Homogeneous and Biphasic Nickel-Catalyzed Isomerization of Allylic Alcohols

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The nickel-catalyzed isomerization of geraniol and prenol in homogeneous and two-phase systems has been investigated. The best results in terms of activity and selectivity have been obtained in homogeneous systems with a bis(cycloocta-1,5-diene)nickel(0)/1,4-bis(diphenylphosphanyl)butane/trifluoroacetic acid combination. Catalyst deactivation occurs in the course of the reaction owing to coordination of the formed aldehyde group to the nickel species or as a result of protonolysis of hydrido- or (π-allyl)nickel complexes.

Introduction

The ability of homogeneous nickel complexes to promote double-bond positional isomerization of simple alkenes and polyenes as well as skeletal isomerization of some dienes is well documented[1]. While the reactions of unfunctionalized alkenes have been quite extensively studied, the case of alkenes bearing polar functional groups has received less attention. Thus, there have been only two reports on the nickel-catalyzed isomerization of allylic alcohols[2][3][4]. The first describes the selective transformation of allyl alcohol into propanal in the presence of a catalytic amount of the Ni^{I} complex Ni$_2$(CN)$_2$(dppb)$_3$ [dppb = 1,4-bis(diphenylphosphanyl)butane], which is either preformed or generated in situ from Ni(dppb)$_2$ and HCN[2]. The second describes a sluggish catalytic system consisting of ethylene(tri-*o*-tolyl phosphite)nickel(0) and hydrogen chloride for the isomerization of various allylic alcohols[3]. Surprisingly, although the catalytic isomerization of terpenic alcohols and related compounds could be of great industrial interest[4h], no attention has been directed towards these substrates in the previous studies.

Our continuing interest in the reactivity of zerovalent nickel−phosphane catalysts towards allylic substrates[5] has led us to explore the catalytic activity of various homogeneous Ni^{0}/diphosphane/acid systems in the isomerization of geraniol and prenol. We report herein that nickel efficiently catalyzes this process and point out how the catalyst is deactivated in the course of the reaction. An alternative water-soluble catalytic system has also been developed and evaluated.

Results and Discussion

In the light of literature reports and of our own work[5], we decided to use as catalyst precursor the complex Ni(dppb)$_2$, which is easily generated in situ from Ni(COD)$_2$ and two equiv. of dppb[6]. Preliminary experiments aimed at evaluating the efficiencies of the added Brønsted acids were first conducted using geraniol (**1**) as the substrate. Besides the expected isomerization product, citronellal (**2**), several compounds were formed in variable amounts depending on the reaction conditions (Scheme 1). Thus, some of the **2** present was converted into the diastereomeric alcohols isopulegol (**3**) and neoisopulegol (**4**) as a result of a proton-catalyzed cyclization process[7]. Two further side-products **5** and **6** were generated due to esterification of the starting substrate by the carboxylic acid added as a co-catalyst, and acetalization of **2** by **1**, respectively. The results are summarized in Table 1.

The isomerization of **1** did not proceed when 1.5 mol-% of Ni(dppb)$_2$ was used at 80°C in the absence of a co-catalyst (entry 1) or in the presence of methanol (entry 2). In these cases, only small amounts of the dehydration products of **1**, i.e. myrcene (**8**) and ocimene (**9**) were formed, most probably by oxidative addition of **1** followed by a β-H elimination process as these products were not observed in the absence of the nickel catalyst (Schemes 2 and 6).

The addition of 4 equiv. of acetic acid (with respect to Ni) allowed the selective, but sluggish formation of **2** (entry 3). An increase in the amount of acetic acid up to 50 equiv. improved the catalytic activity, but the selectivity significantly decreased with time because of the formation of the ester **5** as a side-product (entry 4). Use of TFA as the co-catalyst proved much more advantageous. With 1 equiv., an almost total selectivity for **2** could be observed, although the reaction stopped after 2 h, reaching a maximum of 30% conversion of **1**. Increasing the amount of TFA up to 2 or 4 equiv. led to a slight improvement of the catalytic activity in the initial stages of the reaction, but the limitation of termination of the reaction after ca. 50% conversion was

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Scheme 1. Isomerization of geraniol (**1**) into citronellal (**2**) and reaction side-products

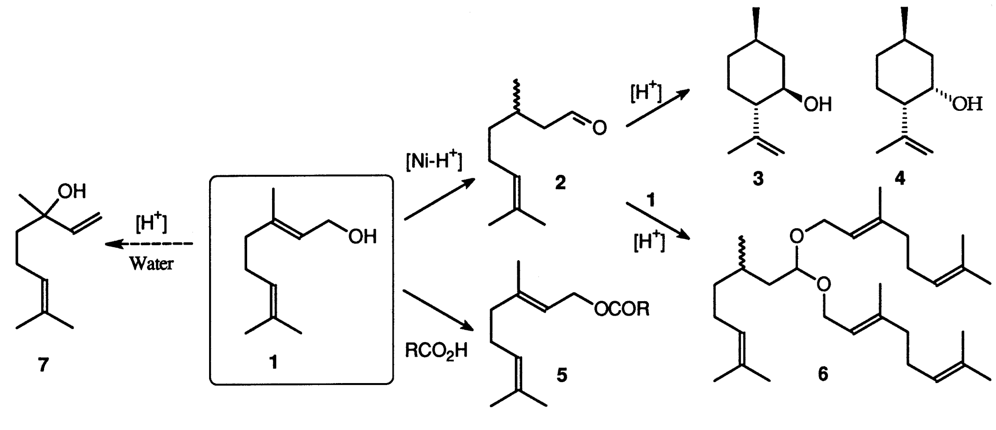


Table 1. Nickel-catalyzed isomerization of geraniol[a]

Entry	Acid (equiv.)[b]	Time [h]	Conv. **1**[c] [mol-%]	Yield **2** [mol-%]	Sel. **2**[c] [mol-%]	Sel. **3** + **4**[c][d] [mol-%]	Sel. **5**[c] [mol-%]	Sel. **6**[c] [mol-%]	Sel. **7**[c] [mol-%]
1	–	16	2[e]	0	0	0	0	0	< 1
2	MeOH (50)	18	3[e]	0	0	0	0	0	< 1
3	AcOH (4)	2	2	2	> 99	< 1	< 1	< 1	< 1
4	AcOH (50)	0.5	19	18	98	< 1	2	< 1	< 1
		2	25	23	92	< 1	6	2	< 1
		16	41	29	71	4	20	5	< 1
5	TFA (1)	0.5	25	25	> 99	< 1	< 1	< 1	< 1
		2	30	30	> 99	< 1	< 1	< 1	< 1
		16	30	30	> 99	< 1	< 1	< 1	< 1
6	TFA (2)	0.5	31	31	> 99	< 1	< 1	< 1	< 1
		2	46	45	97	< 1	< 1	3	< 1
		16	54	49	90	5	< 1	5	< 1
7	TFA (4)	0.5	33	30	91	5	4	< 1	< 1
		2	46	38	82	10	3	5	< 1
		16	58	47	80	10	1	9	< 1
8[f]	TFA (4)	0.5	10	1	10	0	0	0	90
		2	34	1	3	0	0	0	97
		16	65	3	5	0	0	0	95
9[g]	TFA (4)	0.5	10	8	80	4	0	0	16
		2	15	13	86	4	0	0	10
		16	19	14	74	11	0	0	15
10[g]	HCl (4)	0.5	9	8	88	1	0	0	11
		2	15	13	86	4	0	0	10
		16	19	14	74	12	0	14	
11[h]	TFA (4)[h]	0.5	20	8(19)[i]	40(96)[j]	4	< 1	< 1	< 1
		2	31	5(30)[i]	17(96)[j]	4	< 1	< 1	< 1
		16	72	8(69)[i]	11(95)[j]	5	< 1	< 1	< 1

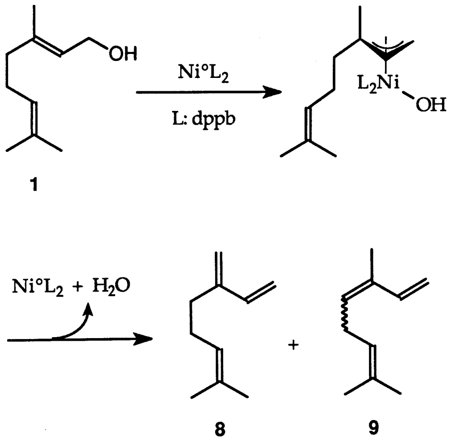
[a] Reaction conditions: Ni(COD)$_2$ 0.13 mmol, dppb 0.26 mmol, geraniol (**1**) 9.1 mmol, toluene 5 ml, T = 80°C. – [b] mol equivalent of protic co-reagent with respect to Ni. – [c] Selectivity = (mmol of product)/(mmol of converted geraniol) × 100; conversion of **1** and selectivities of the formed products were determined by quantitative GLC analysis. – [d] The **3**/**4** ratio was always 60:40. – [e] Myrcene and ocimene account for the conversion. – [f] Two-phase system: Ni(COD)$_2$ 0.13 mmol, dppbts 0.26 mmol, geraniol (**1**) 9.1 mmol, toluene 5 ml, water 10 g, T = 110°C. – [g] Same conditions as in footnote [f] except water 5 g and dimethylformamide 5 g. – [h] Reaction conducted in the presence of butane-1,2-diol (13.7 mmol, 1.5 equiv. with respect to **1**). – [i] The first value indicates the yield of free citronellal (**2**) and the value in brackets the total yield including free and acetalized citronellal (**2** + **15**). – [j] The first value indicates the selectivity for free citronellal (**2**) and the value in brackets the total selectivity including free and acetalized citronellal (**2** + **15**).

still observed (entries 6, 7). Moreover, the presence of an excess of acid with respect to nickel catalyst promoted the cyclization and acetalization, and to a lesser extent the esterification (entry 7).

Similar results were also obtained for the isomerization of prenol (**10**) into isovaleraldehyde (**11**) using the Ni(dppb)$_2$/TFA (1:2) catalyst system (Scheme 3). Besides **11**, the isomeric 3-methyl-3-buten-1-ol (**12**), resulting from isomerization of the double bond in the carbon backbone, was also formed in small amounts. The results are summarized in Table 2.

With 1 equiv. of TFA with respect to Ni(dppb)$_2$, isomerization rapidly ceased, thus allowing the attainment of modest yields only (Table 2, entry 13). On the other hand, excess TFA proved to be detrimental to the selectivity due to acetalization of **11** to give **13** (Table 2, entry 15). A TFA/

Scheme 2. Suggested formation of myrcene (**8**) and ocimene (**9**) from geraniol (**1**)



Scheme 3. Isomerization of prenol (**10**) into isovaleraldehyde (**11**) and reaction side-products

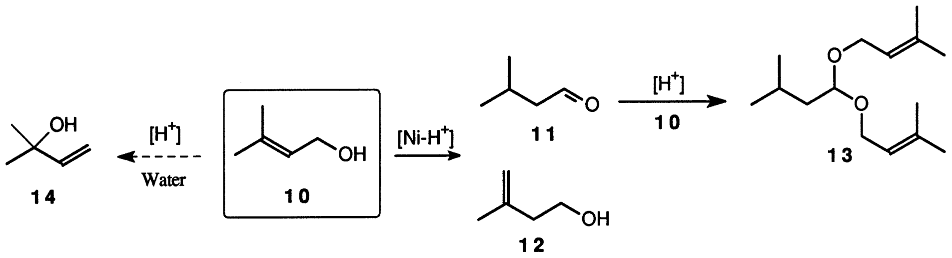


Table 2. Nickel-catalyzed isomerization of prenol[a]

Entry	TFA (equiv.)[b]	Time [h]	Conv. **10**[c] [mol-%]	Yield **11** [mol-%]	Sel. **11**[c] [mol-%]	Sel. **12**[c] [mol-%]	Sel. **13**[c] [mol-%]	Sel. **11**[d] [mol-%]	Sel. **14**[d] [mol-%]
12	0	18	25[e]	0	0	0	0	0	0
13	1	0.5	28	26	92	7	1	93	0
		2	34	31	91	7	2	93	0
		16	35	31	89	8	3	93	0
14	2	0.5	40	34	85	6	9	94	0
		2	55	45	82	5	13	95	0
		16	65	47	72	5	23	95	0
15	4	0.5	46	30	66	3	31	97	0
		2	67	37	55	2	43	98	0
		16	82	43	52	3	45	97	0
16[f]	4[f]	0.5	23	11	47	0	0	47	53
		2	32	12	38	0	0	38	62
		16	55	12	22	0	0	22	78
17[g]	4[g]	0.5	36	10(32)[h]	26(89)[i]	2	9	98	0
		2	47	5(44)[h]	10(94)[i]	2	4	98	0
		4	59	5(57)[h]	8(96)[i]	2	2	98	0
		16	92	5(90)[h]	5(98)[i]	2	0	98	0

[a][b] See Table 1. – [c] Selectivity = (mmol of product)/(mmol of converted prenol) × 100; conversion of **10** and selectivities of the formed products were determined by quantitative GLC analysis. – [d] Calculated selectivity for attainable isovaleraldehyde after hydrolysis. – [e] Isoprene accounts for the conversion. – [f] Two-phase system: $Ni(COD)_2$ 0.13 mmol, dppbts 0.26 mmol, prenol (**10**) 9.1 mmol, toluene 5 ml, water 5 g, dimethylformamide 5 g, $T = 110\,°C$. – [g] Reaction conducted in the presence of butane-1,2-diol (13.7 mmol, 1.5 equiv. with respect to **11**). – [h] The first value indicates the yield of free isovaleraldehyde (**11**) and the value in brackets the total yield including free and acetalized isovaleraldehyde (**11** + **16**). – [i] The first value indicates the selectivity for free isovaleraldehyde (**11**) and the value in brackets the total selectivity including free and acetalized isovaleraldehyde (**11** + **16**).

Ni ratio of 2 appeared to be a good compromise (Table 2, entry 14) but, as in the case of geraniol, a rapid decrease in the catalytic activity after 2 h of reaction and a limit to the degree of conversion was observed.

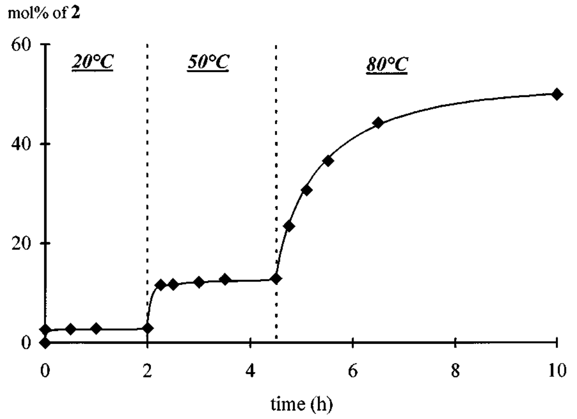
In order to gain further insight into the aforementioned limitation to the extent of conversion, an experiment was conducted with the $Ni(dppb)_2$/TFA (1:2) catalytic system, in which the temperature was varied during the course of the reaction. The experiment was started at room temperature and the temperature was increased when the progress of the reaction was seen to falter (Figure 1).

It was found that the limit to the degree of conversion of **1** into **2** increased with temperature, i.e. 5% at 20°C, 13% at 50°C, and ca. 50% at 80°C. As the isomerization of allylic alcohols is a non-reversible process[8], the above data cannot stem from a thermodynamic control of the reaction and are much more likely to be attributable to catalyst deactivation. In fact, we assume that the aldehydes **2** or **11** reversibly coordinate to Ni[9] to form an inactive species, the stability of which would decrease with temperature (Scheme 4).

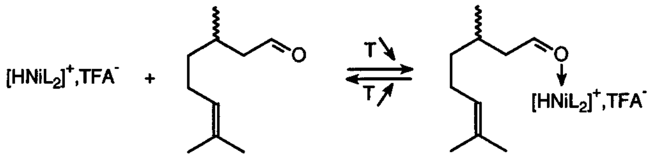
To check this hypothesis, two approaches were considered:

(i) The first of these involved the use of an aqueous/organic two-phase system where the organic compounds, i.e.

Figure 1. Influence of the temperature on the isomerization of geraniol (**1**) into citronellal (**2**); experimental conditions: Ni(COD)$_2$: 0.13 mmol, dppb: 0.26 mmol, **1**: 9.1 mmol, toluene: 5 ml, TFA: 0.52 mmol



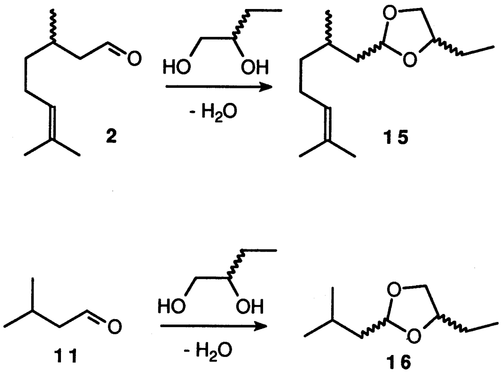
Scheme 4. Reversible coordination of the aldehyde to the nickel center



the allylic alcohol and the aldehyde, were in a different phase from that containing the catalytic system. In such a system, the coordination of the aldehyde group should be less favorable. Unfortunately, the performance of the corresponding water-soluble catalytic system, i.e. a nickel complex of tetrasulfonated 1,4-bis(diphenylphosphanyl)butane in an acidic aqueous solution[10], turned out to be rather disappointing (entries 8–10). Indeed, in a genuine two-phase system, i.e. without a co-solvent, the isomerization of **1** into linalool (**7**) was the major reaction (Scheme 1) and **2** was obtained only in very poor yield (3%, entry 8). Experiments conducted in the absence of a nickel catalyst proved unequivocally that **7** is formed by a proton-assisted process[11]. Such a process did not occur in homogeneous media, probably because of the lower stability of the intermediate allylic carbocation in non-polar organic media. Interestingly, the use of a co-solvent such as dimethylformamide (DMF) reduces the polarity of the aqueous layer and consequently suppresses this undesirable reaction. Indeed, although this catalytic system gave **2** in poor yields irrespective of the acid used, the selectivity for the desired aldehyde reached 86%, compared to 3% without DMF (entries 9, 10). Owing to the high solubility of prenol in water, it is noteworthy that DMF does not suppress the proton-catalyzed side reaction (Table 2, entry 16). Furthermore, in all biphasic reactions, a rapid colour change of the aqueous layer from orange to pale-green was observed, thus indicating an irreversible catalyst decay.

(ii) The second approach involved trapping of the aldehyde by acetalization, by including an excess of butane-1,2-diol in the reaction mixture (Scheme 5). Butane-1,2-diol was preferred to ethane-1,2-diol for trapping of the aldehydes because of its total solubility in the reaction mixture.

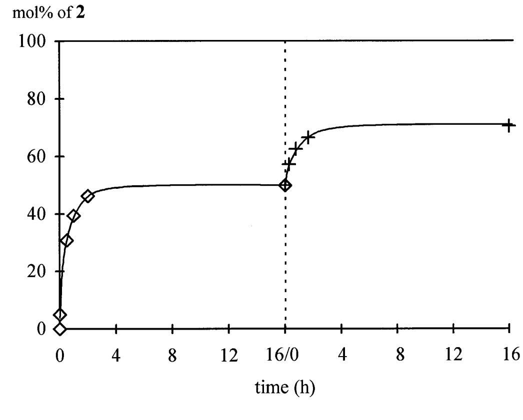
Scheme 5. Acetalization of citronellal (**2**) and isovaleraldehyde (**11**) by butane-1,2-diol



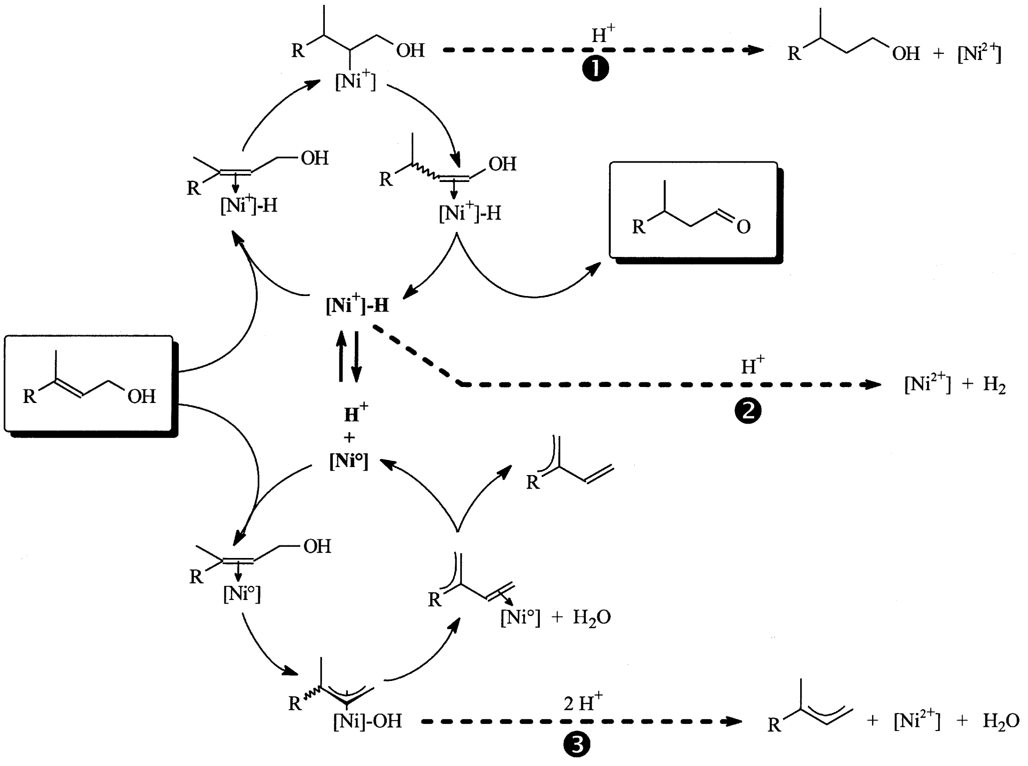
Under these conditions, higher final yields of aldehyde derivatives and higher conversions of **1** and **10** compared to the runs conducted without butane-1,2-diol were obtained. For instance, for the isomerization of **1**, the amounts of by-products **3–6** were significantly decreased in favour of **2** and the corresponding dioxolane **15** (entry 11). In the case of **10**, aldehyde **11** was produced in essentially 90% yield in 16 h (compared with 47% yield in the absence of butane-1,2-diol; Table 2, entry 17). These results are clearly fully supportive of the aforementioned hypothesis of a competitive coordination between the double bond of the alcohol and the aldehyde function to the Ni.

However, even in the presence of butane-1,2-diol, substrates **1** and **10** could not be completely converted and a limit to the degree of conversion was still observed. As the coordination of the aldehyde group leads to unreactive but stable species (Figure 1, vide supra), the progressive loss of activity in the course of the reaction cannot be attributed

Figure 2. Isomerization of geraniol (**1**) into citronellal (**2**) as a function of time and initial mixture composition; test ◇: Ni(COD)$_2$: 0.13 mmol, dppb: 0.26 mmol, **1**: 9.1 mmol, toluene: 5 ml, TFA: 0.26 mmol, test +: Ni(COD)$_2$: 0.13 mmol, dppb: 0.26 mmol, **1**: 4.5 mmol, **2**: 4.5 mmol, toluene: 5 ml, TFA: 0.26 mmol



Scheme 6. Suggested catalytic cycle for isomerization of allylic alcohols and irreversible deactivation pathways of the catalyst



to this phenomenon, but rather to a slow and irreversible catalyst decay. The latter was confirmed by carrying out two further separate experiments under the same reaction conditions, i.e. the isomerization of pure **1** and of a 50:50 mixture of **1** and **2** (Figure 2).

In the first case, the conversion reached 50%, i.e. the same composition as the starting mixture of the second experiment, while in the second case 40% of the **1** initially present was isomerized. This clearly indicates that the **2**/Ni ratio is not the sole parameter affecting the catalytic activity. A further experimental indication of the catalyst decay came from the aforementioned progressive colour change of the homogeneous and biphasic solutions in the course of the reactions. Possible mechanistic pathways for this catalyst deactivation are the well-known protonolysis of the active hydride−nickel species[12] or of a π-allyl− or alkyl−nickel species resulting from allylic alcohol insertion into the hydride−nickel bond during the isomerization catalytic cycle (pathways 1, 2, and 3 in Scheme 6).

Conclusion

Although catalyst deactivation appears to be a non-negligible reaction, this study proves that the Ni^0/1,4-bis(diphenylphosphanyl)butane/trifluoroacetic acid combination is efficient for the isomerization of the trisubstituted carbon−carbon double bond in terpenic alcohols and related compounds. Thus, provided that the reaction is conducted in the presence of butane-1,2-diol, a turnover number of 60 and a selectivity of 98% for the free and acetalized isovaleraldehydes can be attained using a homogeneous system. Further experiments aimed at increasing the stability of the catalytic system and with a view to performing asymmetric isomerization are currently under way in our laboratories.

Experimental Section

General: Bis(cycloocta-1,5-diene)nickel, 1,4-bis(diphenylphosphanyl)butane (dppb), trifluoroacetic acid (TFA), geraniol (**1**), and prenol (**8**) were purchased from Strem Chemicals or Aldrich Chemical Co. in the highest available purity and used without further purification. The sodium salt of tetrasulfonated 1,4-bis(diphenylphosphanyl)butane (dppbts) was synthesized according to a literature procedure[13]. All catalytic reactions were performed under nitrogen using standard Schlenk techniques. All solvents and liquid reagents were degassed by two freeze-thaw cycles prior to use.

General Procedure for Isomerization Reactions of Allylic Alcohols: In a typical experiment (Table 1, entry 6), to $Ni(COD)_2$ (36 mg, 0.13 mmol) in a 50-ml glass reactor fitted with a Teflon cap was added a degassed solution of dppb (111 mg, 0.26 mmol) in toluene (5 ml). The solution rapidly turned orange. After 15 min of magnetic stirring, geraniol (**1**) (1.4 g, 9.1 mmol), decane (0.5 g, GLC internal standard) and finally a toluene solution of TFA (0.6 mM, 0.85 ml, 0.51 mmol) were added. The solution immediately became deep-red-orange. Quantitative GLC analysis of this solution (Chrompack, CP Sil 5-CB column, 25 m × 0.32 mm) indicated that 5 mol-% of **1** had been converted into citronellal (**2**). The solution was stirred at 80°C and the reaction was monitored by removing aliquots and subjecting them to GLC analysis. A progressive colour change deep-red-orange to yellow was observed. Reactions in the presence of butane-1,2-diol were conducted in a similar manner.

All products were identified by comparison of retention times and spectral properties with those of authentic samples.

General Procedure for Isomerization Reactions of Allylic Alcohols in Biphasic Media: In a typical experiment, Ni(COD)$_2$ (35 mg, 0.13 mmol), dppbts (217 mg, 0.26 mmol), and either water (10 g) or a mixture of water (5 g) and dimethylformamide (5 g) were introduced under nitrogen into a glass tube reactor. After stirring with a magnetic bar for 2 h at 80°C, the solution took on an orange color and the insoluble Ni(COD)$_2$ had disappeared. This solution was then added to a mixture of **1** (1.4 g, 9.1 mmol), toluene (5 ml), and the chosen acid (0.52 mmol). The resulting mixture was stirred at 1000 rpm at 110°C and the reaction was monitored by GLC analysis of aliquots withdrawn from the organic phase.

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