Tetrahedron Letters, Vol. 33, No. 41, pp. 6187-6190, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

OBSERVATIONS ON A NICKEL-CATALYZED ISOMERIZATION OF ALLYLIC LITHIUM ALKOXIDES

William B. Motherwell* and David A. Sandham

Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, U.K.

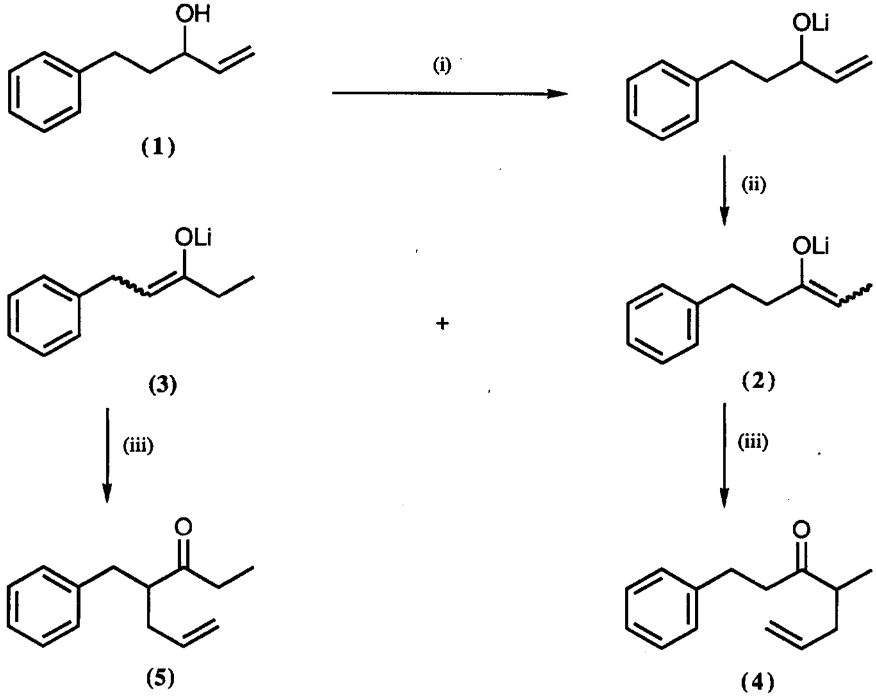
Key Words: aldol reaction; allylic alkoxide; isomerization; lithium enolate; transition metal.

Summary: Use of the complex $(Cy_3P)_2NiCl_2$ rather than $[Rh(dppe)]ClO_4$ as catalyst facilitates regioselective preparation of lithium enolates *via* isomerization of the corresponding allylic alkoxides. The nickel catalyst also succeeds in isomerizing certain di- and trisubstituted allylic alkoxides that are inert to the rhodium system.

In a recent communication,[1] we have introduced the simple concept that transition metal-mediated isomerization of pre-formed allylic alkoxides provides a novel and direct method for the generation of enolate anions without recourse to the chemistry of the carbonyl group. Our initial study focussed on the behaviour of lithium alkoxides derived from monosubstituted alkenes and the selection of the cationic rhodium catalyst $[Rh(dppe)]ClO_4$ for isomerization was made, on the basis of mechanistic considerations relating to the desire for operation of a π-allyl hydride intermediate.[2]

In the course of further experiments designed to extend the range of this approach, we were dismayed however to discover that isomerization of the lithium alkoxide of 1-phenyl-4-penten-3-ol (**1**) under our standard conditions[1] for seven hours, led, after allyl bromide quench, to isolation of *both* regioisomers (**4**) and (**5**) of alkylated products (79%, (**4**):(**5**); 1:1.2) (Scheme 1). Although we had anticipated that isomerization of the initial alkoxide would, unlike the resultant enolate (**2**), benefit in energy terms from oxygen lone pair participation, further isomerization of (**2**) was clearly occurring at an unacceptable rate. Indeed, careful monitoring of the isomerization revealed that both enolates (**2**) and (**3**), between which there is no distinct kinetic or thermodynamic preference, were present at an early stage of the reaction. The possibility that enolate equilibration was catalyzed by the presence of a small concentration of the free carbonyl compound[3] was effectively ruled out in an experiment using 1.5 molar equivalents of butyllithium with respect to alcohol (**1**). In this case both isomers (**4**) and (**5**) were again isolated (70%, (**4**):(**5**); 1:1.3). All efforts to enhance the rate of the initial isomerization through production of "monomeric" lithio species[4] by using additives such as TMEDA, HMPA, DMPU, crown ethers[5] and podand ligands[6] were uniformly unsuccessful.

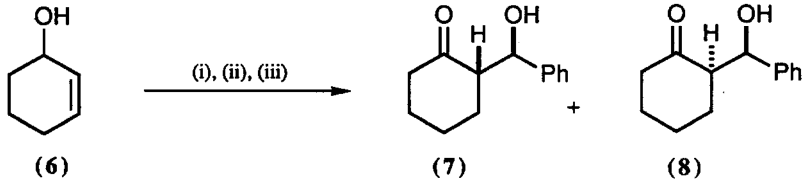
At this stage, we therefore elected to study the possibility of using an alternative transition metal catalyst. We were particularly intrigued by an isolated report describing the preparation of an isolable nickel hydride, $(Cy_3P)_2NiHCl$, by hydride transfer from an alkoxide to the dichloride $(Cy_3P)_2NiCl_2$[7] and reasoned that *in situ* generation of such a species could provide a suitable catalyst for allylic alkoxide isomerization. In the event, addition of $(Cy_3P)_2NiCl_2$ (10mol%) to a thoroughly degassed THF solution of the lithium alkoxide (1.25mmol), generated by addition of *excess* *n*-butyllithium (1.05 equivalents with respect to alcohol (**1**)),



Reagents: (i) *n*-BuLi; (ii) catalyst; (iii) allyl bromide

CATALYST	YIELD	(4) : (5)
[Rh(dppe)]ClO_4	79%	1:1.2
$(Cy_3P)_2NiCl_2$	78%	15:1

SCHEME 1



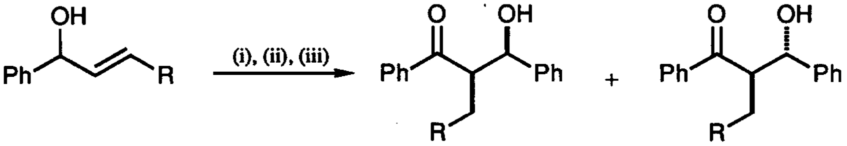
4.2 : 1 (64%)

Reagents: (i) *n*-BuLi (1.05eq); (ii) $(Cy_3P)_2NiCl_2$ (10mol%); (iii) PhCHO, -78°C

SCHEME 2

followed by heating at reflux for one hour, afforded, after alkylation, ketone (**4**). Only a trace of the undesired regioisomer (**5**) was observed (Scheme 1).

The nickel system was also successfully employed for the isomerization of the lithium alkoxide of 2-cyclohexen-1-ol (**6**) (Scheme 2). Thus, although a longer reaction time (24 hours) was required for isomerization, trapping of the resultant enolate with benzaldehyde afforded a good yield of aldol products (**7**) and (**8**) whose diastereomeric ratio was in accord with the reported literature range.[8(a)-(c)] Contrastingly, in this case where geometric constraints impose mandatory formation of an *E*-enolate (*vide infra*), use of the [Rh(dppe)]ClO$_4$ catalyst led to recovery of starting material.



(**9**) R=H
(**12**) R=CH$_3$

(Z-enolate)
(**10**) R=H
(**13**) R=CH$_3$

(*E*-enolate)
(**11**) R=H
(**14**) R=CH$_3$

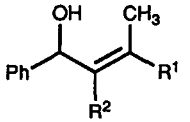
Reagents: (i) *n*-BuLi (excess with catalyst B); (ii) catalyst A: [Rh(dppe)]ClO$_4$ or catalyst B: (Cy$_3$P)$_2$NiCl$_2$; (iii) PhCHO, -78°C

SUBSTRATE	CATALYST (mol%)	PRODUCTS (Ratio and yield)		
(9)	A (2%)	(10):(11)	8.6:1	(84%)
(9)	B (10%)	(10):(11)	6.6:1	(81%)
(12)	A (2%)	(13):(14)	3:1	(71%)
(12)	B (10%)	(13):(14)	3:1	(86%)

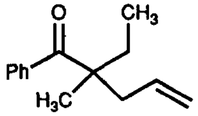
SCHEME 3

As we had previously noted a Z-enolate selectivity for monosubstituted acyclic alkoxides using the [Rh(dppe)]ClO$_4$ catalyst, it was of interest to examine the stereochemical behaviour of the nickel species in this context and also to extend these types of reaction to more highly substituted allylic alcohols. The comparative results for a series of aldol reactions under kinetic control[8(c)] using alcohols (**9**) and (**12**) are shown in Scheme 3 and indicate that, although the present nickel catalyst system is slightly inferior to that employing rhodium, an inherent preference for Z-enolate formation is nevertheless maintained. Clearly, increased substitution around the double bond is also a contributory factor in determining the degree of stereoselection in the reaction.

Finally, we have also examined reactions of the trisubstituted allylic alcohols (**15**) and (**16**), for which transition metal-mediated isomerization is generally acccepted to be a more demanding process.[9] Indeed, attempted isomerization of the lithium alkoxide of (**15**) using either the rhodium or nickel systems led essentially to recovery of starting materials. However, generation of the tetrasubstituted enolate from the lithium alkoxide of **(16)** was most effectively accomplished using the nickel catalyst (20mol% for 24 hours in refluxing THF) as measured by isolation of the alkylated derivative **(17)** (75%) from quenching with allyl bromide. Interestingly, isolation of the "unreacted" alcohol **(16)** from this reaction revealed that substantial isomerization of the double bond had occurred, with conversion of the original 7:1 *Z:E* ratio of geometric isomers to a 2.8:1 ratio. Under similar conditions using the rhodium catalyst, the recovered alcohol was unchanged in isomeric composition and only 5% of the alkylated derivative **(17)** was obtained.



(15) R^1=CH_3, R^2=H
(16) R^1=H, R^2=CH_3



(17)

Mechanistic studies are currently underway to resolve the differing behaviour of the rhodium and nickel catalysts and hence enable the design of more selective systems. Nevertheless, the present communication has shown that the nickel system offers several advantages, insamuch as it provides a high degree of regiocontrol for enolate generation and also gives a workable method for isomerizing certain di- and trisubstituted allylic alkoxides.

Acknowledgments: We thank the S.E.R.C. for the provision of a studentship (to D.A.S.) and Quest International for invaluable financial assistance

References and notes.

1. Edwards, G.L.; Motherwell, W.B.; Powell, D.M.; Sandham, D.A., *J. Chem. Soc., Chem. Commun.*, 1991, 1399
2. For a detailed mechanistic discussion of these processes, see Bergens, S.H.; Bosnich, B., *J. Am. Chem.Soc.*, 1991, **113**, 958.
3. Rathke, M.W.; Lindert, A., *Synth. Commun.*, 1978, **8**, 9.
4. Seebach, D., *Angew. Chem. Int. Ed. Engl.*, 1988, **27**, 1624.\
5. Anet, F.A.L.; Krane, J.; Dale, J.; Daasvatn, K.; Kristiansen, P.O., *Act. Chem. Scand.*, 1973, **27**, 3395.
6. Heimann, U.; Heizholt, M.; Votgle, F., *Chem. Ber.*, 1979, **112**, 1392.
7. Kalies, W.; Witt, B.; Gaube, W., *Z. Chem.*, 1980, **20**, 310.
8. (a) Seebach, D.; Hidber, A., *Chimia*, 1983, **37**, 449. (b) Hirama, M.; Noda, T.; Takeishi, S., *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2645. (c) Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.C.; Sohn, J.E.; Lampe, J., *J. Org.Chem.*, 1980, **45**, 1066.
9. Baudry, D.; Ephritikhine, M.; Felkin, H., *Nouv. J. Chem.*, 1978, **2**, 355.

(Received in UK 28 July 1992)