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DIRECTED REGIOSELECTIVE Ni-CATALYZED ALKYLATION AND HYDRIDE ADDITION OF ALLYLIC ETHERS. A REMARKABLE TURNOVER IN REGIOSELECTIVITY

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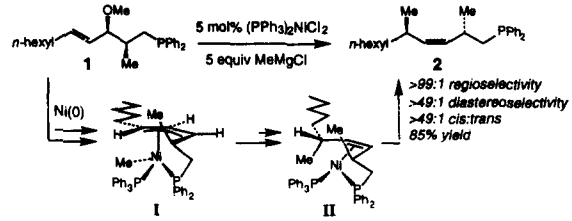
Abstract. Various allylic ethers are reduced efficiently in the presence of $Ni(PPh_3)_2Cl_2$ (5 mol%) and EtMgCl (5 equiv) with excellent regioselectivity (>99:1). The sense of regiochemical control in these reactions is opposite to that observed in Ni-catalyzed alkylations of the same substrates. A mechanistic working model that accounts for the observed levels and trends in selectivity is presented. Copyright © 1996 Published by Elsevier Science Ltd

Among various approaches that elevate the efficiency of an otherwise sluggish process and impart high levels of regio- and/or stereoselectivity to a regularly non-discriminating transformation is the directed reaction protocol.[1] In this strategy, pre-association of the reacting partners through Lewis acid-base interactions leads to a transient substrate-reagent complex to give rise to unusually facile and selective processes. This scheme has been successfully utilized in a number of important stereoselective transition metal-catalyzed and metal-mediated bond forming reactions.[2] Phosphine-directed Rh-catalyzed hydroformylation[3] and phosphinite-directed Rh-catalyzed hydroboration[4] are two examples where an internal phosphine-containing functional group has been shown to have a profound influence on the regio- and diastereochemical outcome of these transformations. In both instances, the reaction profiles proposed involve initial addition of a metal-hydride, so that the transition metal is eventually positioned proximal to the directing phosphorous (P→M interaction is maintained by the smallest possible cyclic structure). Herein, we report the results of our studies on directed Ni-catalyzed hydride additions to acyclic allylic ethers; the data presented below shed light on some of the intricacies of these metal-catalyzed processes, and should allow for the design of more practical catalytic alkylations in the future.

Scheme I

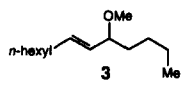
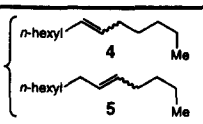
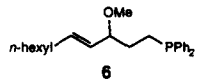
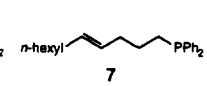
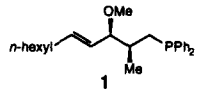
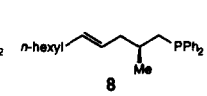
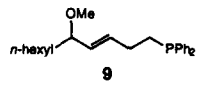
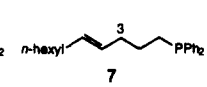
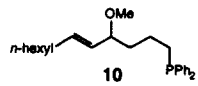
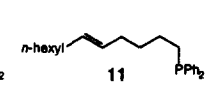
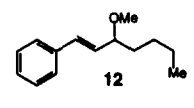
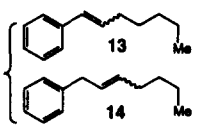
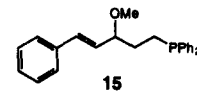
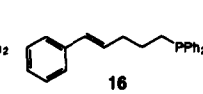


We recently reported that in phosphine-directed Ni-catalyzed addition of Grignard reagents to allylic ethers,[5] there is a significant influence on reaction efficiency and selectivity induced by a resident phosphine. In all cases studied, alkylation with Me- and PhMgBr led to the formation of a major product regioisomer, where the olefin unit resides at the site more near the directing group. Since the catalytic cycle likely involves the intermediacy of alkene-Ni complexes **I** and **II**, we argued that the observed sense of regiocontrol arises from the propensity of the transition metal to be installed at the site that ensures a stronger Ni-P association.

One important point in the above mechanistic picture was seriously challenged upon our examination of the phosphine-directed Ni-catalyzed addition of hydrides to allylic ethers. As illustrated in Table 1 (entries 1 and 6), similar to catalytic alkylations, in the absence of a resident Lewis basic directing group, reduction is non-selective and relatively sluggish. As was observed in catalytic alkylations, with an internal coordinating phosphine ligand available, hydride addition is notably more facile and the catalytic transformation proceeds with excellent levels of

regiochemical control. *However, in stark contrast to Ni-catalyzed phosphine-directed alkylations, the sense of regioselective hydride delivery is such that in all products the olefin is formed at the more distal position relative to the directing group* (compare entries 2 or 3 to **1**→**2** in Scheme I).

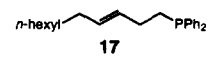
Table 1. Directed Ni-Catalyzed Reduction of Allylic Ethers.[a]

entry	substrate	product	regioselec.[b]	E:Z[c]	yield (%),[d] time
1	 **3**	 **4** / **5**	4:5=4:1	nd	24, 1.9 hrs
2	 **6**	 **7**	>99:1	>95:5	82, 1.7 hrs
3	 **1**	 **8**	>99:1	>95:5	81, 3 hrs
4	 **9**	 **7**	>99:1	>95:5	93, 1.5 hrs
5	 **10**	 **11**	>99:1	nd	86, 16 hrs
6	 **12**	 **13** / **14**	13:14=1.5:1	>95:5[e]	72, 12 hrs
7	 **15**	 **16**	>95:5	>95:5	92, 2.5 hrs

a. Conditions: 5 mol% $(Ph_3P)_2NiCl_2$, 5 equiv EtMgBr, THF, 22 °C. *b.* Regioselection by GLC, in comparison with authentic materials (entry 7 by ^1H NMR). *c.* Determined by analysis of 300 MHz ^1H NMR spectra. *d.* Isolated yield after silica gel chromatography. *e.* *E*/*Z* ratio determined for **13** only.

The result shown in entry 4 of the Table illustrates that the regioselective Ni-catalyzed reduction likely proceeds through a π-allyl Ni complex, since isomeric allylic ethers **6** and **9** both afford **7** with excellent levels of regiocontrol. The high yielding conversion of **10** to **11** suggests that a more remote directing group can direct the regioselective H-addition as well, but in a less efficient manner (16 h vs. 1.7 h for **6**). The reaction in entry 6 shows the non-directed process is not regioselective, in spite of the fact that one product isomer carries an olefin that is conjugated with the aromatic π system. The directed variant of the reaction, as shown in entry 7, proceeds with excellent regioselection.

Several additional observations related to the data summarized in Table 1 merit additional comments: (**1**) Treatment of **9** with 5 mol% $(PPh_3)_2NiCl_2$ in the presence of five equiv d_5-EtMgCl at 22 °C leads to the formation of **7** where deuterium incorporation occurs exclusively at C3 (>98%, judged by 400 MHz ^2H NMR; entry 4, Table 1). (**2**) Subjection of **17** (minor isomer in reduction of **6**; not detected in catalytic reactions) to the catalytic hydride addition conditions leads to <2% alkene isomerization. (**3**) When *iso*-butylmagnesium bromide is used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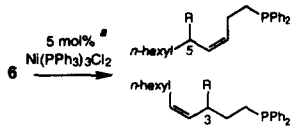
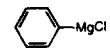
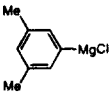
instead of EtMgBr, **6** is converted to **7** in similarly high levels of regiochemical control (<5% alkylation is observed). These data indicate that: (i) The alkylmagnesium halide is the exclusive hydride source (β-hydride elimination, followed by alkyl-hydride reductive elimination). (ii) The observed regioselectivities are due to kinetic control and not caused by subsequent alkene isomerization.

Table 2. Regiocontrol in Directed Ni-Catalyzed Alkylations.[a]

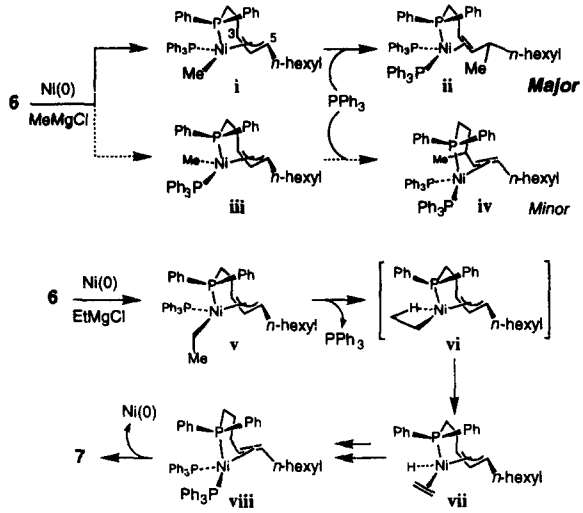


RMgCl	C5 : C3 (yield) b c
MeMgCl	>99:1 (70%)
	8:1 (70%)
	4:1 (78%)

a-c. Identical to Table 1.

The dramatic turnover in regioselectivity of directed Ni-catalyzed hydride addition versus alkylation is noteworthy and demonstrates that, contrary to the aforementioned mechanistic dictum, the product alkene does not necessarily prefer to be proximal to the directing group. As illustrated in Scheme II, a mechanistic working model that accounts for the observed trends in regioselectivity may be proposed. Formation of π-allyl complex **i**, wherein the methyl group is situated properly for a syn reductive elimination (→**ii**), is in agreement with studies reported by Kurosawa,[6] Tatsumi[7] and Yamamoto.[8] The latter reports indicate that Ni-based dialkyl reductive eliminations are significantly more facile when transformations proceeds via a pentacoordinate intermediate,[9] involving the η^3-allyl system. Thus, according to previous studies, availability of an internal phosphine greatly facilitates dialkyl reductive elimination, in the same manner that a bidentate phosphine ligand positively influences the rate of catalytic alkylations (see ref 9). Positioning of the internal phosphine unit in the apical position of the square pyramidal complex, with the PPh_3 trans to an alkyl site involved in reductive elimination, is consistent with previously reported mechanistic principles as well.[7,10]

Scheme II



Examination of molecular models indicate that the alternative intermediate **iii** would suffer from significant steric repulsion between the phenyl groups of the tethered diphenylphosphine and the bound PPh_3 group; formation of **ii** should therefore be favored. Data depicted in Table 2, illustrating the regiocontrol in Ni-catalyzed alkylation reactions as a function of the steric bulk of the alkylmagnesium halide support the proposed working model: as the size of the alkyl unit is increased, preference for complex **i** over **iii** is diminished and regiochemical control suffers. The reversal of selectivity in hydride addition reactions can be explained within the context of this paradigm. Intermediacy of **v**, in analogy to **i**, would lead to the formation of **vii**, through **vi**, which subsequently

undergoes an alkyl-hydride reductive elimination, in the sense opposite to that observed in related alkylations (→**7** as major isomer). Dissociation of the PPh_3 ligand in **v**, making available a coordination site for Ni-H interaction, is likely required for the β-hydride elimination process (**vi**→**vii**). Under identical conditions, when $dppeNiCl_2$ (5 mol%) is used as catalyst, the product mixture consists of 53% of the alkylation product (Et addition) and 27% of hydride transfer (reduction). This experimental observation supports the aforementioned significance of an empty ligation site on the transition metal complex, since the bidentate dppe ligand would be less amenable to vacating a coordination position on Ni.[11] Importantly, neither of the latter reaction products are formed regioselectively, presumably because the bidentate phosphine ligand largely preempts association of the internal directing group with Ni.

We emphasize that mechanistic paradigms presented herein are to serve exclusively as models; a more rigorous reaction profile must certainly await future investigations. For example, although the proposed scheme readily explains why cis alkenes are formed in catalytic alkylations, whereas products of catalytic hydride additions are exclusively trans, it is not clear at present why **vii** would not be converted to a complex resembling **i** before reductive elimination (an issue that is difficult to address in the absence of extensive kinetic data). Nonetheless, the above proposal provides a plausible rationale for the unusual sense and levels of regioselection in Ni-catalyzed alkylations and hydride additions.

Data reported herein indicate that in directed metal-catalyzed processes, the regiochemical outcome is not necessarily dictated by the most proximal positioning of the chelated metal to the internal Lewis base. These and related principles should prove critical in developments in the area of selective catalytic reactions, since appreciation of factors that control reaction selectivities (both regio- and stereo-) are central to our ability to design and develope new transformations.

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REFERENCES & FOOTNOTES

(1) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

(2) For a recent example, see: Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367-11368.

(3) 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.

(4) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671-6679.

(5) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273-7274.

(6) (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.

(7) Tatsumi, K.; Nakamura, A.; Komiya, S.; Yamamoto, A.; Yamamoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 8181-8188.

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

(9) The significance of a pentacoordinate intermediate is further supported by the observation that, in contrast to $(PPh_3)_2NiCl_2$, which is highly inefficient (<5% after six h) in promoting catalytic alkylations (unless in presence of a directing group), reactions with $dppeNiCl_2$ proceed smoothly without an internal directing group (for example, **3** with PhMgCl proceeds to afford the alkylation product in 85% yield in 3h, as a 1:1 mixture of regioisomers).

(10) Similar arguments may be applied to trigonal bipyramidal complexes, where the alkyl unit (Me in **i**) and the C3 site occupy apical positions (the two phosphines and C5 would be equatorial). Thus, as indicated by studies of Tatsumi (ref 7), one alkyl group involved in reductive elimination is situated apically and the other equatorially, rendering the C-C bond forming process symmetry-allowed.

(11) Addition of excess PPh_3 (3 equiv) to either catalytic alkylation or reduction mixtures does not significantly retard reaction rates; addition of larger amounts of PPh_3 (10-20 equiv) leads to heterogeneous reaction mixtures (low conversions).

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