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Double-Bond Isomerization: Highly Reactive Nickel Catalyst Applied in the Synthesis of the Pheromone (9*Z*,12*Z*)-Tetradeca-9,12-dienyl Acetate

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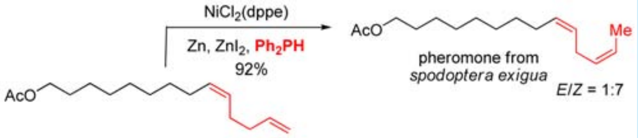
Supporting Information

ABSTRACT: A highly reactive nickel catalyst comprising NiCl$_2$(dppp) or NiCl$_2$(dppe) with zinc powder, ZnI$_2$ and Ph$_2$PH, was applied in the isomerization of terminal alkenes to *Z*-2-alkenes. The double-bond geometry of the 2-alkene can be controlled via the reaction temperature to yield the 2-*Z*-alkenes in excellent yields and high *Z*-selectivities. The formation of other constitutional isomers, such as 3-alkenes, is suppressed on the basis of the proposed mechanism via a 1,2-hydride shift from the metal to the Ph$_2$P ligand. The nickel-catalyzed isomerization reaction was then applied in the synthesis of (9*Z*,12*Z*)-tetradeca-9,12-dienyl acetate, a pheromone with a 2*Z*,5*Z*-diene subunit.

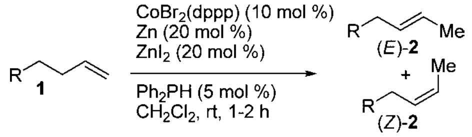


The selective isomerization of terminal alkenes into 2-alkenes has been investigated for decades utilizing different transition-metal catalysts.[1] A general feature of these catalysts is the proposed reaction mechanism in which the formation of the reactive transition-metal hydride species is postulated. These metal hydride species undergo reversible addition/elimination to the alkene, which leads to a change in the double-bond position within the molecule.[2] This explains that, in many transformations, the formation of the other constitutional isomers of the alkene is not easily suppressed when isomerization along an unsubstituted carbon chain is possible. The isomerization of a terminal alkene into a 2-alkene, with high ratios of the *Z*-configured double bond, is only successfully observed if two conditions are fulfilled: (a) the terminal alkene starting material has a higher binding affinity than the 2-alkene as well as the other constitutional isomers and (b) the *Z*-isomer is predominantly formed in a kinetically controlled process.[3,4] In both cases, the ligand system plays an important role in these reactions. The coordination sphere around the transition metal must not only restrict the coordination of the 1-alkene, but also repulsive steric interactions between the substituents of the alkene and the ligand system must be strong enough for the selective *β*-hydride elimination of the pro-*Z* hydrogen from the intermediately formed alkyl—metal complex.

Some time ago, we identified a cobalt—catalyst system which led to significantly better results compared to many other transition-metal catalysts for the isomerization of terminal alkenes toward *Z*-2-alkenes. In these reactions, PPh$_2$H was used as coligand, which made the significant impact (Scheme 1).[4]

The cobalt catalyst allows not only formation of the desired 2-*Z*-alkenes but also suppression of the formation of higher alkenes.

Scheme 1. Cobalt-Catalyzed Isomerization of Terminal Alkenes



The cobalt precatalyst CoBr$_2$(dppp) is easy to handle. In the presence of reducing agent (Zn), the mild Lewis acid ZnI$_2$, and the coligand Ph$_2$PH, the reactions proceeded in a rather short period of time at ambient temperatures. While for a number of alkenes very good results could be obtained, the catalyst system exhibits two drawbacks: First, for an increase in *Z*-selectivity, lowering the reaction temperature should be advantageous to favor the kinetic product, but with the cobalt catalyst significantly reduced reactivity was observed. Second, increasing the reactivity by heating the dichloromethane solution did not result in better conversions of sterically hindered starting materials when the cobalt catalyst system was utilized. Therefore, the temperature corridor for the cobalt-catalyzed process is narrow, and this will be problematic, particularly when branched alkenes and functionalized alkenes are used.[4]

Accordingly, we investigated the reactivity of neighboring nickel catalysts, namely NiBr$_2$(dppp), in an isomerization reaction.[1g,5,6] To our delight, the isomerization of 1-octene with the cobalt catalyst system, which took 1 h at ambient temperatures for the formation of the desired 2-*Z*-alkene, was completed with the NiBr$_2$(dppp), Zn, ZnI$_2$, Ph$_2$, and PH catalyst mixture within a few minutes at room temperature. This considerable increase in reactivity by orders of magnitude

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intrigued us to investigate the nickel-catalyzed reaction in more detail. Most importantly, the isomerization reaction could be performed at lower temperatures, and eventually, the isomerization of 1-alkene to the 2-*Z*-alkene was still successful at temperatures as low as −50 °C and went to completion within only 2 h reaction time, resulting in the formation of the 2-*Z*-alkene in an excellent *E*/*Z* ratio of 1:30. This outstanding result led us to the conclusion that a highly reactive nickel catalyst could be useful for the isomerization of terminal alkenes when the reaction temperature is adjusted to find the right balance between reactivity and selectivity. Accordingly, the isomerization reactions of various terminal alkenes were investigated using the nickel precatalyst $NiBr_2$(dppp) with Ph_2PH as co-ligand under the conditions exemplified in Scheme 2.

Scheme 2. Nickel-Catalyzed Isomerization of Terminal Alkenes

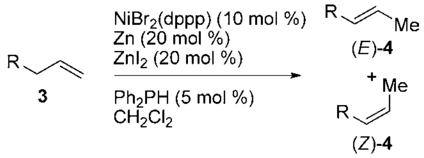
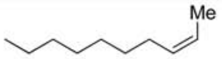
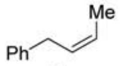
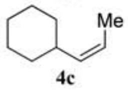
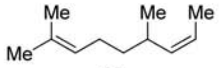
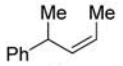
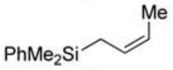
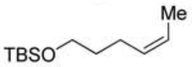
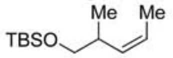
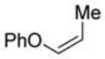
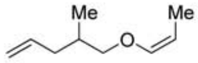
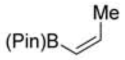
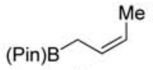
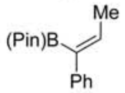
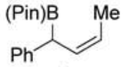


Table 1. Results of the Nickel-Catalyzed Isomerization of Terminal Alkenes[a]

entry	2-alkene, **4**	yield (conversion) T / t *E*/*Z* ratio (sum of other isomers)
1	 **4a**	72% (90%) −60 °C / 6 h 28:72 (<1%)
2	 **4b**	85% (90%) −40 °C / 9 h 10:90 (<1%)
3	 **4c**	85% (93%) −40 °C / 7 h >1:99 (8%)
4	 **4d**	90% (>99%) −20 °C / 2 h & −10 °C / 4 h 8:92 (<1%)
5	 **4e**	93% (88%) −15 °C / 3 h 10:90 (<1%)
6	 **4f**	83% (>99%) −50 °C / 2 h 6:94 (<1%)
7	 **4g**	90% (>99%) −35 °C / 2 h >1:99 (6%)
8	 **4h**	87% (85%) −20 °C / 4 h >1:99 (<1%)
9	 **4i**	89% (97%) 25 °C / 18 h 5:95 (<1%)
10	 **4j**	80% (83%) −50°C / 4 h & −20°C / 4 h 4:96 (2%)
11	 **4k**	95% (97%) −25 °C / 3 h & −15 °C / 4 h 20:80 (<1%)
12	 **4l**	80% (>99%) −40°C / 3 h 3:97 (3%)
13	 **4m**	85% (>99%) 25 °C / 2 h 13:87 (<1%)
14	 **4n**	32% (>99%) −20°C / 3 h 14:86 (3%)

[a] Reaction conditions: $NiBr_2$(dppp) (10 mol %), Zn, ZnI_2 (20 mol % each), Ph_2PH (5 mol %), 1-alkene **3** (0.5 mmol, 1.0 equiv), CH_2Cl_2; different reaction temperatures and times are listed in the table. The reaction temperature was adjusted with a dry ice/acetone bath. Unreacted starting material and other isomers were not separated and are included in the yield. Conversion and *E*/*Z* ratio were determined by ^{1}H NMR spectroscopy and GC or GC−MS analysis (Pin = pinacol).

The results of these transformations are summarized in Table 1. The application of unbranched alkenes (**3a**/**3b**) led to the desired 2-*Z*-alkenes with good results. The nickel catalyst system is by far more reactive for unbranched terminal aliphatic alkenes than the cobalt catalyst system. Even at temperatures as low as −60 °C, the nickel catalyst is able to catalyze the isomerization, whereas the cobalt catalyst is essentially unreactive for most starting materials below room temperature. Unfortunately, longer alkyl side chains, such as in 1-hexadecene, are at a disadvantage since these starting materials solidify at −60 °C and are not converted at these temperatures. At elevated temperatures (room temperature), the isomerization is complete within minutes, but the *E*/*Z* ratio is only moderate. Nevertheless, branched alkenes, such as **3c**−**e**, could be applied successfully at somewhat elevated temperatures (−15 to −40 °C) (Table 1, entries 3−5). Although **4c** was accompanied by larger amounts of the other constitutional isomers (8%), this represents a considerable improvement compared to the cobalt-catalyst system, where branched alkenes could not be applied successfully. Also, functional groups, such as a silyl-functionalized alkene, as well as a number of silyl-protected oxygen-functionalized alkenes **3f**−**j** were applicable with good to excellent results. Of particular interest was the substrate **3j** where only the chemoselective isomerization of the allyl ether functionality was observed, while the other terminal double bond remained untouched. This result can be rationalized in that the nickel catalyst does not coordinate well to silyl-protected oxygen donors for steric reasons but has a pronounced tendency to coordinate to the much less hindered ether donor functionality. When the reaction of **3j** was continued for more than 4 h at −30 °C, isomerization of the other double bond accompanied by other isomers was observed. In addition, the isomerization of the allyl phenyl ether led to the 2-*E*-alkene **4i** when the cobalt-catalyst system was applied. In contrast, the nickel catalyst produced the *Z*-isomer in good yield and very good *Z*-selectivity (*E*/*Z* = 5:95).

Finally, we investigated the application of pinacol boronic esters **3k**−**n** in the nickel-catalyzed isomerization reaction. The double-bond migration alters the reactivity of the boron-functionalized building blocks so that allylboron products were obtained at low temperatures.[7]

The isomerization of these boron-functionalized starting materials, such as **3l**, leads to **4l** in a good yield of 80% with a very good *E*/*Z*-selectivity of 3:97. In a similar fashion, the vinyl boronic esters **4k** and **4n** could be of interest for cross-coupling reactions or metatheses.[8] The results concerning in situ follow-up reactions of these materials are under investigation.

Some of the nickel-catalyzed isomerization reactions should be stopped before the starting material is consumed completely. Otherwise, the 2*Z*-configured products will be converted into the thermodynamically more stable 2*E*-isomer or into the undesired other constitutional isomers (see the Supporting Information).

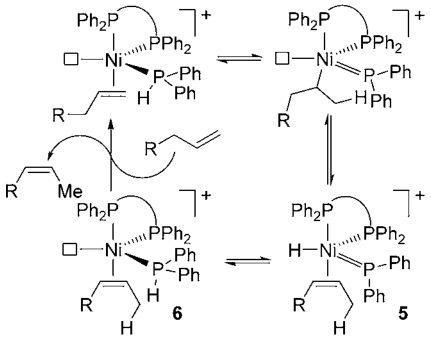
From a mechanistic point of view, we are convinced that the reactive catalyst species is a nickel complex with dppp and Ph_2PH in the ligand sphere. The presence of an additional bromide ligand (see the Supporting Information, EPR measurements) is possible; EPR measurements are inconclusive as an equilibrium between a $Ni^{I}Br(dppp)(PHPh_2)$ complex and a cationic $[Ni^{I}(dppp)(PHPh_2)]^+$ species could explain the hyperfine coupling pattern of the EPR spectra. Theoretical investigations are underway to verify the proposed mechanism in terms of ligand sphere and chemo-/stereoselectivities.

A major difference between the cobalt and nickel systems can be observed in electroanalytical measurements. The cyclic voltammograms of the $CoBr_2(dppp)$ complex changed significantly after addition of zinc powder and zinc iodide, indicating that the cobalt(II) is easily reduced by zinc powder in the presence of a Lewis acid, such as zinc iodide, to the corresponding cobalt(I) complex (see the Supporting Information). This change in oxidation state is easily visible by a distinct color change of the dichloromethane solution from blue to red. In contrast, the corresponding cyclic voltammograms of the nickel complex $NiBr_2(dppp)$ exhibit no significant change after addition of zinc powder and zinc iodide. However, after addition of Ph_2PH to this mixture, the cyclic voltammograms showed new peaks, in combination with the characteristic color change from red to deep brown. In addition, the EPR measurements indicated that under these reaction conditions a paramagnetic nickel(I) species is formed via reduction of the nickel(II) precursor.

Accordingly, we propose the 1,2-hydride shift from the metal (**5**) to the ligand (**6**) to be a crucial step in the reaction mechanism, in line with the proposed mechanism of the cobalt-catalyzed isomerization reaction. Therefore, the formation of other constitutional isomers via metal hydride readdition to the 2-alkene followed by β-hydride elimination might be prohibited (Scheme 3).

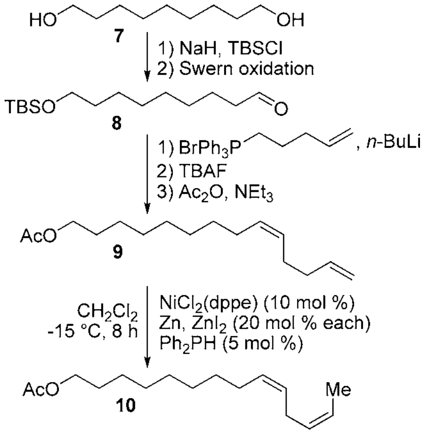
In order to further illustrate the usefulness of the nickel-catalyzed isomerization reaction, we selected (9*Z*,12*Z*)-tetradeca-9,12-dienyl acetate **10**, which was identified as a pheromone component of the species *Spodoptera exigua* (owlet moth), as the synthetic target.[9] The challenges for a nickel-catalyzed isomerization reaction are 3-fold: (a) the catalyst must generate the 12*Z*-double bond with high *Z*-selectively; (b) the isomerization must not convert the 9*Z*,12*Z*-diene subunit into a conjugated diene (e.g., 9*Z*,11*Z*-diene); and (c) the double-bond configuration at position 9 must not be altered by the catalyst.

Scheme 3. Proposed Key Step (5 → 6) in the Mechanism of the Nickel-Catalyzed Isomerization Reaction



The synthesis of the pheromone precursor was initiated from the commercially available diol **7**, which was converted into the monoprotected alcohol followed by a Swern oxidation, leading to the aldehyde **8** in 64% yield over two steps (Scheme 4). After a *Z*-selective Wittig reaction of **8** with 1-pentenyltriphenylphosphorylide, deprotection, and acetylation, the 1,5-diene **9** was generated in 68% yield over three steps.

Scheme 4. Synthesis of Pheromone 10 via a Nickel-Catalyzed Isomerization in the Key Step



Originally, the $NiBr_2(dppp)$ complex was applied for the isomerization of **9** as reported before. However, the additional 5*Z*-double bond had a significant influence upon this nickel-catalyzed reaction, resulting in a very moderate 1:2 *E*/*Z* selectivity. A short screening of bidentate phosphine ligands revealed that for $NiCl_2(dppe)$ as catalyst precursor the best results were obtained. Accordingly, the isomerization of **9** utilizing $NiCl_2(dppe)$[6] as catalyst precursor gave the desired product **10** in 92% yield as a mixture of $E/Z = 12{:}88$ (96% conversion after 8 h reaction time at −15 °C). The 9*Z*,12*Z*-configured product could be purified on a silver nitrate doped silica gel column to obtain **10** with significantly increased purity (>95%).[10]

In conclusion, we were able to show that a nickel-catalyzed isomerization of terminal alkenes to *Z*-2-alkenes can be realized. As in the cobalt-catalyzed reaction, Ph_2PH must be present to initiate the reaction. The isomerization, which can be performed at temperatures as low as −60 °C, led predominantly to the *Z*-configured isomers, and the catalyst tolerates a number of functional groups which will be useful in follow-up reactions. A considerable improvement of the nickel-catalyzed process over the cobalt-catalyzed isomerization is the possibility of applying branched alkenes with good to excellent success. In addition, the nickel-catalyzed isomerization of terminal alkenes was applied in the synthesis of pheromone **10** with good success, despite a challenging and sensitive 9*Z*,12*Z*-diene subunit.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis, analytical data, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01230.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(6) dppp = 1,3-bis(diphenylphosphino)propane, dppe = 1,2-bis(diphenylphosphino)ethane.

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(10) No difference in yield or selectivities was observed when either nickel chloride or nickel bromide complexes were applied. Therefore, we rationalize that the halides are not part of the active species.