From Allylic Alcohols to Aldols via a Novel, Efficient Reaction Catalyzed by Ni-Complexes

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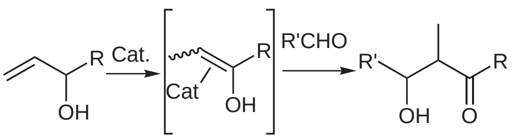
Received 10 October 2003

Abstract: Allylic alcohols react with aldehydes, in an atom economic aldol-type reaction, in the presence of a catalytic amount of (dppe)NiHCl/$MgBr_2$ mixture. This reaction occurs in good to excellent yields with total regiocontrol and very high chemo control under mild conditions. It is compatible with various types of aldehydes including very bulky ones.

Key words: allylic alcohols, double bond isomerization, aldol reaction, nickel hydrides

The aldol reaction is a fundamental process for the creation of C-C bonds.[1] We have recently developed a novel tandem isomerization–aldol condensation mediated by transition metal catalysts.[2] Following a known process,[3] an allylic alcohol is converted by the catalyst to a complexed enol and/or a transition metal enolate that is trapped in situ by an aldehyde to give an aldol product (Scheme 1).[4]



Scheme 1

The reaction has first been performed using iron catalysts such as $Fe(CO)_5$, (bda)$Fe(CO)_3$ or (COT)$Fe(CO)_3$.[2a–c] Then, it has been extended to Ru and Rh catalysts[2d,5] [e.g. $(PPh_3)_3RhH$ or $(PPh_3)_3RuHCl$]. It must be underlined that, in all cases, these reactions occur under mild conditions and furthermore are atom economic processes.[6] The limitation of the use of an iron catalyst is the competitive formation of regioisomeric aldols and ketones. Moreover, the diastereoselectivity of the reaction is low. In the presence of Ru or Rh catalysts, the reaction is regioselective but has a much narrow scope.

In order to improve the selectivity and the efficiency of this reaction, we have screened various nickel complexes and we report here our preliminary results demonstrating that some nickel hydride catalysts are able to perform the reaction very efficiently and with a complete control of the regio- and the chemoselectivities, however with a modest diastereoselectivity.

It has been demonstrated previously that using appropriate Ni or Rh based catalysts, allylic alcoholates have been isomerized to the corresponding enolates, followed by aldol reactions.[7] However, this original stepwise procedure is less efficient in term of atom economy. Nickel enolates have been isolated and used in various reactions, including aldol condensations.[8] Recently, some nickel hydride derivatives {(e.g. NiI_2[(–)-Me-DUPHOS]/$LiBHEt_3$} have also been reported to be excellent catalysts for the asymmetric isomerization of cyclic allyl acetals.[9] So, it was anticipated that such Ni-H complexes would be able to catalyze also the isomerization of allylic alcohols. However, even if the isomerization step could be expected to proceed, the possibility for the intermediate to be trapped by a carbonyl derivative was more challenging. Therefore, we have tested three different nickel hydride catalysts **1**–**3** (Figure 1) to perform our tandem allylic alcohol isomerization-aldol condensation reaction using octen-3-ol **4** and isovaleraldehyde as models.

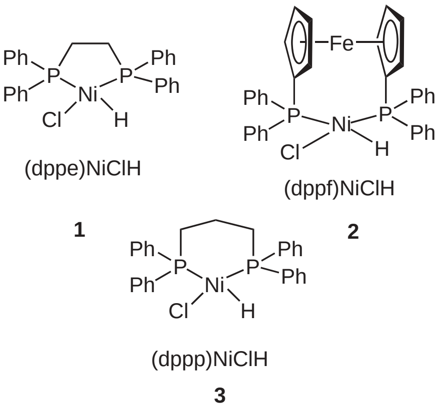


Figure 1

Catalyst **1** was first generated from (dppe)$NiCl_2$ and $LiBHEt_3$[9] (Scheme 2, method A) and tested at 5 mol% (Scheme 3 and entry 1, Table 1). The mixture of two diastereoisomeric aldols was isolated in only 26% yield, the main compound formed in the reaction being ketone **6**. Such Ni-H complexes can also be obtained by reaction of the nickel chloride complex and a Grignard reagent followed by addition of TMSCl to the resulting intermediate.[10] (Table 1 and Scheme 2, method B).

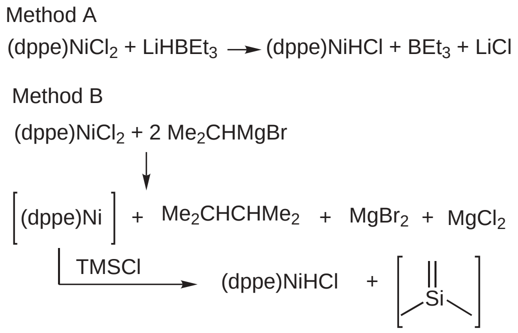
SYNLETT 2004, No. 1, pp 0093–0096
Advanced online publication: 4.12.2003
DOI: 10.1055/s-2003-43373; Art ID: G27603ST

Table 1 Catalyst Optimization

Entry	R′	Cat.[a] amount (mol%)	Co-reagent (mol%)	Time	**5** Yield (%)	**5** *Syn*/*anti*[12]	**6** Yield (%)
1	Me_2CHCH_2	A, 5	–	2 h	26	76/24	51
2	Me_2CHCH_2	B, 5	–	1 h 25 min	94	60/40	1
3	Me_2CHCH_2	A, 5	$MgBr_2$, 5	40 min	95	70/30	–
4	Me_2CHCH_2	A, 3	$MgBr_2$, 3	50 min	92	70/30	2
5	Me_2CHCH_2	B, 5	BEt_3, 5	45 min	89	60/40	5
6	Ph	B, 5	–	3 h 45 min	85[b]	60/40	–
7	Ph	B, 5	BEt_3, 5	2 h	99	60/40	–
8	Ph	A, 3	$MgBr_2$, 3	50 min	99	60/40	–
9	Ph	C, 3	$MgBr_2$, 3	1 h	97	62/38	–

[a] Method A: (dppe)$NiCl_2$ (**1**) + $LiHBEt_3$; method B: (dppe)$NiCl_2$ (**1**) + 2 $Me_2CHMgBr$ then TMSCl; method C: (dppf)$NiCl_2$ (**2**) + $LiHBEt_3$.

[b] +12% Recovered starting material.

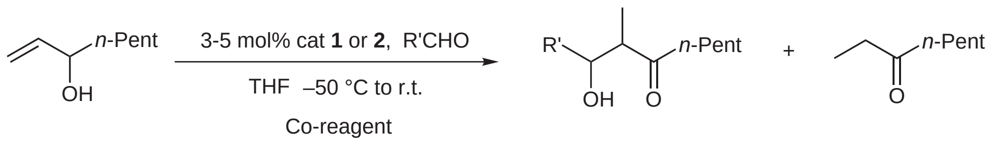


Scheme 2

Thus, Ni-H complex **1** was generated in this way and tested. We observed a significant increase of the efficiency of the reaction as the aldol products were isolated in 94% yield (entry 2). Such a result could be explained by a possible key role of $MgBr_2$, which is a by-product in the formation of the active catalyst in method B. So, the reaction has been performed with a solution of the catalyst **1** obtained from $LiHBEt_3$ and in the presence of 5% $MgBr_2$. In this case, the reaction was completed in 40 minutes and the mixture of the two aldols was isolated in 95% yield. No trace of ketone or regioisomeric aldol was isolated (entry 3). This result demonstrates the critical importance of the presence of $MgBr_2$. Although the exact role of $MgBr_2$ has not yet been established, it is known to act as a coordinating agent in aldol reactions.[11] Finally, it must be underlined that the reaction can be performed with only 3 mol% of the Ni-H hydride catalyst and 3 mol% of $MgBr_2$ (entry 4).

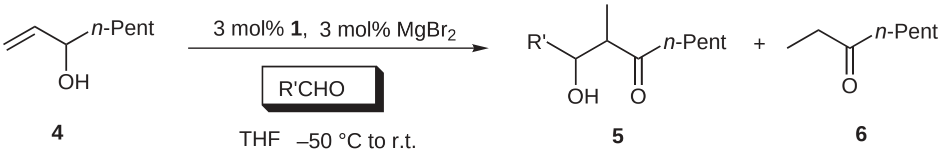
Moreover, formation of the catalyst from $LiHBEt_3$ generates BEt_3 as a by-product in the reaction mixture. Therefore, we tried to evaluate the putative influence of this compound on the reaction. We compared the reactivity of the catalyst formed following the ‘Grignard’ procedure (method B) in the presence and in the absence of added BEt_3 (5%). We could observe a slight increase of the reactivity when benzaldehyde was used as the carbonyl compound. Such improvement could not be noticed when isovaleraldehyde was used (entries 5–7). So, it is clear that BEt_3 plays a less important role than $MgBr_2$ in this reaction.

Then, we tried catalysts **2** and **3**, which bear different phosphine ligands. In the presence of 3 mol% of catalyst **2** and 3 mol% of $MgBr_2$ (Table 1, method C), the reaction of octen-3-ol and benzaldehyde was completed after 1 hour and the mixture of the two diastereoisomeric aldols was isolated in 97% yield (entry 9). So, catalyst **2** exhibits a close reactivity compared to catalyst **1** (entry 8). On the contrary, catalyst **3** is completely inefficient not only in the aldolization reaction but also in the isomerization of octen-3-ol to octanone **6**, starting material being fully recovered. This establishes that the nature of the phosphine ligand has a critical effect on the reaction.



4 **5** **6**

Scheme 3



Scheme 4

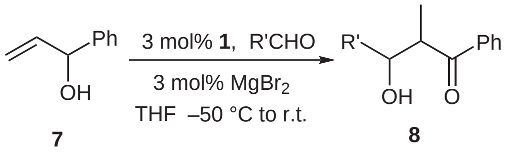
Table 2 Extension to Various Aldehydes

Entry	R′	Time	**5** Yield (%)	**5** *Syn*/*anti*	**6** Yield (%)
1	Ph	50 min	99	60/40	–
2	Me$_2$CH	1 h	93	66/34	2
3	Et$_2$CH	2 h 30 min	84	69/31	4
4	AcNHPh	1 h	91	67/33	–
5	tBu	55 min	68	76/24	15
6	AcOCH$_2$furyl	45 min	94	57/43	–
7	EtCH=CH(CH$_2$)$_2$	1 h	94[a]	–	–

[a] Partial isomerization of the double bond of the aldehyde part was observed.

Having a very efficient catalyst in hands we screened various aldehydes (Scheme 4, Table 2). The reaction is compatible with many different aldehydes even with those bearing a very bulky or a functionalized group. The results obtained with pivalaldehyde (entry 5) and 2-ethylbutyraldehyde (entry 3) are particulary noteworthy as very few aldol reactions (0–20% yield) were observed previously with Fe, Rh or Ru catalysts.

Phenyl allyl alcohol **7** proved to be also a very good substrate for the reaction. Under the same reaction conditions it gave excellent yields both with benzaldehyde and isobutyraldehyde (Scheme 5).



R' = Me$_2$CH : 86% yield; *syn*/*anti* :50/50

R' = Ph : 97% yield ; *syn*/*anti* : 60/40

Scheme 5

To conclude, we have shown that NiHCl(dppe)/MgBr$_2$ is a very active catalytic system for the isomerization–aldolization reaction of allylic alcohols and aldehydes. The reaction is compatible with a wide range of aldehydes including very bulky ones. It gives good to excellent yields and is completely regioselective, however with a modest diastereoselectivity. It proceeds at, or below, room temperature and in the presence of a rather low catalyst loading (3 mol%). The reaction is far more efficient than the Ru-H or Rh-H catalyzed reaction[2d] as the latter is only possible with a narrow panel of substrates. Furthermore, the latter reactions were occurring at reflux of THF. Similarly, the RuCl$_2$(PPh$_3$)$_3$ catalyzed reaction needs high temperatures (90–110 °C).[5] A final advantage of these Ni-H catalysts is that the use of chiral non racemic ligands can now be envisaged for this reaction. Therefore, extensions to asymmetric catalysis and total synthesis are currently under way.

Procedure for Aldolization of an Allylic Alcohol with an Aldehyde via a Nickel Complex as Catalyst: Method A.
To a solution of (dppe)NiCl$_2$ (30 mg, 0.0567 mmol) and anhyd MgBr$_2$ (10 mg, 0.0567 mmol) in anhyd THF (3 mL) under a nitrogen atmosphere was added a 1 M LiBHEt$_3$ solution in THF (57 μL, 0.0567 mmol). The reaction mixture was stirred at r.t. for 5 min and cooled to –50 °C. Aldehyde (2.08 mmol) and allylic alcohol (1.89 mmol) were successively added. The temperature was raised to r.t. and the reaction mixture was followed by TLC until disappearance of the allylic alcohol. The reaction mixture was quenched with a sat. solution of NH$_4$Cl (15 mL) and the aq phase was extracted with Et$_2$O (3 × 50 mL). The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.[12]

Acknowledgment

We thank P. Guenot (CRMPO Rennes) for performing mass experiments.

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