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From Allylic Alcohols to Aldols through a New Nickel-Mediated Tandem Reaction: Synthetic and Mechanistic Studies

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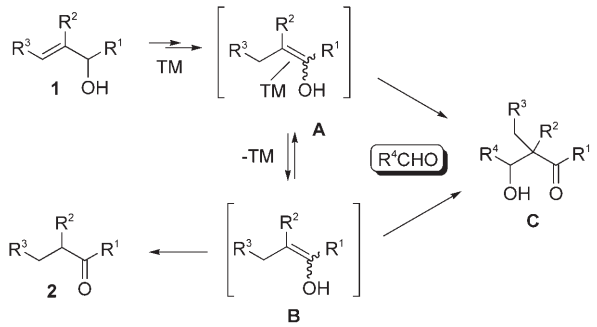
Abstract: Nickel hydride type complexes have been successfully developed as catalysts for the tandem isomerization–aldolization reaction of allylic alcohols with aldehydes. Optimization of the reaction conditions has shown that a cocatalyst, such as $MgBr_2$, has a very positive effect on the kinetics of the reaction and in the yields of aldols. Under such optimized conditions {[NiHCl(dppe)] + $MgBr_2$ at 3–5 mol%)}, this reaction affords the aldols in good to excellent yields. It is a full-atom-economy-type reaction that occurs under mild conditions. Furthermore, it has a broad scope for the allylic alcohols and it is compatible with a wide range of aldehydes, including very bulky derivatives. The reaction is completely regioselective, but it exhibits a low stereoselectivity, except for allylic alcohols with a bulky substituent at the carbinol center. The use of chiral nonracemic catalysts was not successful, affording only racemic compounds. However, it was possible to use asymmetric synthesis for the preparation of optically active aldols. Various mechanistic studies have been performed using, for instance, a deuterated alcohol or a deuterated catalyst. They gave strong support to a mechanism involving first a transition-metal-mediated isomerization of the allylic alcohol into the free enol, followed by the addition of the latter intermediate onto the aldehyde in an "hydroxyl–carbonyl–ene" type reaction. These results confirm that allylic alcohols can be considered as new and useful partners in the development of the aldol reaction.

Keywords: aldol reaction · allylic compounds · ene reaction · enols · nickel

Introduction

The aldol reaction is one of the most commonly used reactions to create new C–C bonds. The original direct aldol condensation between two carbonyl components was performed under acid or base catalysis.[1] It is an early example of a full-atom-economy reaction,[2] but the lack of regio- and stereocontrol, as well as the presence of evolution products (such as alkenes by crotonization), were some of the limitations of this process. However, in the last 10 years many efforts have been devoted to overcome these limitations and to obtain fully controlled direct aldol reactions. Highly successful developments include the uses of: 1) catalytic antibodies,[3] 2) proline and analogues derived catalysts ("organocatalysis"),[4] and 3) transition-metal complexes.[5] Our goal was to develop a new, full-atom-economy approach to the aldol reaction starting from easily available allylic alcohols, as indicated in Scheme 1.

The transposition of allylic alcohols **1** into saturated carbonyls **2**, mediated by transition-metal catalysts (TM), is a known process.[6] Mechanistic studies have strongly suggest-



Scheme 1. Working hypothesis for the tandem isomerization–aldolization process.

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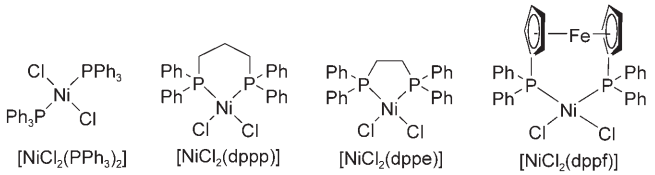
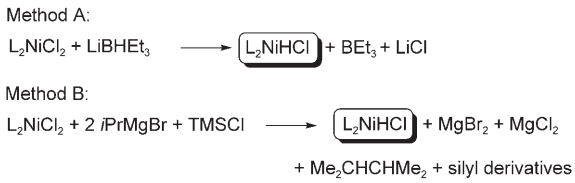
ed that it involves, as late intermediates, type **A** enols complexed to the transition-metal catalyst as well as the free enols **B**. Therefore, as a working hypothesis we considered the possibility to trap such intermediates by aldehydes in a new aldol-type process. Support to this was given by an early work indicating that $RuCl_3$ could perform an isomerization–aldolization followed by crotonization.[7] Furthermore, previous results from Bosnich's group have demonstrated that it is possible to trap free enols by strong electrophiles, such as iminium salts or TCNE.[8] Finally, the results from Motherwell's group demonstrating the possible use of rhodium or nickel catalysts to isomerize allylic alcoholates into the corresponding enolates and trap the latter derivatives in aldol reactions are also to be noticed.[9] Our first experiments were performed by using iron–carbonyl-derived catalysts, which proved to be very efficient for this new tandem isomerization–aldolization process.[10] The corresponding reactions occurred under very mild conditions and gave, in most cases, good yields in aldol products. However, they were not fully regiocontrolled and the stereocontrol was also poor. Therefore, other transition-metal complexes were screened for this tandem reaction. Among them, rhodium and ruthenium derivatives were demonstrated as possible catalysts: they perform this reaction with a complete regiocontrol, but with a low stereocontrol and a more limited scope.[11,12] Nickel catalysts appeared of much interest to us, since such derivatives have been used in the isomerization of allylic alcohols into saturated carbonyls.[13] Furthermore, they have also been successfully developed recently in the asymmetric isomerization of cyclic allylic ethers into vinyl ethers in very good yields and excellent enantiomeric excesses (*ee*'s).[14] Therefore the purpose of this paper is: 1) to describe our efforts in the development of new nickel hydride catalysts for the tandem isomerization–aldolization of allylic alcohols, 2) to define the scope and limitations of these new catalysts, 3) to report our results regarding their extension to asymmetric synthesis and catalysis, and 4) to present the results of experiments using labeled compounds. Based on these data, a tentative mechanism will be proposed for these reactions: the transition-metal catalyst induces first the isomerization of the allylic alcohols into the free enols. In a second step, these derivatives react with the aldehydes in an "hydroxyl–carbonyl–ene" type reaction to afford the aldol products.[15] Such a mechanism not only accounts for the experimental results, but it is also in full agreement with the conclusions obtained from recent high-level computational studies, using iron–carbonyl species as catalysts.[16]

Results and Discussion

Development of new nickel hydride catalysts for the tandem isomerization–aldolization: The nickel hydrides appeared as very attractive candidates as catalysts, since they can be prepared from nickel dichloride precursors bearing a large variety of ligands L_2, including chiral nonracemic derivatives. In a first step, four commercially available complexes **3–6** have been selected.

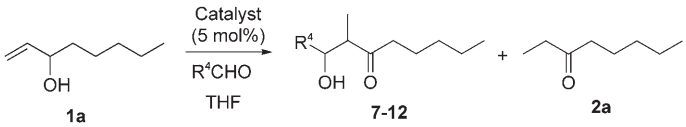


Essentially two methods have been developed to prepare the nickel hydrides: they involve the reaction of nickel dichloride complexes either with $LiBHEt_3$ (Method A),[17] or with a combination of isopropyl Grignard and Me_3SiCl (Method B, Scheme 2).[18]



Scheme 2. Methods used for the synthesis of the nickel hydride catalysts.

Therefore, the first step of our study was to select the appropriate catalysts and to optimize the reaction conditions. The reaction of octen-3-ol (**1a**) with benzaldehyde was chosen as a model reaction to screen the activity of the catalysts derived from the four nickel complexes **3–6** (Scheme 3).



Scheme 3. Model reaction used for the selection of the catalyst.

In a first series of experiments, these catalysts were generated by addition of one molar equivalent of the Super-Hydride™ solution to the nickel complexes in THF (Method A), followed by addition of octen-3-ol and benzaldehyde at room temperature. The results are given in Table 1: at 5 mol%, the catalysts derived from complexes **3** and **4** were completely inactive and only the starting products were recovered (entries 1 and 2). In contrast, in the case of complexes **5** and **6**, a total conversion was observed and the aldol products **7** could be obtained in 44 and 32% yield, respectively, together with the isomerization product **2a**. Only a low stereoselectivity was obtained in favor of the *syn* isomer (entries 3 and 5). However, it was of much interest to notice that this reaction was highly regiocontrolled, since no trace of the regioisomeric aldols could be detected by

Table 1. Selection of the nickel hydride catalysts.

	Precatalyst	R^4	T [°C]	t [min]	Conversion [%]	Aldol yield [%]	*syn*/*anti*	**2a** [%]
1	**3**	Ph	RT	120	0	–	–	–
2	**4**	Ph	RT	240	0	–	–	–
3	**5**	Ph	RT	100	100	**7** (44)	(60:40)	32
4	**5**	Ph	−50 to RT	120	100	**7** (81)	(60:40)	15
5	**6**	Ph	RT	30	100	**7** (32)	(74:26)	43
6	**6**	Ph	−50 to RT	90	100	**7** (37)	(67:33)	33
7	**5**	H	−50 to RT	300	100	**8** (30)	–	53
8	**5**	CH_3	−50 to RT	240	100	**9** (26)	(68:32)	39
9	**5**	nC_5H_{11}	−50 to RT	170	100	**10** (15)	(72:28)	60
10	**5**	*i*Bu	−50 to RT	120	100	**11** (26)	(76:24)	51
11	**5**	*i*Pr	−50 to RT	165	100	**12** (18)	(70:30)	64

NMR analysis of the crude reaction mixtures. Lowering the temperature afforded a significant improvement in yield in the case of the complex **5** (entry 4), but no significant change was observed in the case of **6** (entry 6). The same reaction conditions were applied to formaldehyde and several aliphatic aldehydes (entries 7 to 11), but the yields remained low (<30%).

So, clearly, a further optimization of the nature of the catalyst and reaction conditions had to be performed and this was done using octen-3-ol and isovaleraldehyde as models (Table 2). We first checked the method used for the preparation of the nickel hydride catalyst: to our surprise, by using the second method with the Grignard reagent and Me_3SiCl, a quantitative transformation was observed and the aldols were obtained in excellent overall yield (94%) with only traces of the octan-3-one (entry 2).

This was a strong indication that, besides the nickel hydride, some other important co-reagent was present when the second method was used. Based on the proposed mechanism, it appeared that magnesium salts could be generated under those conditions.[18] Therefore, in a complementary experiment, one equivalent of $MgBr_2$ was added to the catalyst generated by the first method (using $LiBHEt_3$) before starting the reaction with the allylic alcohol and the aldehyde: under those conditions, the aldols were obtained in excellent yield (95%) and in only 40 min (entry 3)! With this new catalytic system, it became possible to use only 3 mol% of the catalysts (entry 4) and furthermore, similar results were obtained with benzaldehyde (entries 5, 6). Therefore, the magnesium salt plays a key role as a cocatalyst for this reaction. Such a catalytic effect of $MgBr_2$ has already been observed in aldol reactions and this could be explained by the activation of the carbonyl component by the Lewis acid character of this salt.[19] The same results were obtained starting from the diferrocenyl complex **6** (entry 7). Using the same model reaction and under these optimized reaction conditions, a large variety of other salts have been evaluated as possible cocatalysts (Table 3).

From these results, it is clear that many of them can be used in this reaction, except the very strong Lewis Acids such as $BiCl_3$ or $TiCl_4$. It is worth noting that for these nickel hydride catalysts, $In(OAc)_3$ is not very efficient

Table 2. Optimization of the reaction conditions.

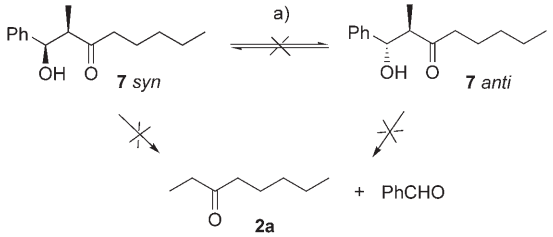
	R^4	Catalyst amount [mol%]	Method	Co-reagent (amount [mol%])	t [min]	Aldol (yield [%])	*syn*/*anti*	**2a** [%]
1	*i*Bu	5	A	–	120	**11** (26)	76:24	51
2	*i*Bu	5	B	–	85	**11** (94)	60:40	1
3	*i*Bu	5	A	$MgBr_2$ (5)	40	**11** (95)	70:30	–
4	*i*Bu	3	A	$MgBr_2$ (3)	50	**11** (92)	70:30	2
5	Ph	5	B	–	225	**7** (85)	60:40	–
6	Ph	3	A	$MgBr_2$ (3)	50	**7** (99)	60:40	–
7	Ph	3[a]	A	$MgBr_2$ (3)	60	**7** (97)	62:38	–

[a] In this reaction [$NiCl_2$(dppf)] (**6**) was used as the precatalyst.

Table 3. Isomerization–aldolization in the presence of various Lewis acid type salts.

	R^4	Co-reagent (amount [mol%])	Catalyst amount [mol%]	t [min]	Conversion [%]	Aldol (amount [%])	*syn*/*anti*	**2a** [%]
1	Ph	$MgCl_2$ (5)	5	45	100	**7** (90)	63:37	7
2	Ph	YCl_3 (5)	5	75	100	**7** (89)	50:50	traces
3	Ph	$YbCl_3$ (5)	5	105	100	**7** (87)	55:45	8
4	Ph	$InCl_3$ (7)	7	130	100	**7** (67)	73:27	10
5	Ph	$CaCl_2$ (5)	5	50	100	**7** (66)	68:32	11
6	Ph	$BiCl_3$ (5)	5	1260	0	–	–	–
7	Ph	$TiCl_4$ (5)	5	480	0	–	–	–
8	Ph	$MgBr_2$ (3)	3	50	100	**7** (99)	60:40	–
9	Ph	LiBr (5)	5	30	100	**7** (71)	60:40	20
10	Ph	$InBr_3$ (5)	5	90	100	**7** (63)	73:27	30
11	Ph	$ZnBr_2$ (7)	7	60	100	**7** (48)	74:26	46
12	Ph	$Ti(OiPr)_4$ (5)	5	120	100	**7** (63)	66:34	20
13	Ph	$In(OAc)_3$ (7)	7	375	25	**7** (15)	78:22	5
14	Ph	–	5	120	100	**7** (81)	60:40	15
15	*i*Bu	$MgBr_2$ (3)	3	50	100	**11** (92)	70:30	2
16	*i*Bu	YCl_3 (5)	5	50	100	**11** (87)	58:42	9
17	*i*Bu	$YbCl_3$ (5)	5	80	100	**11** (87)	63:37	13
18	*i*Bu	$InCl_3$ (7)	7	100	100	**11** (40)	74:26	34
19	*i*Bu	$ZnBr_2$ (7)	7	75	100	**11** (38)	78:22	54
20	*i*Bu	LiBr (5)	5	40	100	**11** (47)	70:30	41
21	*i*Bu	$Ti(OiPr)_4$ (5)	5	960	77	**11** (40)	70:30	20
22	*i*Bu	–	5	120	100	**11** (26)	76:24	51

(entry 13), contrary to the results obtained with ruthenium catalysts in water and protic solvents.[11b] In our case, $MgBr_2$ proved to be the most active, since it is the only one allowing a total conversion of the starting material at doses below 5 mol%. Similar results have been obtained by using isovaleraldehyde as the carbonyl component and $MgBr_2$ proved to be also the best cocatalyst. However with this aliphatic aldehyde, the reactions performed in the presence of the Lewis acids gave always improved yields as compared to the reactions with the nickel hydride alone. It is worth noting that the nature of the cocatalyst does not have any critical influence on the diastereoselectivity of the reaction. Furthermore, using the benzaldehyde adducts as models, we have established that this tandem isomerization–aldolization reaction is occurring under kinetic control: in the presence of the catalytic system (nickel hydride either with, and without, $MgBr_2$) both pure diastereoisomers **7** *syn* and **7** *anti* are found to be stable. There is neither epimerization nor retro-aldolization observed under these reaction conditions (Scheme 4). This result is also in sharp contrast to the data obtained with ruthenium catalysts used in dynamic kinetic resolution and racemization processes.[20]



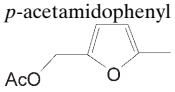
Scheme 4. a) **7** *syn* (or **7** *anti*) (1 equiv), [$NiCl_2$(dppe)] (5 mol%), $LiBHEt_3$ (5 mol%), $MgBr_2$ (5 mol%), THF, −50°C to RT, 1.5 h.

With this optimized catalytic system in hand, it became possible to extend this reaction to a large variety of aldehydes (Table 4).

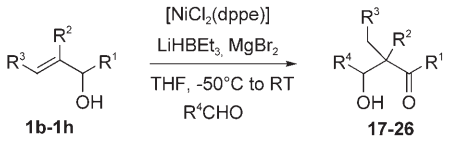
The reaction gave excellent yields with aromatic (entries 1, 6), heteroaromatic (entry 7) as well as with aliphatic aldehydes (entries 2 to 5). It is particularly noteworthy that highly sterically hindered aldehydes (including pivalaldehyde) gave very high yields in aldol products. In all cases, the diastereoselectivity remained low (2 or 3 to 1 in favor of the *syn* diastereoisomer).

In the case of the allylic ether isomerization by nickel hydrides, the reaction was sensitive to the nature of the halogens on the nickel and higher yields were obtained with the iodo complexes.[14] However, in our isomerization–aldol reaction, the iodo complex [NiI_2(dppe)] gave the same results as the corresponding dichloride.

Table 4. Reactions of octen-3-ol with various types of aldehydes.

	R^4	*t* [min]	Aldol	Yield [%]	*syn*/*anti*	**2a** [%]
1	Ph	50	**7**	99	60:40	–
2	Me_2CHCH_2	50	**11**	92	70:30	2
3	Me_2CH	60	**12**	93	66:34	2
4	Et_2CH	150	**13**	84	69:31	4
5	*t*Bu	55	**14**	68	76:24	15
6	*p*-acetamidophenyl	60	**15**	91	67:33	–
7		45	**16**	94	57:43	–

The reaction was then extended to various types of allylic alcohols with substituents on the different positions (Scheme 5 and Table 5)



Scheme 5. Tandem isomerization–aldolization of various allylic alcohols with two model aldehydes.

Starting from the 2-methylocten-3-ol (**1b**), neither the isomerization nor the aldol reactions were observed and the starting materials were fully recovered (entry 1). Therefore, a substituent in the R^2 position clearly inhibits the action of the transition-metal catalyst. In contrast, it was possible to introduce a methyl group in position R^3: although the reaction proceeded more slowly, **1c** afforded in a good yield (80%) the desired aldol products (entry 2). Finally, a large variety of substituents can be introduced in position R^1, as in the alcohols **1d** to **1h**. In each case, excellent yields were obtained, including for very bulky groups such as the *t*Bu or the gemdimethyl ester system (entries 3 to 10). Furthermore, it is worthy of note that with the last substituents, the diastereoselectivity became excellent in favor of the *syn* isomer (over 90 and 95% respectively, entries 8 to 10). The relative configuration of these aldols have been attributed as follows: for known compounds (**7**,[21] **19**,[22] **20**,[22a,23] **21**,[22a] **24**[22a]) the *syn*/*anti* configurations were established by comparison with literature data. For the other aldols, the follow-

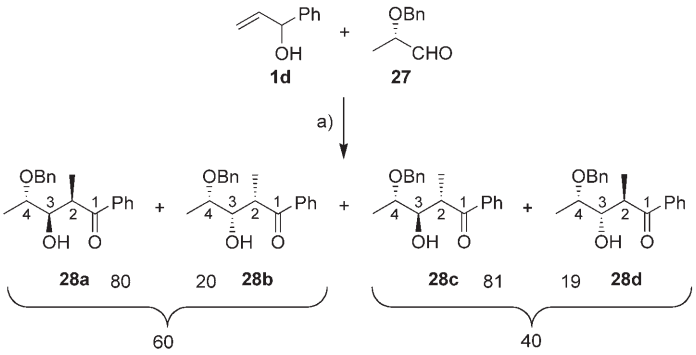
Table 5. Tandem isomerization–aldolization of allylic alcohols with model aldehydes.

	1	R^1	R^2	R^3	R^4	Cat. [%]	*t* [min]	Aldol (yield [%])	*syn*/*anti*
1	**1b**	nC_5H_{11}	Me	H	Ph	7	240	**17** (0)	–
2	**1c**	nC_5H_{11}	H	Me	Ph	7	1260	**18** (80)	55:45
3	**1d**	Ph	H	H	Ph	3	75	**19** (97)	60:40
4	**1d**	Ph	H	H	Me_2CH	3	70	**20** (86)	50:50
5	**1e**	Me_2CH	H	H	Ph	5	40	**21** (68)	75:25
6	**1f**	Et_2CH	H	H	Ph	5	105	**22** (90)	70:30
7	**1f**	Et_2CH	H	H	Me_2CHCH_2	5	45	**23** (88)	69:31
8	**1g**	*t*Bu	H	H	Ph	5	30	**24** (89)	90:10
9	**1h**	$C(Me)_2CO_2Et$	H	H	Ph	5	120	**25** (93)	>95:5
10	**1h**	$C(Me)_2CO_2Et$	H	H	Me_2CHCH_2	3	70	**26** (88)	>95:5

ing empirical rule was followed: The *C* atom of the *C*HOH group is deshielded in the *anti* adduct relative to that of the *syn* adduct, while the *H* atom of the C*H*OH group is shielded in the *anti* adduct. Moreover, except in one case (**14**), the ^3J(H,H) coupling constant between the C*H*OH group and the C*H*C=O group is larger in the *anti* aldol.

Development of the tandem isomerization–aldolization in asymmetric synthesis and asymmetric catalysis: The next step in the development of this reaction was the extension to asymmetric synthesis. For the corresponding studies we selected two model allylic alcohols **1d** and **1h** and the chiral lactaldehydes **27** and **29** bearing two different types of alcohol protective groups.

Under the previously optimized reaction conditions, the addition of the allylic alcohol **1d** to the 2-(*S*)-benzyloxypropanal **27**[24] afforded a mixture of four diastereoisomers (**28a–d**) in 79% overall yield (Scheme 6).



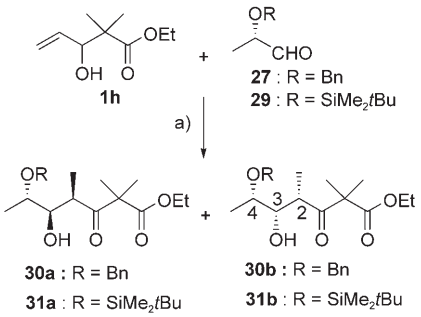
Scheme 6. a) **1d** (1 equiv), **27** (1.1 equiv), [$NiCl_2$(dppe)] (5 mol%), $LiBHEt_3$ (5 mol%), $MgBr_2$ (5 mol%), THF, −50°C to RT, 1 h10 min, overall yield 79%.

Their stereochemistry has been established by comparison of their ^{1}H and ^{13}C NMR data with literature.[25] A careful study of the latter data (Table 6) showed that the diastereoisomer **29a** had a strongly shielded methyl group (δ = 11.8 ppm), together with a very large chemical shift difference between the two methyl groups ($\Delta\delta$ = 3.7 ppm versus 0.1 to 1.6 ppm). This characteristic appears general and will be of much use with the other models. The ratio between the diastereoisomers has been established by ^{1}H NMR spectroscopy. The ratio between the isomers having the *syn* versus the *anti* configuration at the C2/C3 level (**28a** and **28b** versus **28c** and **28d**, respectively) was 60:40; it is worth noting that exactly the same ratio was observed for the reaction of the alcohol **1d** with benzaldehyde. This indicates that the chiral substituent vicinal to the carbonyl group has no effect on the diastereoselectivity of this C2–C3 bond formation. On the other hand, if one considers the C3–C4 relationship, there is a good stereoselectivity in favor of the *anti* diastereoisomer: in each case the facial stereoselectivity induced by the chiral substituent is around 80:20.

Table 6. ^{13}C Chemical shift comparison for the methyl groups in aldol products **28a** to **28d**.

	28a	**28b**	**28c**	**28d**
$\delta(CH_3)$ [ppm]	11.8	14.2	15.6	15.2
$\delta(CH_3)$ [ppm]	15.5	15.8	15.7	15.7
$\Delta\delta$ [ppm]	3.7	1.6	0.1	0.5

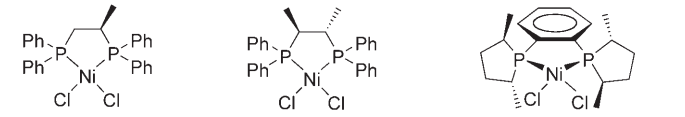
To obtain more information on the effect of the substituents, this reaction was extended to the alcohol **1h** having a very bulky substituent at the carbinol center and to the aldehydes **27** and **29**.[26] In each case, the reaction afforded a mixture of two aldol products in excellent yields (Scheme 7). Their stereochemistry was established by NMR spectroscopy, using the previously described criterion.



Scheme 7. a) **1h** (1 equiv), **27** (or **29**) (1.1 equiv), [$NiCl_2$(dppe)] (5 mol%), $LiBHEt_3$ (5 mol%), $MgBr_2$ (5 mol%), THF, −50°C to RT, 1.5 h, overall yield 95%.

In agreement with the results obtained previously with achiral aldehydes, this allylic alcohol afforded only the *syn* diastereoisomers at the C2/C3 level. The facial diastereoselectivity was again excellent with the following *syn*/*anti* ratios at the C3/C4 level: 78:22 for **30a** and **30b**, and 83:17 in the case of **31a** and **31b**. These stereoselectivity results will be discussed in the last part of this publication.

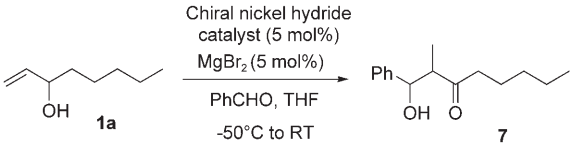
After these encouraging results in asymmetric synthesis, we were interested in the possibility to develop into asymmetric catalysis. Taking into account the excellent results obtained in the asymmetric isomerization of cyclic allyl ethers, we selected three model nickel dichlorides **32**, **33**, and **34** as precatalysts and studied the reactions with two different allylic alcohols, the derivatives **1a** and **1h**. NMR measure-



ments in the presence of a chiral shift reagent were selected as the analytical technique to measure the *ee*'s, since we have established that the corresponding racemic aldol adducts, previously prepared by using the dppe catalyst, exhib-

ited excellent separations of the signals of the carbinol protons in the presence of [Eu(tfc)$_3$].

The complexes **32** and **33** are not commercially available and they were prepared following a literature method.[27] The Me-DuPHOS complex **34** was obtained by the method of Frauenrath.[14] The corresponding nickel hydride catalysts were prepared by reaction of the nickel dichlorides with one equivalent of LiBHEt$_3$ and used under the previously optimized reaction conditions, in the presence of one molar equivalent of MgBr$_2$ as cocatalyst (Scheme 8). The results of the reactions performed starting from alcohol **1a** are given in Table 7.



Scheme 8. Isomerization–aldolization reaction from alcohol **1a** with three chiral nickel hydride catalysts.

Table 7. Isomerization–aldolization of alcohol **1a** with three chiral nickel hydride catalysts.

Catalyst	Yield [%]	*syn*/*anti*	*syn* (*ee*)	*anti* (*ee*)
32	95	60:40	0	0
33	91	62:38	0	0
34	23	60:40	0	0

Starting with the PROPHOS and the CHIRAPHOS catalysts, excellent chemical yields were obtained and the *syn*/*anti* selectivities were also very similar to the results obtained with the dppe complex. The diastereoisomeric aldols were separated by chromatography and their optical purity established by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent [Eu(tfc)$_3$]. With both the chiral catalysts, only racemic mixtures were obtained. The same reaction was also performed with the Me-DuPHOS catalyst: in that case, a lower yield in aldols (23%) was obtained and only the *syn* diastereoisomer could be isolated in pure form. Analysis by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent indicated again that a racemic mixture was obtained for this compound. In conclusion, the three model chiral catalysts afforded only racemic mixtures of aldols from this allylic alcohol. Therefore, it was of much interest to study another alcohol, such as **1h**, which was known to give a higher *syn* selectivity in the aldol reactions (Scheme 9).

Scheme 9. Conditions: **1h** (1 equiv), PhCHO (1.1 equiv), **32** (or **33**) (5 mol%), LiBHEt$_3$ (5 mol%), MgBr$_2$ (5 mol%), THF, −50°C to RT, 1.5 h, overall yield 96%.

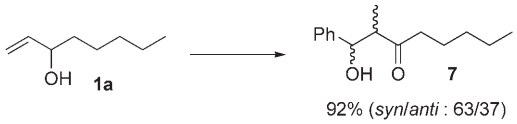
The results of these reactions are given in Table 8. Here again, the yields and selectivities were similar to those obtained previously with the dppe complex. Analysis by NMR spectroscopy with the same chiral shift reagent gave again a

Table 8. Isomerization–aldolization of alcohol **1h** with two chiral nickel hydride catalysts.

Catalyst	Yield [%]	*syn*/*anti*	*syn* (*ee*)
32	96	>95:5	0
33	96	94:6	0

disappointing 0% *ee* for these reactions. We had demonstrated earlier that these reactions are under kinetic control, excluding both epimerizations and reversibility. Therefore, a racemization process on both stereocenters of these aldol adducts, seems also very unlikely. As a conclusion of these experiments, it appears that the chiral ligands on the transition-metal catalysts have no effect on the enantioselectivity of this aldol reaction. As will be discussed later, a likely explanation for this result is that the transition-metal complex is not involved in the key C–C bond-forming step in the aldolization reaction: therefore, this step has to be envisaged at later stage and the free enol appears as a very plausible candidate as the key intermediate.

Mechanistic studies using labeled compounds: Two sets of experiments with deuterium labeled compounds were performed in order to obtain more information about the mechanism of this tandem isomerization–aldolization reactions. The first reaction involved the use of a deuterated catalyst, prepared from LiBDEt$_3$ and MgBr$_2$. Furthermore, 0.5 molar equivalent of the catalytic system was used in order to minimize the risks of losing some of the label in the experiment. The model reaction between octen-3-ol and benzaldehyde was performed with this labeled catalyst and the results are reported in Scheme 10. The reaction afforded

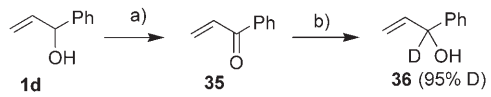


Scheme 10. Conditions: **1a** (1 equiv), PhCHO (1.1 equiv), [NiCl$_2$(dppe)] (0.5 equiv), LiBDEt$_3$ (0.5 equiv), MgBr$_2$ (0.5 equiv), THF, −50°C to RT, 40 min, overall yield 92%.

excellent yields in the aldol products in the usual 2:1 *syn*/*anti* selectivity and analysis by high-field NMR spectroscopy indicated that deuterium was not incorporated in the products. This result clearly excludes a mechanism in which the catalyst reacts by an addition–elimination sequence: in this last case deuterium would have been introduced either on the methyl group, or on the next carbon atom or even on both carbon atoms.[6a]

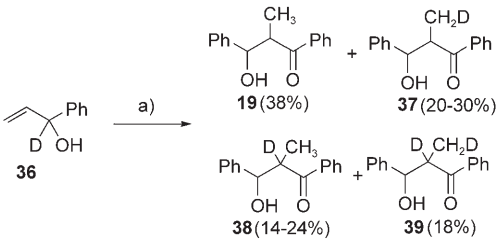
A second series of experiments was performed, starting from a deuterated allylic alcohol. The compound **36**, select-

ed as a model for this study, was prepared by reduction of the enone **35** with $NaBD_4$ (Scheme 11) and ^1H NMR analysis gave a 95% deuterium content for **36**.



Scheme 11. a) **1d** (1 equiv), IBX (1.5 equiv), DMSO, RT, 80%; b) $NaBD_4$ (1 equiv), $CeCl_3$ (1 equiv), MeOH, RT, 77%.

Under the same reaction conditions as before (with 3 mol% catalyst) this alcohol afforded a complex mixture of four aldol products **19**, **37**, **38**, and **39** in excellent yield (Scheme 12). A careful analysis by mass spectrometry indicated a mixture of a nondeuterated aldol **19** (38%), a monodeuterated species (44%), and a bisdeuterated aldol (18%). A further analysis by ^1H and ^{13}C NMR spectroscopy confirmed these data and gave information on the position of the deuterium label: within the monodeuterated compounds the derivative with the label on the methyl group **37** represented 20–30%, while the derivative with the deuterium in central position **38** was in the range 14–24%. For the bisdeuterated compound **39**, the deuterium atoms were both on the methyl group and also on the vicinal carbon atom.



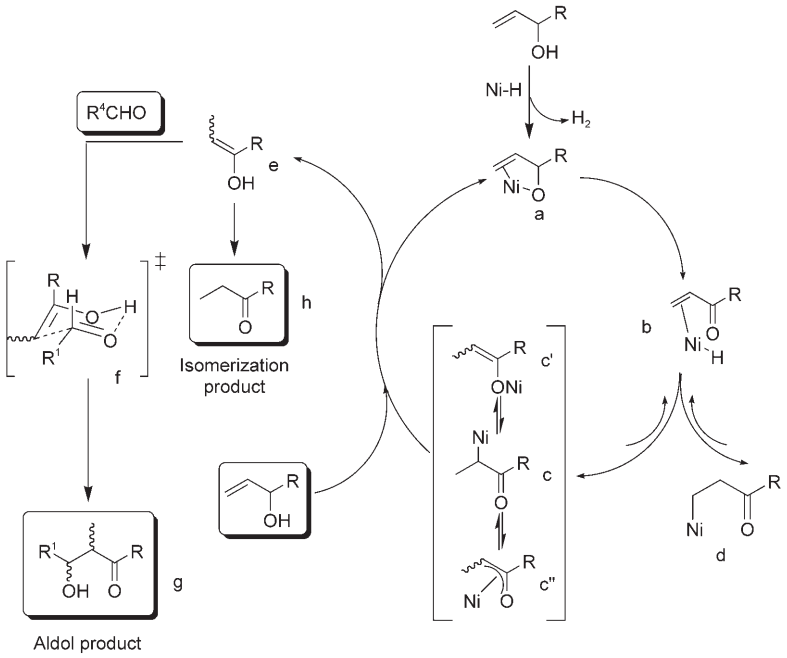
Scheme 12. a) **36** (1 equiv), $[NiCl_2(dppe)]$ (3 mol%), $LiBHEt_3$ (3 mol%), $MgBr_2$ (3 mol%), PhCHO (1.1 equiv), THF, −50°C to RT, 50 min, overall yield 98%.

These results clearly excludes a mechanism through π-allyl intermediates:[6a] in such a case, the deuterium label should be exclusively on the methyl group (affording type **37** aldols).

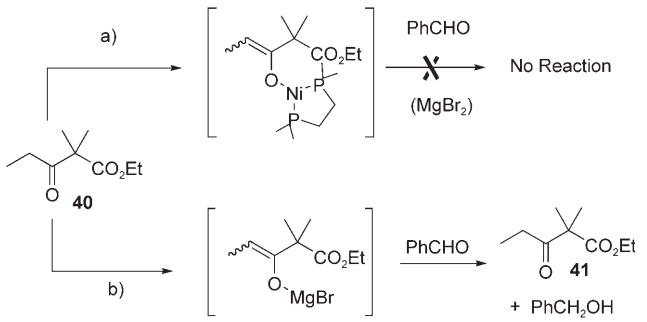
Tentative mechanistic proposal for the nickel hydride mediated tandem isomerization–aldolization: Based on the results described in the previous parts, we propose the mechanism described in Scheme 13. The reaction of the allylic alcohol with the nickel hydride generates first an alcoholate complexed to the nickel catalyst (**a**). A β-hydride elimination process leads to the enone coordinated to the nickel hydride (**b**). Then, nonregioselective and reversible additions on the double bond, afford the type **d** and **c** intermediates. The latter compounds are known to exist in the σ-bound form **c**, in equilibrium with the nickel enolate form ***c′*** as well as with the π-oxo allyl complex ***c″***.[28] It is important to note that this type of mechanism has been already proposed in the isomerization of allylic alcohols, mediated by ruthenium and rhodium complexes.[29,11d]

This type **c** intermediate reacts with another molecule of allylic alcohol to regenerate the corresponding alcoholate **a** and to liberate the free enol **e**. The latter key intermediate can either tautomerize to the saturated carbonyl compound **h** or react with the aldehyde to afford the aldol product **g**. The different lines of evidence in favor of such a mechanistic proposal are the following:

- The nickel enolates, which could be considered as alternative intermediates in this reaction, have been clearly excluded. The nickel enolate derived from ketone **40** was prepared following literature procedure for similar compounds.[28] In the presence of benzaldehyde (with or without $MgBr_2$), no reaction was obtained and only the starting materials were recovered (Scheme 14).[30] This result is in agreement with the literature data indicating that the nickel enolates derived from ketones have a very low



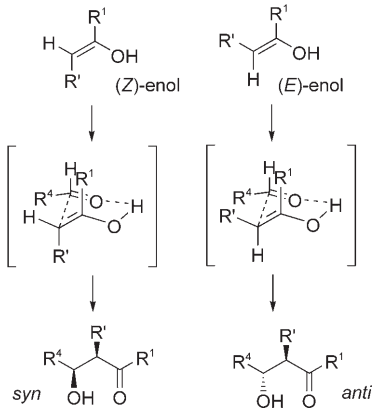
Scheme 13. Mechanistic proposal for the tandem isomerization–aldolization, mediated by nickel hydride catalysts.



Scheme 14. a) LDA (1 equiv), THF, −78 °C, 1 h, then $[NiCl_2(dppe)]$ (1 equiv), −30 °C, 3 h, then $MgBr_2$ (1 equiv) and PhCHO (1.1 equiv), −50 °C to RT, 12 h; b) LDA (1 equiv), THF, −78 °C, 1 h, then $MgBr_2$ (1 equiv), −78 °C, 1.5 h, then PhCHO (1.1 equiv), −50 °C to RT, 12 h.

reactivity, affording very small amount of the expected aldol products.[28]

- The magnesium enolates, which could be also considered as possible intermediates by metal exchange from the nickel enolates, were unambiguously excluded as well. The magnesium enolate derived from ketone **40** was prepared independently from lithium enolate. Under our standard reaction conditions, it afforded only the reduction product (benzyl alcohol) and no aldols (Scheme 14). Furthermore it is worth mentioning that the magnesium enolates are known to afford mainly the *anti* adducts,[31a] eventually by means of epimerization processes,[31b] while our reaction affords the *syn* adducts as major compounds (>90 % in the case of **1h**, the allylic alcohol corresponding to **40**). Finally, a transformation of the free enol into the magnesium enolate appears also very unlikely, since it would generate HBr, which is a very efficient catalyst for the tautomerization of enols into saturated carbonyls.[8] Therefore, the role of $MgBr_2$ as a cocatalyst appears to be a Lewis acid type activation of the carbonyl compound.
- As demonstrated in the previous part, various chiral ligands on the nickel catalysts have no effect on the enantioselectivity of the reaction. This is a strong indication that the transition-metal complex is no longer involved during the formation of the key C–C bond in the aldol.
- This mechanism is in full agreement with previous computational studies, although these have been performed with a different catalyst (iron–carbonyl compounds). These calculations have shown that the addition of the free enol is the strongly favored pathway and this process can be considered as an "hydroxyl–carbonyl–ene" type reaction.[16a]
- It is fully consistent with our labeling studies: no deuterium was obtained in the aldol product when the reaction was performed with a deuterated catalyst. The allylic alcohol deuterated on the carbinol center afforded a mixture of aldols: this is fully consistent with reversible additions, on both directions, of the nickel hydride on the enone, together with ligand exchanges between the deuterated and nondeuterated **b** type intermediates.
- If we use a Zimmermann–Traxler transition state with the hydrogen atom coordinating the two oxygen atoms, it is also possible to rationalize the trends in the *syn*/*anti* stereoselectivity of this aldol reaction (Scheme 15). The



Scheme 15. Aldol reactions starting from (*Z*)- and (*E*)-enols.

isomerization of the allylic alcohol can afford either the (*Z*)-enol (leading to the *syn* aldols) or the (*E*)-enol (affording the *anti* aldols). If we assume that the steric interaction between the groups R^1 and R′ controls the enol geometry, then it should be directly connected to the *syn*/*anti* ratios. This tendency has been indeed observed in this tandem reaction (Table 9): for groups with a limited steric bulk the *syn*/*anti* ratios remained low (2:1 to 3:1). In contrast, the bulky R^1 groups such as the *t*Bu or the gemdimethyl ester afforded very high *syn* selectivities (over 90–95 %).

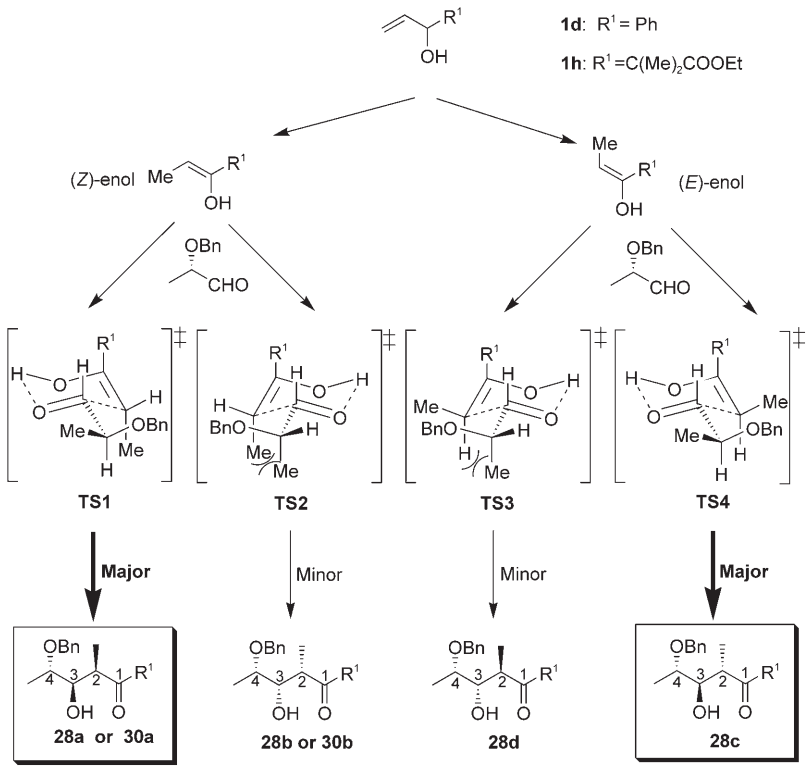
Table 9. *Syn*/*anti* stereoselectivity dependence as a function of the nature of the R^1 group.[a]

Allylic alcohol	R^1	*syn*	*anti*
1a	nC_5H_{11}	60	40
1e	Me_2CH	75	25
1f	Et_2CH	70	30
1g	*t*Bu	90	10
1h	CMe_2CO_2Et	>95	<5

[a] Data for: R^4 = Ph; R′ = Me.

- The facial selectivity can also be rationalized by using the free enols as the key intermediates (Scheme 16).

Recent literature data have established that, for the aldol reactions, the Felkin–Anh–Houk model is not suitable and the Cornforth model has to be used preferentially.[32] In this model, the polar group has to be situated as far as possible of the carbonyl group to minimize the dipole moment. In the case of the (*Z*)-enol, the transition state **TS2** is strongly disfavored by a strong *syn*-pentane interaction between the two methyl groups. Such an interaction is not anymore present in **TS1** and explains the favored formation of the *anti*



Scheme 16. Transition-state models for the aldolization reactions starting from chiral aldehydes.

C3C4 diastereoisomer **28a** or **30a**. This is in full agreement with the experimental results: the allylic alcohol **1h**, with the bulky $C(Me)_2CO_2Et$ substituent on the carbinol center, afforded a 78:22 mixture of **30a** and **30b** aldols. Starting now from the (*E*)-enol two transition states are again possible; **TS3** is disfavored with respect to **TS4** by the *syn* interaction between the methyl group and the axial hydrogen. Therefore, for these compounds, the *anti* C3/C4 isomer should be favored: this is indeed observed in the addition of allylic alcohol **1d** with the protected lactaldehyde **27** (the C3C4 *anti*/*syn* ratio was 81:19 for **28c**/**28d**).

Conclusion

In conclusion, we have demonstrated that the [NiHCl(dppe)]/$MgBr_2$ combination is a very active catalytic system for the tandem isomerization–aldolization reaction of allylic alcohols with aldehydes. The reaction has a large scope in term of allylic alcohols and it is compatible with a wide range of aldehydes, including very bulky ones. This reaction proceeds at, or below, room temperature and in the presence of a low catalyst loading (3 mol%). It affords aldols in good to excellent yields and it is completely regioselective. Although asymmetric catalysis could not be developed at this stage, asymmetric synthesis can be used for the preparation of aldols in optically active form. Detailed mechanistic studies afforded strong support to a mechanism involving first a transition-metal-mediated isomerization of the allylic alcohol into the free enol, followed by the addition of the latter intermediate onto the aldehyde in a "hydroxyl–carbonyl–ene" type reaction. These results confirm that allylic alcohols can be considered as new and useful partners in the development of the aldol reaction.

Experimental Section

General methods: Tetrahydrofuran was distilled from sodium/benzophenone ketyl. All aldehydes were freshly purified before reactions. The NMR data were obtained at 400 MHz for ^1H and 100 MHz for ^{13}C. IR spectra were recorded on a FT-IR instrument by using NaCl plates. Elemental analyses and mass spectral analyses were performed at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO) in Rennes (France).

Allylic alcohols **1a** and **1d** are commercially available. The others have been prepared by standard procedure: addition of Grignard (**1e**,[33] **1f**, **1g**[33]) or organolithium derivatives (**1b**,[34] **1c**,[34] **1h**[35]) on the corresponding aldehyde.

Procedure for aldolization of an allylic alcohol with an aldehyde by means of a nickel complex as catalyst—method A (with $MgBr_2$): A 1 M solution of $LiBHEt_3$ in THF (57 μL, 0.0567 mmol) was added to a solution of [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol) in anhydrous THF (3 mL) at room temperature under nitrogen. The reaction mixture was stirred at room temperature for 5 min before to be transferred into a flask containing anhydrous $MgBr_2$ (10 mg, 0.0567 mmol). This reaction mixture was stirred at room temperature for a further 5 min and was cooled to −50 °C. Then, the aldehyde (2.08 mmol) and allylic alcohol (1.89 mmol) were added successively. The temperature was raised to room temperature and the reaction mixture was monitored by TLC until the disappearance of the allylic alcohol. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL) and the aqueous phase was extracted with Et_2O (3×50 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the desired aldol products.

The same procedure was used with [$NiCl_2$(dppf)] as precatalyst.

Procedure for aldolization of an allylic alcohol with an aldehyde with a nickel complex as catalyst—method B: A 1 M solution of isopropylmagnesium bromide in THF (379 μL, 0.379 mmol) was added to a solution of [$NiCl_2$(dppe)] (100.0 mg, 0.189 mmol) in anhydrous THF (10 mL) at 0 °C under nitrogen. The temperature was raised to room temperature, then TMSCl (24 μL, 0.189 mmol) was added. The reaction mixture was stirred at room temperature for 5 min and cooled to −50 °C. Then the aldehyde (4.17 mmol) and allylic alcohol (3.79 mmol) were added successively. The temperature was raised to room temperature and the reaction mixture was monitored by TLC until the disappearance of the allylic alcohol. The reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL) and the aqueous phase was extracted with Et_2O (3×50 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the desired aldol products.

1-Hydroxy-2-methyl-1-phenyloctan-3-one (7): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), $MgBr_2$ (10 mg, 0.0567 mmol), benzaldehyde (211 μL, 2.08 mmol), and **1a** (292 μL, 1.89 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 then 2:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti* 62:38 by ^{1}H NMR spectroscopy, 438.3 mg, 99% yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 10:1 v/v).

Compound **7** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.2$ Hz, 3H; CH_3CH_2), 1.07 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.18–1.35 (m, 4H; $CH_2CH_2CH_3$), 1.50–1.60 (m, 2H; CH_2CH_2CO), 2.33 (dt, $J = 17.2$, 7.3 Hz, 1H; CH_2CO), 2.45 (dt, $J = 17.2$, 7.4 Hz, 1H; CH_2CO), 2.83 (dq, $J = 4.0$, 7.2 Hz, 1H; $CHCH_3$), 3.20 (d, $J = 2.5$ Hz, 1H; O*H*), 5.05 (dd, $J = 2.5$, 4.0 Hz, 1H; C*H*OH), 7.23–7.38 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.5$, 13.8, 22.4, 23.0, 31.2, 42.2, 52.4, 73.2, 125.9, 127.3, 128.2, 141.8, 216.0 ppm.

Compound **7** a*nti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 7.1$ Hz, 3H; CH_3CH_2), 0.94 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.15–1.35 (m, 4H; $CH_2CH_2CH_3$), 1.47–1.59 (m, 2H; CH_2CH_2CO), 2.41 (dt, $J = 17.2$, 7.2 Hz, 1H; CH_2CO), 2.51 (dt, $J = 17.2$, 7.5 Hz, 1H; CH_2CO), 2.92 (dq, $J = 8.1$, 7.2 Hz, 1H; $CHCH_3$), 2.96 (d, $J = 4.6$ Hz, 1H; O*H*), 4.75 (dd, $J = 4.6$, 8.1 Hz, 1H; C*H*OH), 7.23–7.38 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$, 14.3, 22.4, 22.9, 31.2, 43.2, 52.7, 76.5, 126.5, 127.8, 128.4, 142.1, 215.8 ppm; elemental analysis calcd (%) for (*syn*/*anti* mixture) $C_{15}H_{22}O_2$: C 76.88, H 9.46; found: C 76.67, H 9.56.

2,5-Dimethyl-4-hydroxyundecan-6-one (11): These aldols were obtained by using the general procedure (method A) using [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), $MgBr_2$ (10 mg, 0.0567 mmol), isovaleraldehyde (227 μL, 2.08 mmol), and **1a** (292 μL, 1.89 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 then 2:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 70:30 by ^{1}H NMR spectroscopy, 370.4 mg, 92% yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 8:1 v/v).

Compound **11** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$–0.94 (m, 9H; $(CH_3)_2CH$, CH_3CH_2), 1.01–1.09 (m, 1H; CH_2CHOH), 1.12 (d, $J = 7.1$ Hz, 3H; CH_3CH), 1.21–1.35 (m, 4H; $CH_2CH_2CH_3$), 1.46 (ddd, $J = 5.6$, 9.4, 14.4 Hz, 1H; CH_2CHOH), 1.57 (ddt, $J = 7.4$, 7.4, 7.4 Hz, 2H; CH_2CH_2CO), 1.70–1.82 (m, 1H; $CH(CH_3)_2$), 2.44 (dt, $J = 17.0$, 7.4 Hz, 1H; CH_2CO), 2.51 (dt, $J = 17.0$, 7.6 Hz, 1H; CH_2CO), 2.48–2.55 (m, 1H; C*H*CO), 2.70 (br d, $J = 2.8$ Hz, 1H; O*H*), 3.96–4.03 ppm (m, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.9$, 13.9, 22.0, 22.4, 23.2, 23.4, 24.5, 31.4, 41.9, 43.0, 50.2, 68.8, 216.6 ppm.

Compound **11** *anti:* ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$–0.95 (m, 9H; $(CH_3)_2CH$, CH_3CH_2), 1.12 (d, $J = 7.1$ Hz, 3H; CH_3CH), 1.15–1.43 (m, 6H; CH_2CHOH, $CH_2CH_2CH_3$), 1.52–1.62 (m, 2H; CH_2CH_2CO), 1.79–1.90 (m, 1H; $CH(CH_3)_2$), 2.42 (dt, $J = 17.0$, 7.4 Hz, 1H; CH_2CO), 2.51 (dt, $J = 17.0$, 7.6 Hz, 1H; CH_2CO), 2.55–2.63 (m, 1H; C*H*CO), 2.57 (d, $J = 6.6$ Hz, 1H; O*H*), 3.70–3.79 ppm (m, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$, 14.2, 21.5, 22.5, 23.1, 23.8, 24.4, 31.4, 43.0, 44.0, 51.6, 71.8, 216.7; IR (neat): $\tilde{\nu} = 3470$ (w), 1703 cm^{-1}; HRMS (EI; 70 eV): *m*/*z* calcd for $C_{13}H_{24}O$: 196.1827 $[M-H_2O]^+$; found: 196.1822 (2 ppm); elemental analysis calcd (%) for (*syn*/*anti* mixture) $C_{13}H_{26}O_2$: C 72.84, H 12.22; found: C 72.59, H 12.35.

2,4-Dimethyl-3-hydroxydecan-5-one (12): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), $MgBr_2$ (10 mg, 0.0567 mmol), isobutyraldehyde (190 μL, 2.08 mmol), and **1a** (292 μL, 1.89 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 then 2:1 v/v) yielded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 66:34 by ^{1}H NMR spectroscopy, 352.3 mg, 93% yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 8:1 v/v).

Compound **12** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (d, $J = 6.8$ Hz, 3H; $(CH_3)_2CH$), 0.90 (t, $J = 7.1$ Hz, 3H; CH_3CH_2), 1.02 (d, $J = 6.5$ Hz, 3H; $(CH_3)_2CH$), 1.11 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.22–1.38 (m, 4H; $CH_2CH_2CH_3$), 1.53–1.72 (m, 3H; CH_2CH_2CO, $CH(CH_3)_2$), 2.47 (dt, $J = 17.1$, 7.3 Hz, 1H; CH_2CO), 2.53 (dt, $J = 17.1$, 7.5 Hz, 1H; CH_2CO), 2.73 (dq, $J = 2.9$, 7.2 Hz, 1H; C*H*CO), 2.88 (d, $J = 3.2$ Hz, 1H; O*H*), 3.51 ppm (ddd, $J = 2.9$, 3.2, 8.5 Hz, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.3$, 13.8, 18.9, 19.0, 22.4, 23.2, 30.5, 31.3, 41.6, 47.3, 76.2, 216.5 ppm.

Compound **12** *anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.1$ Hz, 3H; CH_3CH_2), 0.91 (d, $J = 6.7$ Hz, 3H; $(CH_3)_2CH$), 0.96 (d, $J = 6.8$ Hz, 3H; $(CH_3)_2CH$), 1.11 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.21–1.35 (m, 4H; $CH_2CH_2CH_3$), 1.52–1.61 (m, 2H; CH_2CH_2CO), 1.66–1.79 (m, 1H; C*H*-$(CH_3)_2$), 2.46 (dt, $J = 17.4$, 7.3 Hz, 1H), CH_2CO, 2.55 (dt, $J = 17.4$, 7.5 Hz, 1H; CH_2CO), 2.58 (d, $J = 6.9$ Hz, 1H; O*H*), 2.76 (dq, $J = 6.9$, 7.2 Hz, 1H; C*H*CO), 3.44 ppm (ddd, $J = 4.9$, 6.9, 6.9 Hz, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 14.3, 15.9, 19.9, 22.4, 22.9, 30.4, 31.3, 42.9, 48.2, 78.3, 216.8 ppm. IR (neat): $\tilde{\nu} = 3487$ (w), 1705 cm^{-1}; HRMS (EI; 70 eV): *m*/*z* calcd for $C_{11}H_{21}O_2$: 185.1542 $[M-Me]^+$; found: 185.1570 (15 ppm); elemental analysis calcd (%) for (*syn*/*anti* mixture) $C_{12}H_{24}O_2$: C 71.95, H 12.08; found: C 71.74, H 12.24.

3-Ethyl-4-hydroxy-5-methylundecan-6-one (13): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), $MgBr_2$ (10 mg, 0.0567 mmol), 2-ethylbutanal (256 μL, 2.08 mmol), and **1a** (292 μL, 1.89 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 then 2:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 69:31 by ^{1}H NMR spectroscopy, 363.0 mg, 84% yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 6:1 v/v).

Compound **13** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.83$–0.92 (m, 9H; CH_3CH_2), 1.12 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.19–1.46 (m, 8H; CH_2CH, $CH_2CH_2CH_3$), 1.53–1.70 (m, 3H; C*H*CHOH, CH_2CH_2CO), 2.45 (dt, $J = 17.1$, 7.3 Hz, 1H; CH_2CO), 2.52 (dt, $J = 17.1$, 7.5 Hz, 1H; CH_2CO), 2.67 (d, $J = 3.4$ Hz, 1H; O*H*), 2.73 (dq, $J = 3.2$, 7.2 Hz, 1H; C*H*CO), 3.78 ppm (ddd, $J = 3.2$, 3.4, 6.7 Hz, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.8$, 10.2, 10.4, 13.9, 20.2, 20.8, 22.5, 23.3, 31.4, 41.8, 42.0, 47.1, 71.8, 216.7 ppm.

Compound **13** *anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$–0.94 (m, 9H; CH_3CH_2), 1.09 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.19–1.62 (m, 11H; CH_2CH, $CH_2CH_2CH_3$, CH_2CH_2CO, C*H*CHOH), 2.46 (dt, $J = 17.3$, 7.3 Hz, 1H; CH_2CO), 2.51 (d, $J = 6.6$ Hz, 1H; O*H*), 2.55 (dt, $J = 17.3$, 7.5 Hz, 1H; CH_2CO), 2.81 (dq, $J = 7.2$, 7.2 Hz, 1H; C*H*CO), 3.71 ppm (ddd, $J = 3.9$, 6.6, 7.2 Hz, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.4$, 11.8, 13.9, 14.4, 20.4, 22.4, 23.0, 31.3, 42.9, 43.2, 48.2, 74.6, 216.8 ppm. IR (neat): $\tilde{\nu} = 3493$ (w), 1703 cm^{-1}; HRMS (EI; 70 eV): *m*/*z* calcd for $C_{13}H_{25}O_2$: 213.1855 $[M-Me]^+$; found: 213.1853 (1 ppm); elemental analysis calcd (%) for (*syn*/*anti* mixture) $C_{14}H_{28}O_2$: C 73.63, H 12.36; found: C 73.37, H 12.54.

3-Hydroxy-2,2,4-trimethyldecan-5-one (14): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), $MgBr_2$ (10 mg, 0.0567 mmol), pivalaldehyde (226 μL, 2.08 mmol), and **1a** (292 μL, 1.89 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 then 2:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (syn/*anti*: 76:24 by ^{1}H NMR spectroscopy, 275.5 mg, 68% yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 6:1 v/v).

Compound **14** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 7.1$ Hz, 3H; CH_3CH_2), 0.94 (s, 9H; *tBu*), 1.14 (d, $J = 7.1$ Hz, 3H; CH_3CH), 1.21–1.38 (m, 4H; $CH_2CH_2CH_3$), 1.52–1.61 (m, 2H; CH_2CH_2CO), 2.45 (dt, $J = 17.2$, 7.3 Hz, 1H; CH_2CO), 2.47 (d, $J = 3.7$ Hz, 1H; O*H*), 2.54 (dt, $J = 17.2$, 7.5 Hz, 1H; CH_2CO), 2.83 (dq, $J = 2.9$, 7.1 Hz, 1H; C*H*CO), 3.58 ppm (dd, $J = 2.9$, 3.7 Hz, 1H; C*H*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.5$, 13.9, 22.5, 23.3, 26.7, 31.3, 35.4, 41.5, 46.5, 76.9, 216.1 ppm.

Compound **14** *anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (s, 9H; *tBu*), 0.90 (t, $J = 6.9$ Hz, 3H; CH_3CH_2), 1.22–1.38 (m, 4H; $CH_2CH_2CH_3$), 1.29 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.47–1.64 (m, 2H; CH_2CH_2CO), 2.46–2.64 (m, 2H; CH_2CO), 2.87 (dq, $J = 2.2$, 7.2 Hz, 1H; C*H*CO), 3.22 (dd, $J = 2.2$, 8.9 Hz, 1H; C*H*OH), 4.24 ppm (d, $J = 8.9$ Hz, 1H; O*H*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.9$, 18.1, 22.4, 22.7, 26.7, 31.1, 36.1, 43.4, 43.8, 84.3, 219.1 ppm; IR (neat): $\tilde{\nu} = 3503$ (w), 1701 cm^{-1}; HRMS (EI; 70 eV): *m*/*z* calcd for $C_{12}H_{23}O_2$: 199.1698 $[M-Me]^+$; found: 199.1691 (3 ppm); el-

emental analysis calcd (%) for (*syn*/*anti* mixture) $C_{13}H_{26}O_2$: C 72.85, H 12.23; found: C 72.61, H 12.31.

1-(4-*N*-acetamidophenyl)-1-hydroxy-2-methyloctan-3-one (15): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), and $MgBr_2$ (10 mg, 0.0567 mmol). In this case, solid 4-*N*-acetamidobenzaldehyde (340 mg, 2.08 mmol) and **1a** (292 μL, 1.89 mmol) were dissolved in anhydrous THF (4 mL) before addition to the reaction mixture. Column chromatography on silica gel (CH_2Cl_2/MeOH; 98:2 v/v) afforded an inseparable mixture of diastereoisomeric aldols as a white solid (*syn*/*anti*: 67:33 by ^{1}H NMR spectroscopy, 500.3 mg, 91 % yield).

Compound **15** *syn, anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (*syn*) (t, $J = 7.4$ Hz, 3H; CH_3CH$_2$), 0.87 (*anti*) (d, $J = 7.4$ Hz, 3H; CH_3CH), 0.88 (*anti*) (t, $J = 7.2$ Hz, 3H; CH_3CH$_2$), 1.07 (*syn*) (d, $J = 7.1$ Hz, 3H; CH_3CH), 1.13–1.35 (*syn, anti*) (m, 4H; CH_2CH$_2$CH$_3$), 1.43–1.53 (*syn*) (m, 2H; CH_2CH$_2$CO), 1.51–1.60 (*anti*) (m, 2H; CH_2CH$_2$CO), 2.11 (*syn, anti*) (s, 3H; CH_3CO), 2.25–2.58 (*syn, anti*) (m, 2H; CH_2CO), 2.81 (*syn*) (dq, $J = 4.7$, 7.1 Hz, 1H; C*H*CO), 2.88 (*anti*) (dq, $J = 8.5$, 7.2 Hz, 1H; C*H*CO), 3.44 (*anti*) (d, $J = 4.2$ Hz, 1H; O*H*), 3.62 (*syn*) (d, $J = 2.7$ Hz, 1H; O*H*), 4.66 (*anti*) (dd, $J = 4.2$, 8.5 Hz, 1H; C*H*OH), 4.93 (*syn*) (dd, $J = 2.7$, 4.7 Hz, 1H; C*H*OH), 7.14–7.23 (*syn, anti*) (m, 2H; H_{Ar}), 7.37–7.46 (*syn, anti*) (m, 2H; H_{Ar}), 8.17 (*syn*) (s, 1H; N*H*), 8.22 ppm (*anti*) (s, 1H; N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.8$ (*syn*), 13.8 (*syn*), 13.8 (*anti*), 14.2 (*anti*), 22.3 (*syn*), 22.4 (*anti*), 22.9 (*syn*), 22.9 (*anti*), 24.2 (*syn*), 24.2 (*anti*), 31.1 (*syn*), 31.2 (*anti*), 42.2 (*syn*), 43.0 (*anti*), 52.4 (*syn*), 52.8 (*anti*), 73.1 (*syn*), 76.1 (*anti*), 119.8 (*syn*), 119.9 (*anti*), 126.5 (*syn*), 127.0 (*anti*), 137.1 (*syn*), 137.6 (*anti*), 137.7 (*syn*), 137.9 (*anti*), 168.9 (*anti*), 169.0 (*syn*), 216.0 (*anti*), 216.1 ppm (*syn*); IR (neat): $\tilde{\nu} = 3461$ (w), 3250, 3190, 3121, 3067, 1699, 1661 cm^{-1}; HRMS (EI; 70 eV): *m*/*z* calcd for $C_{17}H_{25}NO_3$: 291.1834 [*M*]$^+$; found: 291.1829 (1 ppm); elemental analysis calcd (%) for (*syn*/*anti* mixture) $C_{17}H_{25}NO_3$: C 70.07, H 8.65, N 4.81; found: C 70.11, H 8.72, N 4.75.

1-(5-Acetoxymethyl-2-furyl)-1-hydroxy-2-methyloctan-3-one (16): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), and $MgBr_2$ (10 mg, 0.0567 mmol). In this case, solid 5-acetoxymethyl-2-furaldehyde (349 mg, 2.08 mmol) and **1a** (292 μL, 1.89 mmol) were dissolved in anhydrous THF (2 mL) before addition to the reaction mixture. Column chromatography on silica gel (toluene/AcOEt, 20:1 then 13:1 then 5:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 57:43 by ^{1}H NMR spectroscopy, 525.3 mg, 94 % yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 4:1 v/v).

Compound **16** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.1$ Hz, 3H; CH_3CH$_2$), 1.18 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.21–1.36 (m, 4H; CH_2CH$_2$CH$_3$), 1.55 (ddt, $J = 7.3$, 7.4, 7.4 Hz, 2H; CH_2CH$_2$CO), 2.08 (s, 3H; CH_3CO), 2.42 (dt, $J = 17.3$, 7.3 Hz, 1H; CH_2CO), 2.51 (dt, $J = 17.3$, 7.4 Hz, 1H; CH_2CO), 3.04 (dq, $J = 4.4$, 7.2 Hz, 1H; C*H*CO), 3.09 (br d, $J = 3.9$ Hz, 1H; O*H*), 5.01 (s, 2H; CH_2O), 5.03 (br dd, $J = 3.9$, 4.4 Hz, 1H; C*H*OH), 6.25 (d, $J = 3.2$ Hz, 1H; H_{furyl}), 6.35 ppm (d, $J = 3.2$ Hz, 1H; H_{furyl}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.2$, 13.9, 20.9, 22.4, 23.0, 31.3, 41.8, 49.6, 58.1, 68.3, 107.7, 111.5, 148.6, 155.3, 170.6, 215.1 ppm.

Compound **16** *anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.1$ Hz, 3H; CH_3CH$_2$), 1.05 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.19–1.36 (m, 4H; CH_2CH$_2$CH$_3$), 1.57 (ddt, $J = 7.2$, 7.5, 7.3 Hz, 2H; CH_2CH$_2$CO), 2.07 (s, 3H; CH_3CO), 2.46 (dt, $J = 17.3$, 7.2 Hz, 1H; CH_2CO), 2.55 (dt, $J = 17.3$, 7.5 Hz, 1H; CH_2CO), 3.17 (dq, $J = 7.3$, 7.2 Hz, 1H; C*H*CO), 3.30 (d, $J = 6.2$ Hz, 1H; O*H*), 4.77 (dd, $J = 6.2$, 7.3 Hz, 1H; C*H*OH), 5.01 (s, 2H; CH_2O), 6.25 (d, $J = 3.2$ Hz, 1H; H_{furyl}), 6.35 ppm (d, $J = 3.2$ Hz, 1H; H_{furyl}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.8$, 14.0, 20.8, 22.4, 22.9, 31.2, 42.8, 49.5, 58.0, 70.0, 108.3, 111.3, 149.0, 155.6, 170.6, 215.3 ppm; IR (neat): $\tilde{\nu} = 3465$ (w), 1742, 1712 cm^{-1}; HRMS (EI; 70 eV): *m*/*z* calcd for $C_{16}H_{24}O_5$: 296.1624 [*M*]$^+$; found: 296.1627 (1 ppm); elemental analysis calcd (%) for (*syn*/*anti* mixture) $C_{16}H_{24}O_5$: C 64.84, H 8.16; found: C 64.89, H 8.34.

3-[Hydroxy(phenyl)methyl]nonan-4-one (18): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (63 mg, 0.119 mmol), a 1 M solution of $LiBHEt_3$ (119 μL, 0.119 mmol), $MgBr_2$ (22 mg, 0.119 mmol), benzaldehyde (190 μL, 1.87 mmol), and **1c** (295 μL, 1.70 mmol). Column chromatography on silica gel (pentane/Et_2O, 8:1 then 2:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 55:45 by ^{1}H NMR spectroscopy, 336.1 mg, 80 % yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 8:1 v/v).

Compound **18** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.83$ (t, $J = 7.5$ Hz, 3H; CH_3), 0.84 (t, $J = 7.2$ Hz, 3H; CH_3), 1.07–1.16 (m, 2H; CH_2), 1.17–1.28 (m, 2H; CH_2), 1.32–1.50 (m, 2H; CH_2), 1.62–1.84 (m, 2H; CH_2), 2.16 (ddd, $J = 6.5$, 8.0, 17.6 Hz, 1H; CH_2CO), 2.29 (ddd, $J = 6.5$, 8.2, 17.6 Hz, 1H; CH_2CO), 2.79 (d, $J = 2.4$ Hz, 1H; O*H*), 2.81 (ddd, $J = 4.0$, 6.0, 9.8 Hz, 1H; C*H*CO), 4.85 (dd, $J = 2.4$, 6.0 Hz, 1H; C*H*OH), 7.23–7.36 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.1$, 13.8, 20.5, 22.3, 22.5, 31.1, 45.1, 60.3, 74.0, 126.2, 127.6, 128.3, 142.1, 215.3 ppm.

Compound **18** *anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.6$ Hz, 3H; CH_3), 0.86 (t, $J = 7.1$ Hz, 3H; CH_3), 1.13–1.32 (m, 4H; CH_2CH$_2$CH$_3$), 1.34–1.45 (m, 1H; CH_2CH), 1.44–1.53 (m, 2H; CH_2CH$_2$CO), 1.54–1.67 (m, 1H; CH_2CH), 2.31 (dt, $J = 17.7$, 7.3 Hz, 1H; CH_2CO), 2,39 (dt, $J = 17.7$, 7.4 Hz, 1H; CH_2CO), 2,84 (ddd, $J = 5.2$, 7.1, 8.8 Hz, 1H; C*H*CO), 2.94 (d, $J = 5.7$ Hz, 1H; O*H*), 4.80 (dd, $J = 5.7$, 7.1 Hz, 1H; C*H*OH), 7.25–7.38 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.7$, 13.9, 22.4, 22.5, 22.8, 31.2, 45.4, 59.8, 75.3, 126.2, 127.8, 128.4, 142.7, 216.2 ppm; HRMS (EI; 70 eV): *m*/*z* calcd for (*syn*/*anti* mixture) $C_{16}H_{22}O$: 230.1671 [*M*−H_2O]$^+$; found: 230.1676 (2 ppm).

1,3-Diphenyl-3-hydroxy-2-methylpropan-1-one (19): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), $MgBr_2$ (10 mg, 0.0567 mmol), benzaldehyde (211 μL, 2.08 mmol), and **1d** (248 μL, 1.89 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 then 2:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 60:40 by ^{1}H NMR spectroscopy, 441.2 mg, 97 % yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 8:1 v/v).

Compound **19** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.19$ (d, $J = 7.2$ Hz, 3H; CH_3), 3.70 (d, $J = 2.1$ Hz, 1H; O*H*), 3.70 (dq, $J = 3.1$, 7.2 Hz, 1H; C*H*CO), 5.24 (dd, $J = 2.1$, 3.1 Hz, 1H; C*H*OH), 7.23–7.50 (m, 7H; H_{Ar}), 7.54–7.61 (m, 1H; H_{Ar}), 7.91–8.01 ppm (m, 2H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.1$, 47.0, 73.0, 126.0, 127.3, 128.2, 128.4, 128.7, 133.6, 135.5, 141.7, 205.8 ppm.

Compound **19** *anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (d, $J = 7.2$ Hz, 3H; CH_3), 3.03 (d, $J = 4.5$ Hz, 1H; O*H*), 3.83 (dq, $J = 8.1$, 7.2 Hz, 1H; C*H*CO), 4.99 (dd, $J = 4.5$, 8.1 Hz, 1H; C*H*OH), 7.23–7.50 (m, 7H; H_{Ar}), 7.54–7.61 (m, 1H; H_{Ar}), 7.91–8.01 ppm (m, 2H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.7$, 47.9, 76.7, 126.7, 127.9, 128.4, 128.5, 128.6, 133.3, 136.6, 142.1, 204.9 ppm.

2,4-Dimethyl-3-hydroxy-1-phenylpentan-1-one (20): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (30 mg, 0.0567 mmol), a 1 M solution of $LiBHEt_3$ (57 μL, 0.0567 mmol), $MgBr_2$ (10 mg, 0.0567 mmol), isobutyraldehyde (190 μL, 2.08 mmol), and **1d** (248 μL, 1.89 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (50:50 by ^{1}H NMR spectroscopy, 335.6 mg, 86 % yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 6:1 v/v).

Compound **20** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (d, $J = 6.8$ Hz, 3H; (CH_3)$_2$CH), 1.04 (d, $J = 6.6$ Hz, 3H; (CH_3)$_2$CH), 1.25 (d, $J = 7.1$ Hz, 3H; CH_3CH), 1.72–1.85 (m, 1H; C*H*(CH$_3$)$_2$), 3.16 (d, $J = 2.8$ Hz, 1H; O*H*), 3.64 (ddd, $J = 2.8$, 2.9, 8.2 Hz, 1H; C*H*OH), 3.68 (dq, $J = 2.9$, 7.1 Hz, 1H; C*H*CO), 7.46–7.53 (m, 2H; H_{Ar}), 7.57–7.63 (m, 1H; H_{Ar}), 7.93–7.98 ppm (m, 2H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.7$, 19.0, 19.1, 30.7, 41.7, 76.6, 128.4, 128.8, 133.4, 135.8, 205.9 ppm.

Compound **20** *anti*: Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.94$ (d, $J = 6.8$ Hz, 3H; (CH_3)$_2$CH), 1.00 (d, $J = 6.7$ Hz, 3H; (CH_3)$_2$CH), 1.28 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.74–1.87 (m, 1H; C*H*(CH$_3$)$_2$), 2.98 (d, $J = 7.6$ Hz, 1H; O*H*), 3.58 (ddd, $J = 5.7$, 7.6, 7.6 Hz, 1H; C*H*OH), 3.71 (dq, $J = 5.7$, 7.2 Hz, 1H; C*H*CO), 7.46–7.52 (m, 2H; H_{Ar}), 7.56–7.62 (m, 1H; H_{Ar}), 7.95–8.00 ppm (m, 2H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.0$,

17.0, 20.0, 31.2, 42.4, 79.2, 128.3, 128.7, 133.4, 136.6, 206.3 ppm; HRMS (EI; 70 eV): *m/z* calcd for (*syn*/*anti* mixture) $C_{10}H_{11}O_2$: 163.0759 $[M-C_3H_7]^+$; found: 163.0757 (1 ppm).

1-Hydroxy-2,4-dimethyl-1-phenylpentan-3-one (21): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (35 mg, 0.066 mmol), a 1 M solution of $LiBHEt_3$ (66 μL, 0.066 mmol), $MgBr_2$ (12 mg, 0.066 mmol), benzaldehyde (147 μL, 1.44 mmol), and **1e** (157 μL, 1.31 mmol). Column chromatography on silica gel (pentane/Et_2O, 8:1 then 2:1 v/v) afforded an inseparable mixture of diastereoisomeric aldols as colorless oil (*syn*/*anti*: 75:25 by ^{1}H NMR spectroscopy, 182.9 mg, 68 % yield).

Compound **21** (*syn*, *anti*): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.97$ (*syn*) (d, $J = 6.9$ Hz, 3H; $(CH_3)_2CH$), 0.98 (*anti*) (d, $J = 7.1$ Hz, 3H; $(CH_3)_2CH$), 1.00 (*anti*) (d, $J = 7.1$ Hz, 3H; $(CH_3)_2CH$), 1.05 (*syn*) (d, $J = 6.9$ Hz, 3H; $(CH_3)_2CH$), 1.07 (*anti*) (d, $J = 7.1$ Hz, 3H; CH_3CH), 1.10 (*syn*) (d, $J = 7.1$ Hz, 3H; CH_3CH), 2.58 (*syn*) (sept, $J = 6.9$ Hz, 1H; $CH(CH_3)_2$), 2.63 (*anti*) (sept, $J = 7.1$ Hz, 1H; $CH(CH_3)_2$), 3.01 (*syn*) (dq, $J = 4.5$, 7.1 Hz, 1H; *CH*CO), 3.04 (*anti*) (d, $J = 5.1$ Hz, 1H; O*H*), 3.09 (*anti*) (dq, $J = 7.3$, 7.1 Hz, 1H; *CH*CO), 3.23 (*syn*) (d, $J = 2.2$ Hz, 1H; O*H*), 4.76 (*anti*) (dd, $J = 5.1$, 7.3 Hz, 1H; *CH*OH), 4.99 (*syn*) (dd, $J = 2.2$, 4.5 Hz, 1H; *CH*OH), 7.23–7.38 ppm (*syn*, *anti*) (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 11.2 (*syn*), 14.9 (*anti*), 17.6 (*anti*), 17.6 (*anti*), 17.7 (*syn*), 17.9 (*syn*), 40.5 (*syn*), 41.3 (*anti*), 50.8 (*syn*), 51.0 (*anti*), 73.6 (*syn*), 76.7 (*anti*), 126.0 (*syn*), 126.4 (*anti*), 127.3 (*syn*), 127.7 (*anti*), 128.2 (*syn*), 128.3 (*anti*), 141.9 (*syn*), 142.4 (*anti*), 219.4 (*syn*), 219.5 (*anti*).

4-Ethyl-1-hydroxy-2-methyl-1-phenylhexan-3-one (22): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (60 mg, 0.114 mmol), a 1 M solution of $LiBHEt_3$ (114 μL, 0.114 mmol), $MgBr_2$ (21 mg, 0.114 mmol), benzaldehyde (255 μL, 2.50 mmol), and **1f** (344 μL, 2.28 mmol). Column chromatography on silica gel (pentane/Et_2O, 8:1 then 2:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti* 70:30 by ^{1}H NMR spectroscopy, 477.8 mg, 90 % yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 6:1 v/v).

Compound **22** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.80$ (t, $J = 7.4$ Hz, 3H; CH_3CH_2), 0.84 (t, $J = 7.4$ Hz, 3H; CH_3CH_2), 1.05 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.34–1.49 (m, 2H; CH_2), 1.50–1.62 (m, 1H; CH_2), 1.61–1.73 (m, 1H; CH_2), 2.39–2.47 (m, 1H; $CHCH_2$), 2.90 (dq, $J = 3.6$, 7.2 Hz, 1H; $CHCH_3$), 3.40 (d, $J = 2.0$ Hz, 1H; O*H*), 5.05 (dd, $J = 2.0$, 3.6 Hz, 1H; *CH*OH), 7.23–7.37 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 9.8, 11.6, 12.0, 23.0, 24.2, 51.9, 54.5, 72.8, 126.0, 127.3, 128.2, 141.7, 219.6 ppm.

Compound **22** *anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0{,}80$ (t, $J = 7.4$ Hz, 3H; CH_3CH_2), 0.83 (t, $J = 7.4$ Hz, 3H; CH_3CH_2), 0.97 (d, $J = 7.3$ Hz, 3H; CH_3CH), 1.28–1.48 (m, 2H; CH_2), 1.52–1.74 (m, 2H; CH_2), 2.37–2.46 (m, 1H; $CHCH_2$), 3.00 (dq, $J = 7.8$, 7.3 Hz, 1H; $CHCH_3$), 3.07 (d, $J = 5.0$ Hz, 1H; O*H*), 4.79 (dd, $J = 5.0$, 7.8 Hz, 1H; *CH*OH), 7.25–7.37 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.3$, 11.8, 14.4, 22.3, 23.3, 52.4, 54.9, 76.4, 126.5, 127.7, 128.3, 142.3, 218.6 ppm; HRMS (EI; 70 eV): *m/z* calcd for (*syn*/*anti* mixture) $C_{15}H_{22}O_2$: 234.1620 $[M]^+$; found: 234.1624 (1 ppm).

3-Ethyl-6-hydroxy-5,8-dimethylnonan-4-one (23): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (66.5 mg, 0,126 mmol), a 1 M solution of $LiBHEt_3$ (126 μL, 0.126 mmol), $MgBr_2$ (23.3 mg, 0.126 mmol), isovaleraldehyde (297 μL, 2.77 mmol), and **1f** (380 μL, 2.52 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 69:31 by ^{1}H NMR spectroscopy, 473.7 mg, 88 % yield). The two diastereoisomers were separated by column chromatography (pentane/Et_2O, 6:1 v/v).

Compound **23** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.4$ Hz, 3H; CH_3CH_2), 0.89 (t, $J = 7.5$ Hz, 3H; CH_3CH_2), 0.92 (d, $J = 6.6$ Hz, 3H; $(CH_3)_2CH$), 0.93 (d, $J = 6.7$ Hz, 3H; $(CH_3)_2CH$), 1.08 (dddd, $J = 1.1$, 4.4, 8.4, 13.9 Hz, 1H; CH_2CHOH), 1.11 (d, $J = 7.2$ Hz, 3H; $CHCH_3$), 1.37–1.53 (m, 3H; CH_2CHOH, CH_2CH_3), 1.57–1.72 (m, 2H; CH_2CH_3), 1.71–1.82 (m, 1H; $CH(CH_3)_2$), 2.45–2.54 (m, $CH(CH_2)_2$), 2.59 (dq, $J = 2.5$, 7.2 Hz, 1H; $CHCH_3$), 2.99 (dd, $J = 1.1$, 2.5 Hz, 1H; O*H*), 3.99 ppm (dddd, $J = 2.5$, 2.5, 4.4, 4.7 Hz, 1H; *CH*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.2$, 11.8, 12.0, 22.1, 23.2, 23.3, 24.5, 24.6, 43.0, 49.4, 54.3, 68.4, 220.3 ppm.

Compound **23** *anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.4$ Hz, 3H; CH_3CH_2), 0.90 (t, $J = 7.4$ Hz, 3H; CH_3CH_2), 0.90 (d, $J = 6.5$ Hz, 3H; $(CH_3)_2CH$), 0.93 (d, $J = 6.7$ Hz, 3H; $(CH_3)_2CH$), 1.12 (d, $J = 7.2$ Hz, 3H; CH_3CH), 1.19 (ddd, $J = 2.9$, 9.7, 12.8 Hz, 1H; CH_2CHOH), 1.35–1.49 (m, 3H; CH_2CHOH, CH_2CH_3), 1.60–1.74 (m, 2H; CH_2CH_3), 1.79–1.94 (m, 1H; $CH(CH_3)_2$), 2.46 (dddd, $J = 5.1$, 6.3, 6.3, 8.2 Hz, 1H; $CH(CH_2)_2$), 2.67 (dq, $J = 6.4$, 7.2 Hz, 1H; $CHCH_3$), 2.74 (d, $J = 6.4$ Hz, 1H; O*H*), 3.77 ppm (dddd, $J = 2.9$, 6.4, 6.4, 9.4 Hz, 1H; *CH*OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.6$, 12.0, 14.0, 21.5, 22.5, 23.8, 23.9, 24.4, 43.9, 51.3, 54.5, 71.7, 219.5 ppm; HRMS (EI; 70 eV): *m/z* calcd for (*syn*/*anti* mixture) $C_{13}H_{24}O$: 196.1827 $[M-H_2O]^+$; found: 196.1839 (5 ppm).

1-Hydroxy-2,4,4-trimethyl-1-phenylpentan-3-one (24): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (68 mg, 0.1285 mmol), a 1 M solution of $LiBHEt_3$ (128 μL, 0.1285 mmol), $MgBr_2$ (24 mg, 0.1285 mmol), benzaldehyde (287 μL, 2.83 mmol), and **1g** (293 mg, 2.57 mmol). Column chromatography on silica gel (pentane/Et_2O, 8:1 then 2:1 v/v) afforded an inseparable mixture of diastereoisomeric aldols as colorless oil (*syn*/*anti*: 90:10 by ^{1}H NMR spectroscopy, 502.8 mg, 89 % yield).

Compound **24** *syn*,*anti*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (*anti*) (d, $J = 7.0$ Hz, 3H; CH_3CH), 1.03 (*anti*) (s, 9H; *tBu*), 1.06 (*syn*) (d, $J =$ 6.9 Hz, 3H; CH_3CH), 1.08 (*syn*) (s, 9H; *tBu*), 3.19 (*anti*) (d, $J = 5.8$ Hz, 1H; O*H*), 3.25 (*syn*) (dq, $J = 4.0$, 6.9 Hz, 1H; $CHCH_3$), 3.32 (*anti*) (dq, $J = 7.0$, 7.0 Hz, 1H; $CHCH_3$), 3.52 (*syn*) (d, $J = 1.4$ Hz, 1H; O*H*), 4.77 (*anti*) (dd, $J = 5.8$, 7.0 Hz, 1H; *CH*OH), 4.89 (*syn*) (dd, $J = 1.4$, 4.0 Hz, 1H; *CH*OH), 7.22–7.36 ppm (*syn, anti*) (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.0$ (*syn*), 16.6 (*anti*), 25.8 (*syn*), 25.9 (*anti*), 45.0 (*anti*), 45.1 (*syn*), 46.2 (*syn*), 46.7 (*anti*), 73.9 (*syn*), 77.4 (*anti*), 126.1 (*syn*), 126.3 (*anti*), 127.4 (*syn*), 127.7 (*anti*), 128.2 (*syn*), 128.3 (*anti*), 141.8 (*syn*), 143.0 (*anti*), 221.1 (*anti*), 221.4 ppm (*syn*); HRMS (EI; 70 eV): *m/z* calcd for (*syn*/*anti* mixture) $C_{14}H_{20}O_2$: 220.1463 $[M]^+$; found: 220.1477 (6 ppm).

Ethyl 4-[hydroxy(phenyl)methyl]-2,2-dimethyl-3-oxopentanoate (25): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (43.6 mg, 0.0825 mmol), a 1 M solution of $LiBHEt_3$ (82 μL, 0.0825 mmol), $MgBr_2$ (15.2 mg, 0.0825 mmol), benzaldehyde (184 μL, 1.81 mmol), and **1h** (293 μL, 1.65 mmol). Column chromatography on silica gel (pentane/Et_2O, 8:1 then 2:1 v/v) afforded the diastereoisomeric aldols as colorless oil (*syn*/*anti* > 95:5 by ^{1}H NMR spectroscopy, 427.2 mg, 93 % yield).

Compound **25** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (d, $J = 6.9$ Hz, 3H; CH_3CH), 1,28 (t, $J = 7.1$ Hz, 3H; CH_3CH_2), 1.31 (s, 3H; CH_3), 1.35 (s, 3H; CH_3), 3.07 (dq, $J = 3.2$, 6.9 Hz, 1H; $CHCH_3$), 3.42 (d, $J = 1.4$ Hz, 1H; O*H*), 4.23 (dd, $J = 10.9$, 7.1 Hz, 1H; CH_2O), 4.26 (dd, $J = 10.9$, 7.1 Hz, 1H; CH_2O), 4.97–5.02 (m, 1H; *CH*OH), 7.23–7.38 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.5$, 14.0, 21.6, 21.6, 48.4, 56.4, 61.6, 73.4, 125.9, 127.4, 128.2, 141.2, 173.1, 214.2; HRMS (EI; 70 eV): *m/z* calcd for $C_9H_{16}O_3$: 172.1100 $[M-C_6H_5CHO]^+$; found: 172.1100 (0 ppm).

Ethyl 5-hydroxy-2,2,4,7-tetramethyl-3-oxooctanoate (26): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$-(dppe)] (32.1 mg, 0.0608 mmol), a 1 M solution of $LiBHEt_3$ (61 μL, 0.0608 mmol), $MgBr_2$ (11.2 mg, 0.0608 mmol), isovaleraldehyde (239 μL, 2.23 mmol), and **1h** (358 μL, 2.03 mmol). Column chromatography on silica gel (pentane/Et_2O, 6:1 then 2:1 v/v) afforded the aldols as colorless oil (*syn*/*anti* > 95:5 by ^{1}H NMR spectroscopy, 460.9 mg, 88 % yield).

Compound **26** *syn*: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.6$ Hz, 3H; $(CH_3)_2CH$), 0.92 (d, $J = 6.7$ Hz, 3H; $(CH_3)_2CH$), 1.03 (dddd, $J = 1.3$, 4.1, 8.6, 13.8 Hz, 1H; CH_2CHOH), 1.12 (d, $J = 7.0$ Hz, 3H; CH_3CH), 1.27 (t, $J = 7.2$ Hz, 3H; CH_3CH_2), 1.38 (s, 3H; CH_3), 1.41 (s, 3H; CH_3), 1.49 (ddd, $J = 5.5$, 9.1, 13.8 Hz, 1H; CH_2CHOH), 1.69–1.81 (m, 1H; $CH(CH_3)_2$), 2.77 (dq, $J = 2.1$, 7.0 Hz, 1H; *CH*CO), 2.97 (dd, $J \approx 1.5$, 1.5 Hz, 1H; O*H*), 3.87 (dddd, $J = 1.5$, 2.1, 4.1, 9.1 Hz, 1H; *CH*OH), 4.20 (dd, $J =$ 10.9, 7.2 Hz, 1H; CH_2O), 4.25 ppm (dd, $J = 10.9$, 7.2 Hz, 1H; CH_2O); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.1$, 14.0, 21.8, 21.8, 22.0, 23.3, 24.5, 43.0, 45.9, 56.3, 61.5, 69.2, 173.1, 214.7; HRMS (EI; 70 eV): *m/z* calcd for $C_9H_{16}O_3$: 172.1100 $[M-C_4H_9CHO]^+$; found: 172.1097 (1 ppm).

(4*S*)-4-(Benzyloxy)-3-hydroxy-2-methyl-1-phenylpentan-1-one (28a–d): These aldols were obtained in 79% overall yield from **1d** and aldehyde **27**,[25] by using the general procedure (method A). Analysis of the crude reaction mixture by ^{1}H and ^{13}C NMR spectroscopy, and by comparison with literature data,[26] indicated the following ratios for the aldol products: **28a** (48%), **28b** (12%), **28c** (32%), **28d** (8%).

(6*S*)-Ethyl 6-(benzyloxy)-5-hydroxy-2,2,4-trimethyl-3-oxoheptanoate (30): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (46.5 mg, 0.088 mmol), a 1 M solution of $LiBHEt_3$ (88 μL, 0.088 mmol), $MgBr_2$ (16.2 mg, 0.088 mmol), **27** (317 μL, 1.94 mmol, 1.1 equiv), and the allylic alcohol **1h** (312 μL, 1.76 mmol). Column chromatography on silica gel (hexane/Et_2O, 7:1 then 4:1 then 2:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 78:22 by ^{1}H NMR spectroscopy, 561.8 mg, 95% yield). The two diastereoisomers were separated by column chromatography (hexane/Et_2O 6:1 v/v).

Compound **30a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.9 Hz, 3H; CH_3CH), 1.22 (t, J = 7.2 Hz, 3H; CH_3CH$_2$), 1.27 (d, J = 6.0 Hz, 3H; CH_3CH), 1.37 (s, 3H; CH_3), 1.39 (s, 3H; CH_3), 3.07 (d, J = 1.6 Hz, 1H; O*H*), 3.28 (dq, J = 2.2, 6.9 Hz, 1H; C*H*CO), 3.38 (dq, J = 8.0, 6.0 Hz, 1H; C*H*O), 3.64 (ddd, J = 1.6, 2.2, 8.0 Hz, 1H; C*H*OH), 4.08–4.18 (m, 2H; CH_2CH$_3$), 4.38 (d, J = 11.8 Hz, 1H; CH_2Ph), 4.63 (d, J = 11.8 Hz, 1H; CH_2Ph), 7.25–7.39 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 13.9, 16.0, 21.8, 21.9, 41.7, 56.3, 61.5, 70.4, 73.6, 74.4, 127.6, 127.8, 128.3, 138.3, 173.1, 215.1 ppm.

Compound **30b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.9 Hz, 3H; CH_3CH), 1.24 (d, J = 6.2 Hz, 3H; CH_3CH), 1.25 (t, J = 7.1 Hz, 3H; CH_3CH$_2$), 1.37 (s, 3H; CH_3), 1.38 (s, 3H; CH_3), 2.59 (d, J = 6.1 Hz, 1H; O*H*), 3.12 (dq, J = 5.5, 6.9 Hz, 1H; C*H*CO), 3.50 (dq, J = 4.4, 6.2 Hz, 1H; C*H*O), 3.68 (ddd, J = 4.4, 5.5, 6.1 Hz, 1H; C*H*OH), 4.16 (q, J = 7.1 Hz, 2H; CH_2CH$_3$), 4.45 (d, J = 11.5 Hz, 1H; CH_2Ph), 4.63 (d, J = 11.5 Hz, 1H; CH_2Ph), 7.26–7.38 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 14.0, 16.2, 22.2, 22.2, 44.1, 56.2, 61.4, 70.8, 75.5, 75.6, 127.6, 128.4, 138.3, 173.3, 212.2; HRMS (EI; 70 eV): m/z calcd for $C_{10}H_{17}O_4$: 201.1127 [$M-C_9H_{11}O$]$^+$; found: 201.1109 (8 ppm).

(6*S*)-Ethyl 6-(*tert*-butyldimethylsiloxy)-5-hydroxy-2,2,4-trimethyl-3-oxoheptanoate (31): These aldols were obtained by using the general procedure (method A) with [$NiCl_2$(dppe)] (55 mg, 0.104 mmol), a 1 M solution of $LiBHEt_3$ (104 μL, 0.104 mmol), $MgBr_2$ (19.2 mg, 0.104 mmol), **29** (495 μL, 2.29 mmol, 1.1 equiv), and allylic alcohol **1h** (369 μL, 2.08 mmol). Column chromatography on silica gel (hexane/Et_2O, 12:1 then 8:1 then 4:1 v/v) afforded a separable mixture of diastereoisomeric aldols as a colorless oil (*syn*/*anti*: 83:17 by ^{1}H NMR spectroscopy, 632.6 mg, 85% yield). The two diastereoisomers **31a** and **31b** were separated by column chromatography (hexane/Et_2O 12:1 v/v).

Compound **31a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 3H; CH_3Si), 0.06 (s, 3H; CH_3Si), 0.87 (s, 9H; *tBu*), 1.07 (d, J = 7.0 Hz, 3H; CH_3CH), 1.19 (d, J = 5.9 Hz, 3H; CH_3CH), 1.26 (t, J = 7.1 Hz, 3H; CH_3CH$_2$), 1.37 (s, 3H; CH_3), 1.38 (s, 3H; CH_3), 3.09 (d, J = 1.3 Hz, 1H; O*H*), 3.29 (dq, J = 2.0, 7.0 Hz, 1H; C*H*CO), 3.46 (ddd, J = 1.3, 2.0, 8.0 Hz, 1H; C*H*OH), 3.62 (dq, J = 8.0, 5.9 Hz, 1H; C*H*O), 4.16 ppm (q, J = 7.1 Hz, 2H; CH_2CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.0, −4.0, 10.8, 14.0, 17.8, 20.7, 21.8, 21.9, 25.7, 41.4, 56.3, 61.4, 67.9, 76.0, 172.9, 215.1 ppm.

Compound **31b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3H; CH_3Si), 0.10 (s, 3H; CH_3Si), 0.90 (s, 9H; *tBu*), 1.14 (d, J = 6.9 Hz, 3H; CH_3CH), 1.17 (d, J = 6.2 Hz, 3H; CH_3CH), 1.27 (t, J = 7.1 Hz, 3H; CH_3CH$_2$), 1.39 (s, 3H; CH_3), 1.41 (s, 3H; CH_3), 2.63 (d, J = 5.3 Hz, 1H; O*H*), 3.02 (dq, J = 4.9, 6.9 Hz, 1H; C*H*CO), 3.52–3.58 (m, 1H; C*H*OH), 3.72 (dq, J = 4.8, 6.2 Hz, 1H; C*H*O), 4.18 ppm (q, J = 7.1 Hz, 2H; CH_2CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.7, −4.0, 12.9, 14.0, 18.1, 20.7, 22.3, 22.4, 25.8, 44.0, 56.1, 61.4, 70.0, 75.4, 173.4, 211.8 ppm; HRMS (EI; 70 eV): m/z calcd for $C_{14}H_{27}O_5Si$: 303.1628 [$M-t$Bu]$^+$; found: 303.1634 (2 ppm).

Catalytic studies using chiral nickel complexes: The complexes **32** and **33** were prepared following a literature method.[27]

Compound **32**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (dd, J = 6.9, 11.9 Hz, 3H; CH_3), 1.90–2.02 (m, 1H; CH_2), 2.12–2.32 (m, 1H; CH_2), 2.44–2.56 (m, 1H; C*H*CH3), 7.43–7.66 (m, 12H; H_{Ar}), 7.71–7.85 (m, 4H; H_{Ar}), 8.20–8.27 (m, 2H; H_{Ar}), 8.30–8.37 ppm (m, 2H; H_{Ar}); ^{31}P{^{1}H} NMR (162 MHz, CD_3COCD_3): δ = 45.9 (d, J = 78.5 Hz), 64.0 ppm (d, J = 78.5 Hz).

Compound **33**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–0.97 (m, 6H; CH_3), 2.11–2.16 (m, 2H; C*H*CH$_3$), 7.46–7.68 (m, 12H; H_{Ar}), 7.72–7.78 (m, 4H; H_{Ar}), 8.32–8.38 ppm (m, 4H; H_{Ar}); ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$): δ = 59.7 ppm (s).

Complex **34** was prepared following the method of Frauenrath.[27]

Starting from each of these three complexes, the experiments were performed by using the previously described procedure (method A) with allylic alcohol **1a** and benzaldehyde. After separation by chromatography, the aldols **7** *syn* and **7** *anti* were studied by ^{1}H NMR spectroscopy with [Eu(tfc)$_3$]. In the presence of this chiral shift reagent, the racemic mixture (±)-**7** *syn*, prepared from the dppe complex, exhibited a nice splitting of the signal of the carbinol proton C*H*OH at δ = 5.49 and 5.56 ppm. Similarly, the (±)-**7** *anti* aldol exhibited a significant splitting of the CHCH_3 signals at δ = 1.06 and 1.07 ppm. For each of the experiments performed with **32**, **33**, and **34**, the NMR spectra obtained for corresponding *syn* and *anti* aldols were identical to those obtained using the racemic catalyst, with equal intensities for the two signals. The same experiments (method A) were performed starting from allylic alcohol **1h** and benzaldehyde. The NMR spectra, in the presence of [Eu(tfc)$_3$], were again identical to those obtained with the racemic aldol (±)-**25** *syn*, with a significant splitting of the signals corresponding to the carbinol proton C*H*OH at δ = 5.43 and 5.49 ppm.

1-Phenylprop-2-en-1-one (35): IBX (10.92 g, 39 mmol, 1.5 equiv) was added portionwise to a solution of **1d** (3.50 g, 26 mmol) in DMSO (25 mL) at room temperature. The reaction mixture was stirred for 1.5 h, then water (15 mL) and CH_2Cl_2 (15 mL) were added. After filtration on Celite, the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were washed with water (2 × 15 mL), dried ($MgSO_4$), and concentrated under vacuum. Purification by column chromatography on silica gel (pentane/Et_2O, 20:1 v/v) afforded the enone **35** as a pale yellow oil (2.75 g, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.92 (dd, J = 1.7, 10.6 Hz, 1H; CH_2=CH), 6.44 (dd, J = 1.7, 17.1 Hz, 1H; CH_2=CH), 7.16 (dd, J = 10.6, 17.1 Hz, 1H; CH$_2$=C*H*), 7.43–7.51 (m, 2H; H_{Ar}), 7.54–7.60 (m, 1H; H_{Ar}), 7.91–7.98 ppm (m, 2H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.5, 128.6, 130.1, 132.2, 132.9, 137.1, 190.9.

1-Deuterio-1-phenylprop-2-en-1-ol (36): $CeCl_3 \cdot 7H_2O$ (7.45 g, 20 mmol, 1 equiv) was added to a solution of **35** (2.68 g, 20 mmol) in methanol (30 mL) at room temperature and under stirring. The reaction mixture was cooled to 0 °C and then $NaBD_4$ (0.85 g, 20 mmol, 1 equiv) was added portionwise. The reaction mixture was stirred at room temperature for 25 min before the addition of a saturated NH_4Cl solution (15 mL). The aqueous phase was extracted with ether (3 × 30 mL), and the organic phases were dried ($MgSO_4$) and concentrated under vacuum. Purification by column chromatography on silica gel (pentane/Et_2O, 4:1 v/v) afforded the alcohol **36** as a colorless oil (2.12 g, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 1H; O*H*), 5.17 (dd, J = 1.4, 10.3 Hz, 1H; CH_2=CH), 5.32 (dd, J = 1.4, 17.1 Hz, 1H; CH_2=CH), 6.02 (dd, J = 10.3, 17.1 Hz, 1H; CH$_2$=C*H*), 7.25–7.36 ppm (m, 5H; H_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.8 (t, J = 43.9 Hz), 115.1, 126.3, 127.7, 128.5, 140.1, 142.4 ppm; HRMS (EI; 70 eV): m/z calcd for C_9H_9DO: 135.0794 [M]$^+$; found: 135.0791 (2 ppm).

The reaction of **36** with benzaldehyde and the nickel catalyst was performed as described earlier for the synthesis of aldols **19**. By suing EI HRMS, the isotopic pattern was analyzed for the [$M-C_6H_5CHO$]$^+$ ions and gave the three species: [D_0] (38%), [D_1] (44%), and [D_2] (18%). The ratio between the two [D_1] compounds was determined by comparison of the integration of the ^{1}H NMR signals of the C*H*OH signals (δ = 5.24 and 5.02 ppm) with both the signals of the C*H*CH$_3$ and the (CH_2D + CH_3) groups. From the integration of the C*H*CH$_3$ signals (at δ = 3.73, 3.48, 2.88 ppm), values 29% for the [D_1](CH_2D) compound and 15% for the [D_1](CDCH_3) compound were obtained. From the integration of the CH_3 and CH_2D signals (at δ = 1.17 and 0.95 ppm) values of 20 and 24% were obtained, respectively. So, the range was evaluated as 20–30% for the [D_1](CH$_2$D) compound and 14–24% for the [D_1](CDCH$_3$) compound. These results were confirmed by the analysis of the methyl

groups signals in the $^{13}C\{^1H\}$ NMR spectra of these aldols. The *anti* adducts exhibited the following signals: $\delta = 15.92$ (s, CH_3 for **19**), 15.82 (s, CH_3 for **38**), 15.66 (t, $J_{CD} = 20$ Hz, CH_3 for **37** or **39**), 15.56 ppm (t, $J_{CD} = 20$ Hz, CH_3 for **39** or **37**). The *syn* adducts exhibit the following signals: $\delta = 12.18$ (s, CH_3 for **19**), 12.11 (s, CH_3 for **38**), 11.92 (t, $J_{CD} = 20$ Hz, CH_3 for **37** or **39**), 11.84 ppm (t, $J_{CD} = 20$ Hz, CH_3 for **39** or **37**).

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