0.85 (3H, d, J=6.6 Hz, $CHCH_3$), 0.85 (3H, t, J=6.8 Hz, CH_2CH_3); ^{13}C NMR: δ 133.8 (d, J_{PC}=19.2 Hz), 132.8 (d, J_{PC}=2.7 Hz), 132.6 (d, J_{PC}=2.8 Hz), 128.5, 128.4 (d, J_{PC}=16.5 Hz), 128.4 (d, J_{PC}=8.3 Hz), 128.4, 127.9 (d, J_{PC}=13.7 Hz), 37.5, 31.8 (d, $J_{P\text{-}C}$=19.2 Hz), 29.4, 28.6 (d, J_{PC}=11.0 Hz), 27.4, 24.0, 23.9, 22.6, 21.2, 14.1. Anal. Calcd for $C_{24}H_{33}P$: C, 81.78; H, 9.44. Found: C, 81.98; H, 9.50.

Proof of structure for 26. Olefin stereochemistry was determined to be cis by analysis of the vinylic coupling constant (J=10.7 Hz). The regiochemistry of alkylation was determined by GLC analysis of the alcohols obtained from ozonolysis/reduction of the reaction product.

(*S,R*)-1-Diphenylphosphino-2-methyl-5-phenyl-*cis*-3-undecene (30). IR (KBr): 2956 (m), 2925 (br m), 2893 (m), 2856 (m), 1430 (m), 739 (m), 696 (m) cm^{-1}; ^1H NMR: δ 7.50-7.10 (15 H, m, aromatic CH), 5.45 (1H, t, J=10.0 Hz, vinylic C_6H_5CHCH), 5.33 (1H, t, J=10.5 Hz, vinylic $C_6H_5CHCHCH$), 3.25 (1H ,m, benzylic CH), 2.68 (1H, m, allylic $CHCH_3$), 2.10 (1H, ddd, J=13.4, 5.80, 1.80 Hz CH_2P), 1.98 (1H, ddd, J=13.5, 8.4, 1.0 Hz, CH_2P), 1.50 (2H, m, $C_6H_5CHCH_2$), 1.20-1.29 (8H, broad m, aliphatic CH_2), 1.19 (1H, d, J=6.60 Hz, $CHCH_3$), 0.91 (3H, t, J=6.70 Hz, CH_3); ^{13}C NMR: δ 135.5, 133.1, 133.0, 127.3, 127.2, 125.8, 125.7, 132.0, 48.6, 43.4, 37.2 (d, J_{PC}=20.0 Hz), 36.6, 31.8, 29.6, 29.2, 27.5, 22.6 (d, J_{PC}=24.0 Hz), 14.1. HRMS for $C_{30}H_{37}P$ (mixture of cis and trans isomers) requires Calcd: 428.2627, found 428.2632.

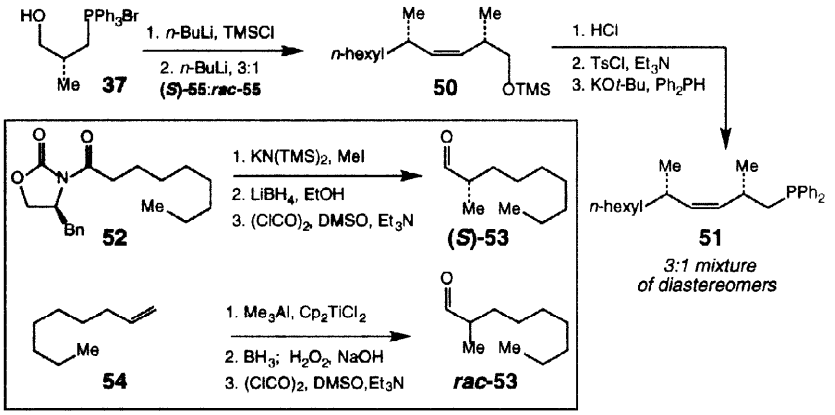
Treatment of **13** with O_3 and subsequent $NaBH_4$ affords 2-phenyl-octan-1-ol. Comparison of the corresponding (*S*)-Mosher's ester (^1H NMR) with an optically pure authentic sample and with authentic racemic mixture is illustrated below. The derived (*S*)-MTPA ester shows a 10:1 mixture of diastereomers, indicating the same level of stereocontrol in the formation of **30** (from **29**).

(*S,R*)-1-Diphenylphosphino-2,5-dimethyl-*cis*-3-undecene (31). IR (KBr): 2955 (3), 2924 (br s), 2869 (m), 2854 (m), 1455 (m), 1434 (s), 1095 (m), 762 (m), 739 (s), 695 (s) cm^{-1}; ^1H NMR: δ 7.38-7.24 (10H, m, aromatic CH), 5.18 (1H, t, J=10.0 Hz, $CHCH(CH_3)CH_2P$), 5.06 (1H, t, J=10.5 Hz,$CHCH(CH_3)CH_2P$), 2.46 (1H, m, allylic $CH(CH_3)CH_2P$), 2.00 (3H, m, CH_2CH_2CH, CH_2P), 1.10 (10H, broad m, aliphatic CH_2) 1.05 (3H, d, J=6.4 Hz, $CHCH_2P$), 0.82 (3H, t, J=7.20 Hz,

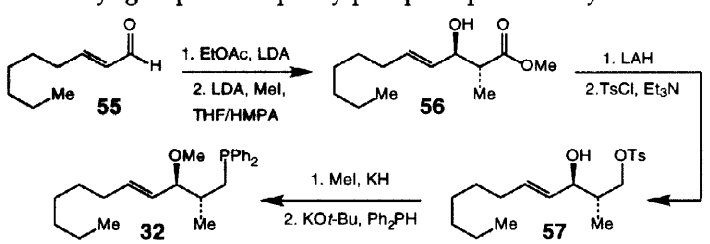
CH_2CH_3), 0.77 (3H, d, J=6.80 Hz, CH_2CHCH_3CH), ^{13}C NMR: δ 134.1, 133.2, 133.1, 131.8, 131.6, 127.4, 127.3, 127.2, 127.1, 36.4, 36.3 (d, J_{PC}=12.3 Hz), 30.9, 28.5, 28.4, 28.3, 26.4, 21.7, 21.6 (d, J_{PC}=15.1 Hz), 20.2, 13.1. HRMS Calcd for $C_{25}H_{35}P$ (mixture of cis and trans isomers) requires 366.2407, found 366.2476.

Proof of structure for 31. The vinylic protons of the reaction product exhibit a coupling constant of 10.0 Hz, indicating that the product contains a *cis*-olefin. The regiochemistry of alkylation was determined through GLC analysis of alcohols obtained from ozonolysis/reduction of the reaction product (1:1 mixture of *cis* to *trans* isomers). The (*S*)-MTPA ester of the major regioisomeric alcohol was compared to an authentic and racemic mixture of Mosher esters. The ^1H NMR thus shows the enantioselectivity to be >98:2.

Proof of stereochemistry for 31. The stereochemistry of **31** was determined by comparison with authentic materials (3:1 mixture of diastereomers), which was prepared according to the route shown below. Oxazolidinone **52** was treated with KHMDS and alkylated with methyl iodide with >98:2 diastereoselection (determined through analysis of the ^1H NMR of derived MTPA esters).[24] The aforementioned alkylation product was treated with $LiBH_4$ (to remove the chiral auxiliary) and subsequently subjected to Swern oxidation conditions to afford aldehyde **53** in the non-racemic form. Racemic **53** was synthesized starting with the commercially available **54** in the straightforward manner shown. As illustrated, a 1:1 mixture of non-racemic and racemic **53** (50% ee) and the phosphonium ylide derived from silylated **37** afforded **50**, which was then converted to **51** (3:1 mixture of diastereomers), in a manner similar to that described above.



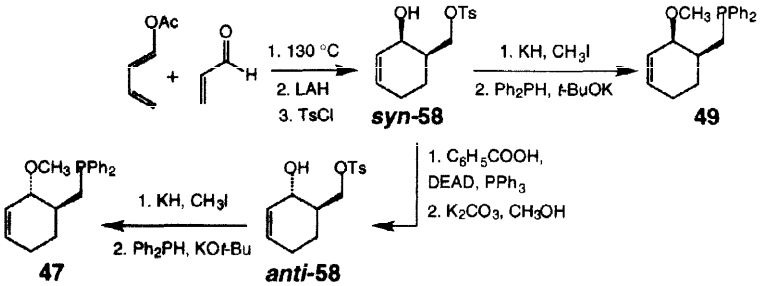
Preparation of substrate 32. The product of the aldol reaction of ethylacetate and *trans*-nonenal was used in a diastereoselective alkylation[25] followed by reduction with LAH to afford the *anti* product in 84% yield. This diol was then treated with one equivalent of tosyl chloride to afford the primary tosylate. Methylation of the secondary alcohol and displacement of the tosyl group with diphenylphosphinopotassium yielded **32** in 70% yield.



(*S,R*)-1-Diphenylphosphino-2-methyl-5-phenyl-*trans*-3-undecene (39). IR (KBr): 3070 (w), 2956 (s), 2926 (br m), 2869 (m), 2855 (m), 1435 (m), 1027 (w), 740 (m), 697 (s), 541 (s) cm^{-1}; ^1H NMR: C_6D_6: δ 7.48-7.34 (10H, m, aromatic $P(C_6H_5)_2$), 7.20-7.00 (5H, m, aromatic CHC_6H_5), 5.52 (1H, dd, J =15.3, 6.62 Hz, vinyl C_6H_5CHCH), 5.44 (1H, dd, J=15.6, 7.20 Hz, $C_6H_5CHCHCH$), 3.14 (1H, q, J=7.5 Hz, benzylic CH), 2.25 (1H, m, allylic $CHCH_3$), 2.05 (1H, dd, J=13.2, 7.5 Hz, CH_2P), 1.95 (1H, dd, J=13.5, 6.9 Hz, CH_2P), 1.66 (2H, m, $C_6H_5CHCH_2$), 1.25-1.15 (8H, broad m, aliphatic CH_2), 1.05 (1H, d, J=6.60 Hz, $CHCH_3$), 0.91 (3H, t, J=6.60 Hz, CH_3); ^{13}C NMR: δ 136, 133.1, 133.0, 128.5, 127.8

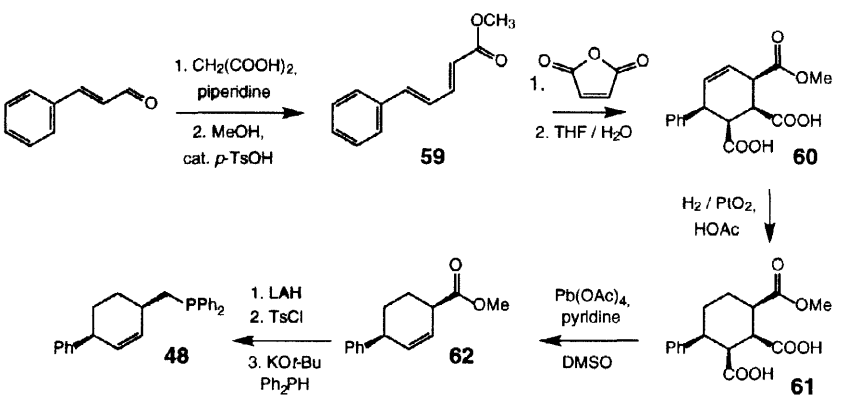
127.5, 126.0, 132.0, 48.9, 36.3, 34.7(d, J_{PC}=14.0 Hz), 32.2 (d, J_{PC}=16.4 Hz), 29.5, 29.4, 27.7, 22.9, 22.6 (d, J_{P-C}=15.2 Hz), 14.3. HRMS Calcd for $C_{30}H_{37}P$ requires 428.2627, found 428.2632.

Preparation of substrates 47 and 49. Diels-Alder reaction[26] of *E*-1-acetoxybutadiene with acrolein, followed by reduction and tosylation affords *syn*-**58**. Starting material **49** was prepared from *syn*-**58** in two steps by alkylation and tosyl displacement. *Anti*-**58** was prepared from *syn*-**58** by a Mitsunobu inversion[27] of the secondary carbinol, followed by hydrolysis of the resulting benzoate group. Allylic ether **47** is prepared from *anti*-**58** in a manner analagous to **49**.



***Cis*-3-phenyl-6-(diphenylphosphino)methylcyclohexene (48).** IR (KBr): 3022 (m), 2927 (m), 1433 (s), 739 (s), 696 (s) cm^{-1}; ^1H NMR: δ 7.55-7.23 (15H, m, aromatic C**H**), 6.01 (1H, broad dt, J=10.0, 1.8 Hz vinylic C**H**), 5.75 (1H, broad d, J=10.0 Hz, vinylic C**H**), 3.42 (1H, m, allylic CHC**H**CH), 2.32-2.15 (3H, m, C**H**$_2$P, allylic CHC**H**C**H**$_2$P), 2.00-1.55 (**4H**, m, alicyclic C**H**$_2$); ^{13}C NMR: δ 145.9, 129.5, 129.5, 128.6, 128.5 (d, J_{PC}=21.2 Hz), 128.4 (d, J_{PC}=15.2 Hz), 128.4, 128.2, 127.9, 126.0, 41.3, 35.4 (d, J_{PC}=13.6 Hz), 32.2 (d, J_{PC}=13.7 Hz), 29.7, 27.1 (d, J_{PC}=9.1 Hz). HRMS Calcd for $C_{25}H_{25}P$ requires 356.1694, found 356.1693.

Proof of sterechemistry for 48. The regiochemistry and stereochemistry of alkylation was determined by comparison of the product obtained from catalytic alkylation with authentic material. Synthesis of *syn*-6-phenyl-3-carbomethoxycyclohexene (**62**) was accomplished by a method similar to those reported in the literature.[28] Knovenagal condensation[29] of malonic acid on *trans*-cinnamaldehyde followed by esterification yields diene (**59**). Subsequent cycloaddition with maleic anhydride,[30] followed by hydrolysis of the anhydride affords **64**. Hydrogenation of **60** provides **61**, which upon decarboxylation[31] effected by $Pb(OAc)_4$ leads to **62**. The desired product (**48**) can be prepared from **62** as illustrated below.



ACKNOWLEDGMENTS. This research was generously supported by the National Institutes of Health (GM-47480) and the National Science Foundation (CHE-9632278). MTD and JPM were recipients of American Chemical Society Graduate Fellowships, sponsored by Monsanto and Glaxo, respectively. AHH is an Alfred P. Sloan Fellow and a Camille Dreyfus Teacher-Scholar. We are grateful to Dr. Enrique Gomez-Bengoa for helpful suggestions.

References & Notes

1) Present address: Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina, 27599.

2) (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079-5080. (b) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950-8952. (c) Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614-6624.

3) (a) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6697-6698. (b) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291-4298.

4) (a) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943-2944. (b) Xu, Z.; Johannes, C. W.; Salman, S. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 10926-10927.

5) Visser, M. S.; Hoveyda, A. H. *Tetrahedron* **1995**, *51*, 4383-4394.

6) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123-3124.

7) (a) Visser, M. S.; Harrity, J. P. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 3779-3780. (b) Harrity, J. P. A.; Visser, M. S.; Gleason, G. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488-1489.

8) For recent impressive advances in connection to Zr-catalyzed enantioselective addition of alkylaluminum agents to olefins, see: (a) Kondakov, D. Y.; Negishi, E.; *J. Am. Chem. Soc.* **1995**, *117*, 10771-10772. (b) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577-1578. For directed, diastereoselective addition of alkylmagnesium halides to cyclic allylic ethers, see: (c) Heron, N. M.; Adams, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205-6206.

9) (a) Hayashi, T.; Konishi, M.; Kumada, M. *J. Organomet. Chem.* **1980**, *186*, C1-C4. (b) Felkin, H.; Joly-Goudket, M.; Davies, S. G. *Tetrahedron Lett.* **1981**, *22*, 1157-1160. (c) Consiglio, G.; Morandini, F.; Piccolo, O. *J. Chem. Soc., Chem. Commun.* **1983**, 112-114. (d) Hayashi, T.; Konishi, M.; Yokota, K-I.; Kumada, M. *J. Organomet. Chem.* **1985**, *285*, 359-373. (e) Consiglio, G.; Piccolo, O.; Roncetti, L. *Tetrahedron* **1986**, *42*, 2043-2053. (f) For an excellent review, see: Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257-276.

10) For a review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

11) For a preliminary account of this work, see: Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273.

12) (a) Kurosawa, H.; Ohnishi, H.; Emoto, M.; Chatani, N.; Kawasaki, Y.; Murai, S.; Ikeda, I. *Organometallics* **1990**, *9*, 3038-3042. (b) Kurosawa, H.; Ohnishi, H.; Emoto, M.; Kawasaki, Y.; Murai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6272-6273.

13) Komiya, S.; Abe, Y.; Yamamoto, A.; Yamamoto, T. *Organometallics*, **1983**, *2*, 1466-1468.

14) (a) Jackson, W. R.; Perlmutter, P.; Suh, G. H.; *J. Chem. Soc., Chem. Commun.* **1987**, 724-725. (b) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *Tetrahedron Lett.* **1990**, *31*, 2461-2462. (c) Jackson, R. W.; Perlmutter, P.; Suh, G. H.; Tasdelen, E. E. *Aust. J. Chem.* **1991**, *44*, 951-966. (d) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237-4240. (e) For a review of hydrocarbonylation reactions of functionalized alkenes, see: Botteghi, C.; Ganzerla, R.; Lenarda, M.; Moretti, G. *J. Mol. Catal.* **1987**, *40*, 129-182.

15) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917-6918. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671-6679.

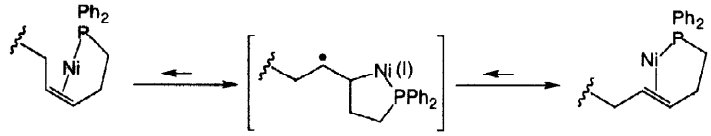
16) Stary, I.; Kocovsky, P. *J. Am. Chem. Soc.* **1989**, *111*, 4981-4982.

17) Reaction regioselectivity throughout this study was established through ozonolysis,

reduction ($NaBH_4$) of the derived aldehydes and subsequent comparison of the primary alcohol ratios by GLC analysis.

18) Addition of *n*-hexylMgBr to epoxide **35** occurs with 2:1 regioselectivity (33% of the alternative regioisomer is isolated as well).

19) An alternative scenario for Ni-catalyzed alkene isomerization may involve formation of a radical-Ni(I) (or cation-Ni(II)) intermediate, as illustrated below. For previous examples of Ni-catalyzed reactions involving radical carbon centers, see: (a) Dayrit, F. M.; Gladkowski, D. E.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 3976-3978. (b) Schwartz, J.; Dayrit, F. *J. Am. Chem. Soc.* **1981**, *103*, 4466-4473.



20) Tatsumi, K; Nakamura, A.; Komiya, S.; Yamamoto, A.; Yamamoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 8181-8188. See also ref 9-10.

21) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *Tetrahedron Lett.* **1996**, *37*, 3613-3616.

22) Van Hecke, G. R.; Horrocks, W. D. *Inorg. Chem.* **1966**, *5*, 1968-1974.

23) Nuzzo, R. G.; Haynie, S. L.; Wilson, M. E.; Whitesides, G. M. *J. Org. Chem.* **1981**, *46*, 2861-2867.

24) DiMare, M. Ph. D. Thesis, Harvard University, **1988**, 69.

25) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825-2828.

26) (a) Gouesnard, J. P.; Martin, G. J. *Tetrahedron* **1974**, *30*, 151-157. (b) Banks, R. E.; Miller, J. A.; Nunn, M. J.; Stanley, P.; Weakley, T. J. R.; Ullah, Z. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 1096-1102.

27) Mitsunobu, O. *Synthesis* **1981**, 1-28.

28) Utley, J. H. P.; Yates, G. B. *J. Chem. Soc., Perkin Trans. II* **1978**, 395-400.

29) Koo, J.; Fish, M. S.; Walker, G. N.; Blake, J. *Org. Syn., Coll. Vol. IV* **1963**, 327-329.

30) Alder, K. V.; Schumaker, M. *Ann. Chem.* **1951**, *571*, 108-122.

31) Chapman, N. B.; Sotheeswaran, S.; Toyne, K. J. *J. Chem. Soc., Chem. Commun.* **1965**, 214.