Directed Regio- and Stereoselective Nickel-Catalyzed Addition of Alkyl Grignard Reagents to Allylic Ethers[1]

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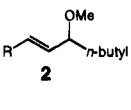
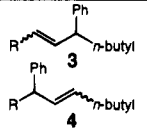
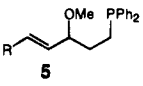
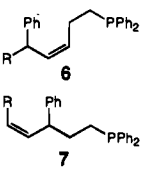
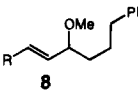
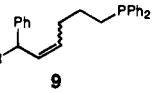
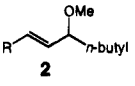
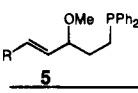
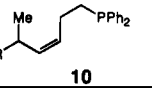
Asymmetric Zr-catalyzed addition of alkylmagnesium halides to allylic ethers provides a method for the regio- and stereoselective addition of ethyl, propyl, and butyl groups to allylic ethers.[2] However, due to established mechanistic principles,[3] Grignard reagents with alkyl groups that do not bear a β-hydride cannot be used. As a result, we have initiated study of transformations which allow for selective C−C bond formation by the reaction of the latter class of Grignard reagents to allylic ethers. Our investigation has focused on the Ni-catalyzed reaction of alkylmagnesium halides with allylic ethers, since these transformations can be performed with alkylmetals that do not bear a β-hydride.[4] However, particularly with secondary allylic ethers, complications related to low reactivity and regioselectivity detract from the usefulness of these potentially powerful transformations. To enhance reactivity and gain control of various selectivity issues in the C−C bond formation, we decided to examine the possible influence of an internal Lewis base that may associate with the transition metal complex. Because of the ability of phosphines to interact effectively with late transition metals, we chose to utilize P-containing ligands to test the feasibility of directed reaction strategy in enhancing the utility of catalytic alkylation reactions. Herein, we report our initial studies on the regio- and diastereoselective addition of methyl- and phenylmagnesium halides to allylic ethers.[5]

As illustrated in Table 1, with 5 mol % $(Ph_3P)_2NiCl_2$ (**1**), reaction of **2** with PhMgBr after 3 h affords **3** and **4** in 10% yield and without regioselectivity (30% yield, 12 h). In contrast, with **5** as substrate, the reaction affords **6** regioselectively (8:1) in 70% yield within the same time period; the observed olefin stereoselectivity in the directed alkylation is higher in favor of the cis isomer.[6] It is noteworthy that compared to **5**, with the more distal internal Lewis base in **8**, **9** is formed at a slower rate and as a mixture of alkene isomers, but with higher regioselection (>99:1 vs 8:1 for **5**). The impressive influence of the Lewis basic directing group is highlighted by the last two entries of Table 1. Treatment of **2** with MeMgBr and 5 mol % **1** leads to the recovery of the starting material, whereas allylic ether **5**, under identical conditions, affords **10** in 70% yield, as a single regiosiomer (>99:1) and with outstanding control of alkene stereochemistry (>49:1).

Table 1. Ni-Catalyzed Addition of PhMgBr and MeMgBr to Allylic Ethers[a]

substrate	grignard reagent	product	regioselec.[b]	c:t[c]	yield (%),[d] time
 **2**	PhMgBr	 **3** + **4**	**3:4** = 1:1	1:3	10, 3 hrs
 **5**	PhMgBr	 **6** + **7**	**6:7** = 8:1	5:1	70, 3 hrs
 **8**	PhMgBr	 **9**	>99:1	1:1	70, 24 hrs
 **2**	MeMgBr	NO REACTION			18 hrs
 **5**	MeMgBr	 **10**	>99:1	>49:1	70, 18 hrs

[a] R = *n*-hexyl. Conditions: 5 mol % $(Ph_3P)_2NiCl_2$, 5 equiv of alkylmagnesium bromide, THF, 22 °C. [b] Regioselection determined by GLC analysis, in comparison with authentic materials. [c] Determined through analysis of 300 MHz ^{1}H NMR spectra. [d] Isolated yield after silica gel chromatography.

In contrast to **1**, (dppe)$NiCl_2$ and (dppb)$NiCl_2$ are ineffective as alkylation precatalysts (<10%, 12 h). Since bidentate phosphines are expected to dissociate less readily than Ph_3P, this observation supports the notion that exchange of the resident directing unit with one of the phosphine moieties of the metal complex is critical to the efficiency and selectivity of the C−C bond formation. It is not clear at present at exactly what stage of the catalytic cycle the directing group exerts its influence.

Association of an internal ligand with the active metal complex leads to significant dependence of reactivity and selectivity on substrate local chirality. As shown in Table 2, whereas silyl ether **11** is inert to alkylation with 5 mol % **1** and PhMgBr, allylic ether **12** is converted to **13** in high yield and with excellent control of regio-, diastereo-, and olefin stereochemistry. Metal-catalyzed alkylation of **12** with MeMgBr proceeds with >98% regio-, diastereo-, and olefin selectivity to afford **14** (75%). Allylic ether **15** undergoes alkylation at a rate superior to that of **12**, indicating that diminution in selectivity is probably not due to the inefficient P−Ni association in the former case.

Although catalytic alkylation of **12** with PhMgBr and MeMgBr affords **13** and **14** with a >49:1 cis:trans ratio, prolonged reaction time provides *trans*-alkenes with low selectivity (1:2 **18**:**13**, 24 h, or 1:2 **19**:**14**, 40 h).[7] Isomerization of the alkylation products (**13** or **14**) to the corresponding *trans*-alkene isomers can, however, be effected readily and efficiently. Cis → trans isomerization of **13** occurs with excellent stereochemical control (94:6 trans:cis) with EtMgBr and 5 mol % **1**, affording **18** in >98% yield (eq 1).[8] Silyl ether **20** provides

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(6) For alkyldiphenylphosphine-directed Rh-catalyzed carbonylation reactions, see: (a) Jackson, R. W.; Perlmutter, P.; Suh, G.-H.; Tasdelen, E. E. *Aust. J. Chem.* **1991**, *44*, 951−966 and references cited therein. See also: (b) Stary, I.; Kocovsky, P. *J. Am. Chem. Soc.* **1989**, *111*, 4981−4982.

(7) The stereochemical identity of **13**, **14**, **18**, and **19** was established through comparison with authentic materials. See the supporting information for details.

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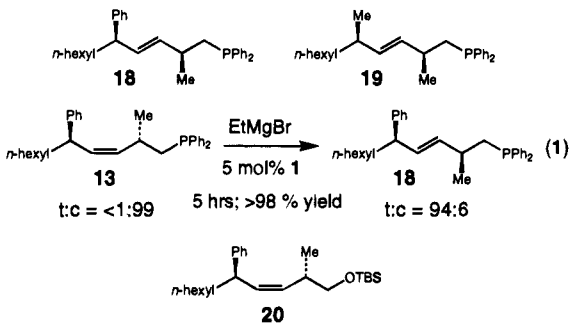
Table 2. Effect of Local Chirality on Efficiency and Selectivity of Ni-Catalyzed Alkylation[a]

substrate	grignard reagent	product	regioselect.	c:t[b]	ds[c]	yield (%)[d] time
11	PhMgBr	NO REACTION				12 hrs
12	PhMgBr	13	>99:1	>49:1	10:1	85 6 hrs
12	MeMgBr	14	>99:1	>49:1	>49:1	75 12 hrs
15	PhMgBr	16 + 17	1:1		1:1	85 3 hrs

[a] R = *n*-hexyl. Conditions: See Table 1. [b] Determined as in Table 1. [c] Determined by 300 MHz ^{1}H NMR. [d] Isolated yield after chromatography.

<2% of the trans isomer under identical conditions. Directed alkene isomerization highlights a particularly 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 transformations.



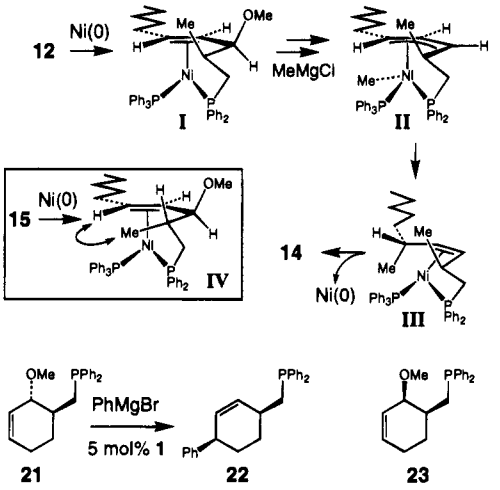
An important feature of the above olefin isomerizations is that in the product *both stereogenic sites retain their stereochemical identity*:[9] hydrido–metal–allyl complexes are likely not involved.[10] Alternatively, it may be that addition of a Ni–H agent followed by β-hydride elimination could cause formation of the trans isomers. We find that alkylation of **12** with C_6D_5MgBr or olefin isomerization of **13** with C_2D_5MgBr affords **13** and **18** with <2% deuterium incorporation at the vinylic positions (5 mol % **1**, ^{2}H NMR); with 30 or 100 mol % **1** and C_2D_5MgBr ≤10% deuterium incorporation is observed. These data, together with the ability of Me- and PhMgBr to effect alkene isomerization, suggest that metal–hydrides may not be solely responsible for the facile isomerization reaction.

(8) Alkylation of substrates shown in Tables 1 and 2 with EtMgCl leads to exclusive transfer of hydride (not Et) with different regiochemical preferences; results of these studies will be reported in due course.

(9) Less than 1% of the derived trisubstituted alkene derivatives are observed.

(10) Cis–trans isomerization could occur through abstraction of an allylic hydride (formation of the hydrido–metal–allyl intermediate) and rotation around a C–C σ bond in the η^1 complex, followed by re-formation of the η^3 system and repositioning of the allylic hydride. Such a mechanism would lead to the inversion of the allylic stereogenic center (not observed).

Scheme 1



It is plausible that Ni-catalyzed alkylation proceeds via a metal–π-allyl complex (*e.g.*, **II** via **I**, Scheme 1), followed by reductive elimination of the dialkylmetal (**II** → **III**). This proposal is supported by the facile conversion of **21** to **22** with >95:5 diastereo- and regioselectivity (1 h, 70%); **23** is inert to the same reaction conditions. It is therefore tenable that the catalytic cycle involves anti insertion of Ni(0) to afford the metal–allyl system, followed by a syn reductive elimination.[11] This paradigm provides a rationale for the outcome of the directed process: C=C in the product is formed at a site proximal to the directing group, so that P–Ni association is better maintained. Since **IV**, derived from **15**, suffers from unfavorable torsional interactions, alternative metal–alkene complexes become competitive, leading to lower levels of selectivity.

These studies demonstrate that, in the presence of a properly positioned Lewis base, addition of alkylmagnesium halides to otherwise unreactive allylic ethers can occur catalytically, with excellent selectivity and in good yield; alkylmagnesium halides used in these processes do not require a β-H. The directing group effectively controls the regiochemistry and stereochemical outcome (of both the alkene and C–C bonds) of the alkylation; moreover, reaction products can be subjected to further directed stereoselective transformations, and the resulting chiral phosphines may be employed as building blocks in C=C synthesis.[12] The inherent organization due to association of the catalytic complex can prove critical to asymmetric catalysis; in the bond formation event, such interactions often allow for effective transfer of chirality. Studies in connection with the range of other directing groups that can be used in the catalytic process, mechanistic details and the asymmetric catalytic alkylations are in progress.

Supporting Information Available: Experimental procedures and spectral and analytical data for all reaction products (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any masthead page for ordering information and Internet access instructions.

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