Ni-Catalyzed Asymmetric Addition of Grignard Reagents to Unsaturated Cyclic Acetals. The Influence of Added Phosphine on Enantioselectivity

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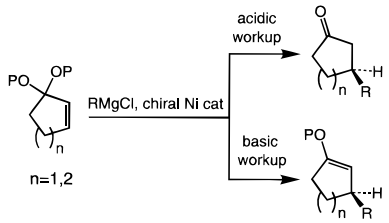
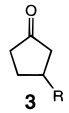
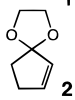
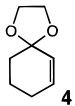
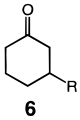
Addition of carbon nucleophiles to alkenes that bear a neighboring C−O bond plays a critical role in the quest for catalytic enantioselective C−C bond-forming processes. Most noteworthy is the Pd-catalyzed additions of "soft" nucleophiles to allylic acetates or carbonates; these transformations offer a gamut of protocols for asymmetric C−C bond synthesis.[1] Ni-catalyzed addition of Grignard reagents ("hard" nucleophiles) to allylic ethers has been reported as well.[2] However, the scope of the reaction is limited: only when EtMgCl is used are appreciable levels of enantioselection detected (>80% ee). Addition of certain aryl Grignard reagents to allylic esters is catalyzed by Ni complexes with up to 89% ee; nonetheless, regioselectivity is low and many Grignard reagents cause nucleophilic removal of the acyl unit.[3] The conjugate addition to unsaturated carbonyls also falls into this general category of reactions, but the corresponding catalytic asymmetric methods, despite recent impressive strides,[4] remain relatively undeveloped.

Scheme 1



A related, but mechanistically distinct, process is the asymmetric Zr-catalyzed addition of ethyl-, propyl-, and butylmagnesium halides to cyclic allylic ethers.[5,6] A limitation of this reaction is the requirement for a β-hydride within the Grignard reagent: these transformations involve the intermediacy of the derived zirconium alkenes.[7] As part of our efforts to address these shortcomings and expand the generality of catalytic addition of alkylmetals to olefins,[8] we initiated a study of the Ni-catalyzed addition of Grignard reagents to allylic acetals.[9] Such processes lead to the formation of synthetically useful adducts (Scheme 1).[10]

Table 1. Ni-Catalyzed Reactions of Et- and PhMgCl with Unsaturated Cyclic Acetals[a]

entry	substrate	Grignard reagent	product		yield (%)[b]
1		PhMgBr		**3a** R=Ph	70
2		EtMgCl		**3b** R=Et	65
3		PhMgCl		**3a** R=Ph	86
4		PhMgBr		**6a** R=Ph	60
5		EtMgCl		**6b** R=Et	90
6		PhMgCl		**6a** R=Ph	92

[a] Conditions: 5 mol % dppeNiCl$_2$, 3 equiv of Grignard reagent, THF, 22 °C, 1−3 h. [b] Isolated yields.

As the data in Table 1 illustrate, when cyclopentenyl and cyclohexenyl acetal derivatives are treated with a Grignard reagent in the presence of 5 mol % dppeNiCl$_2$ (THF, 22 °C), functionalized cyclic ketones are obtained in good yield and with excellent regiochemical control after mild acidic workup (>98% by 400 MHz ^{1}H NMR). With the substrates shown in Table 1, products are formed more efficiently when the transition metal complex is outfitted with a bidentate phosphine ligand. When (PPh$_3$)$_2$NiCl$_2$ is used, reactions are slow. With **1** as the substrate and in the presence of EtMgCl (4 h), ∼25% product is obtained; with **2**, **4**, and **5** as starting materials, <5% product is isolated.[11]

To examine whether a Ni complex bearing a chiral bidentate phosphine would give rise to enantioselective alkylation, we screened a number of potential nonracemic catalysts. To minimize any background reaction arising from the action of an achiral Ni complex (see above), in situ catalyst formation was avoided: chiral metal complexes were prepared[12] and purified for use. As depicted in Scheme 2, reaction of **1** and EtMgCl in the presence of 5 mol % (*S*,*S*)-(chiraphos)NiCl$_2$ (**7**) delivers **3b** in 53% ee (85% yield).[13] As expected, when the catalyst is prepared in situ ((PPh$_3$)$_2$NiCl$_2$ and (*S*,*S*)-chiraphos), stereoselectivity is diminished (15% ee), presumably as a result of adventitious and nonselective catalysis by the achiral (PPh$_3$)$_2$Ni complex.[14] When cyclohexenyl acetal **4** is subjected to identical conditions (i.e., condition A, **7** as the precatalyst), only 11% ee is obtained. Remarkably, when the in situ method is employed (condition B, with **4**), **6b** is formed in 70% ee. That under the latter conditions diminution in enantioselectivity is not detected is consistent with the fact that (PPh$_3$)$_2$NiCl$_2$ does not promote reactions with **4** (see above). An *enhancement* in selectivity with the in situ method, however, was

(1) For a recent review, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.
(2) (a) Consiglio, G.; Indolese, A. *Organometallics* **1991**, *10*, 3425−3427. (b) Nomura, N.; Rajanbabu, T. V. *Tetrahedron Lett.* **1997**, *38*, 1713−1716.
(3) Hiyama, T.; Wakasa, N. *Tetrahedron Lett.* **1985**, *26*, 3259−3262.
(4) For a recent review on asymmetric conjugate addition, see: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771−806. For catalytic asymmetric conjugate additions of "hard" nucleophiles, see: (a) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron Lett.* **1993**, *34*, 7725−7728. (b) Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275−4278. (c) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620−2623.
(5) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291−4298 and references therein. For a recent review, see: Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262−1284.
(6) (a) Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994**, *116*, 3123−3124. (b) Reference 5. (c) Visser, M. S.; Harrity, J. P. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 3779−3780.
(7) Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097−7104.
(8) For previous nonasymmetric efforts in this area, see: Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273−7274.
(9) For previous reports on Ni-catalyzed addition of Grignard reagents to allylic acetals (nonasymmetric), see: (a) Wenkert, E.; Ferreira, T. W. *Organometallics* **1982**, *1*, 1670−1673. (b) Sugimura, H.; Takei, H. *Chem. Lett.* **1985**, 351−354.
(10) Fukutani, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5911−5912.
(11) In all cases, in the absence of a Ni complex, <2% reaction is detected. It is imperative that starting materials of the highest levels of purity are used.
(12) Morandini, F.; Consiglio, G.; Piccolo, O. *Inorg. Chim. Acta* **1982**, *57*, 15−19.
(13) Enantioselectivities were determined by chiral GLC and ^{13}C NMR analysis. For determination of enantiomeric purity by ^{13}C NMR spectroscopy, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183−2186.
(14) Cyclopentenyl acetal **2** afforded racemic products under both conditions (75−90% yield).

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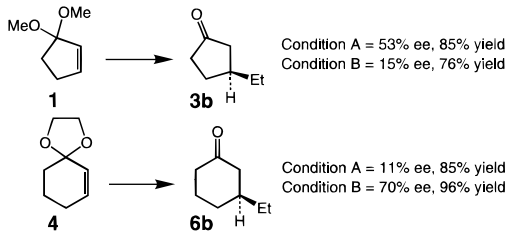
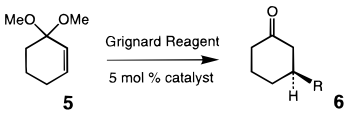
Scheme 2[a]



[a] Condition A: 5 mol % **7**, 3 equiv of EtMgCl, 22 °C, 15 h. Condition B: 5 mol % (*S*,*S*)-chiraphos, 5 mol % $(PPh_3)_2NiCl_2$, otherwise same as A.

Table 2. Ni-Catalyzed Enantioselective Alkylation of Unsaturated Acetal **5**[a]



entry	Grignard reagent	product	enantiomer ratio (% ee)[b]	yield (%)
1	EtMgBr	**6b**; R = Et	92.5:7.5 (85)	90
2	*n*-BuMgCl	**6c**; R = *n*-Bu	92.5:7.5 (85)	85
3	*i*-BuMgCl[c]	**6d**; R = *i*-Bu	85:15 (70)	63
4	PhMgBr	**6a**; R = Ph	91.5:8.5 (83)	67
5	$PhCH_2CH_2MgCl$	**6e**; R = $(CH_2)_2Ph$	92:08 (84)	81

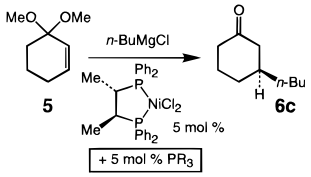
[a] Conditions: Same as condition B in Scheme 2. [b] Determined by chiral GLC analysis (±2%) of ketals from (2*R*,3*R*)-butanediol (ALPHADEX, Alltech for entries 1−3; BETADEX, Alltech for entries 4 and 5) or ^{13}C NMR analysis (±4%; entry 2). Isolated yields. [c] Reaction run at 50 °C (4 h).

unexpected. We subsequently established that excess triphenylphosphine is the reason for the rise in selectivity: with 5 mol % **7** and 10 mol % PPh_3, 70% ee is attained.[15]

The increase in enantioselection due to the presence of additional PPh_3 is yet more pronounced with dimethyl acetal **5**. As shown in entry 1 of Table 2, *when* ***5*** *is treated with 3 equiv of EtMgBr, 5 mol % $(PPh_3)_2NiCl_2$, and 5 mol % (S,S)-chiraphos,* ***6b*** *is obtained in 85% ee in 90% yield after chromatography* (chiral GLC).[16] In contrast, with 5 mol % **7** and no PPh_3, **6b** is isolated in 10% ee (80% yield). Further studies indicated that 10 mol % excess PPh_3 is optimal. For example, with **5** as the substrate and *n*-BuMgCl, *rac*-**6c** is formed with 5 mol % (*S*,*S*)-(chiraphos)$NiCl_2$ (50% yield)); addition of 5 mol % PPh_3 elevates selectivity to 82% ee (65% yield). Whereas with 10 mol % PPh_3, 85% ee is obtained (entry 2, Table 2), when 20 mol % phosphine is used, selectivity is reduced to 76% ee (81% yield). Examination of various other monodentate phosphines, for reactions of **5** with *n*-BuMgCl and PhMgBr, did not provide a more effective auxiliary ligand (Table 3). These results signify that (i) more Lewis basic phosphines (e.g., PBu_3) or phosphines with larger cone angles are detrimental to enantioselection[17] and (ii) higher reaction efficiency does not necessarily accompany better enantioselectivity (e.g., compare entries 1 and 9, Table 3).

High selectivities are achieved with a number of alkylmagnesium halides (Table 2). Several issues in connection to the data in Table 2 merit comment: (1) Asymmetric induction is inferior with Et_2O as solvent (vs THF); as an example, in Et_2O, **5** → **6b** (entry 1, Table 2) proceeds in 79% ee (76% yield). (2) As shown in Table 2, depending on the Grignard reagent used, the corresponding bromide or chloride salts of the Grignard reagent can give rise to different selectivities. For instance, when PhMgCl is used, **6a** is obtained in 66% ee and 70% yield (vs 83% ee and 67% yield with PhMgBr). (3) Chiraphos has so far proved superior to a variety of other chiral bidentate bisphosphines. The following data were obtained for **5** → **6a** (PhMgBr) and are representative: prophos 49% ee (66% yield); binap <5% ee (35%); Me-duphos 26% ee (62%); diop <5% ee (42%); (*S*,*S*)-1,2-ethanebis(methylphenylphosphine)[18] 7% ee (45%).[19]

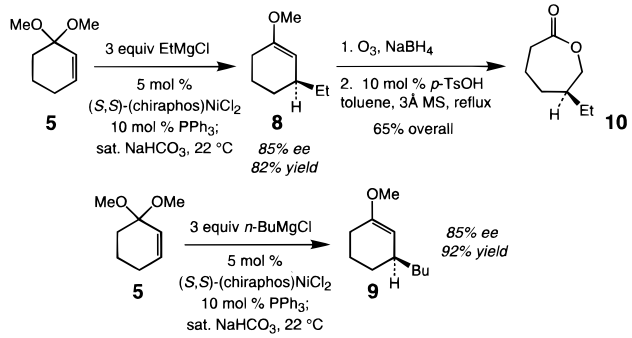
Table 3. Influence of Various Phosphines on Enantioselectivity of the Ni-Catalyzed Reaction[a]



entry	added phosphine	conv (%)	ee (%)
1	PPh_3	61	82
2	$P(p\text{-}FC_6H_4)_3$	80	76
3	$P(m\text{-}ClC_6H_4)_3$	88	78
4	$P(m\text{-}OMeC_6H_4)_3$	87	76
5	P(2-furyl)$_3$	60	40
6	$P(C_6F_5)_3$	66	35
7	PBu_3	56	13
8	PCy_3	50	11
9	$P(o\text{-}MeC_6H_4)_3$	88	<5

The Ni-catalyzed C−C alkylation can lead to the enantioselective synthesis of regioisomerically pure enol ethers (Scheme 3). Reaction of **5** with Et- and *n*-BuMgCl, followed by mild basic workup, results in the formation of enol ethers **8** and **9** in 85% ee (82% and 92% yield, respectively). Development of catalytic alkylations that may be applied to other ring systems with high enantioselectivity is in progress. However, we anticipate that the availability of nonracemic enol ethers will provide access to additional optically enriched ring structures of various sizes (e.g., **5** → **10** in Scheme 3).

Scheme 3



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Supporting Information Available: Experimental procedures and spectral and analytical data for all reaction products (12 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(15) Time-dependent studies indicate that the effect of PPh_3 is not due to stabilization of the active catalyst.

(16) The catalytic process may also be carried out with lower loadings of $(PPh_3)_2NiCl_2$ and (*S*,*S*)-chiraphos; catalytic alkylation of **5** with EtMgCl affords **6b** in 79 and 83% ee (>90% yield) with 1 and 3 mol % Ni complex and the chiral ligand (48 h, 22 °C).

(17) Representative cone angles: PPh_3 145°, $P(C_6F_5)_3$ 184°, $P(o\text{-}MeC_6H_4)$ 194°.

(18) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075−9076.

(19) Reactions in the presence of excess (*S*,*S*)-chiraphos do not afford improved enantioselectivity.