Synthetic Methods

Up the Hill: Selective Double-Bond Isomerization of Terminal 1,3-Dienes towards Z-1,3-Dienes or 2Z,4E-Dienes**

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Carbon–carbon double bonds are among the most versatile functional groups in organic chemistry. Many reactions have been established for the synthesis of double bonds,^[1] while only a relative small number of methods are available for the isomerization of double bonds. A selective isomerization of double bonds towards a uniform olefin geometry can be accomplished utilizing photochemical^[2] and in some cases radical^[3] or transition-metal-catalyzed methods.^[4] Stepwise chemical methods, such as the reaction sequence described by Reetz,^[5c] involving epoxidation of an olefin, ring-opening by a silyl anion, and Peterson-type olefination, are also available for the inversion of the double bond geometry.^[5]

In the course of our ongoing investigation into atomeconomic transformations for the generation of carboncarbon bonds utilizing low-valent cobalt complexes, we found a catalyst system enabling the synthesis of 1,3,6-trienes of type **3.** Starting from an aryl-substituted 1,3-diene (**1**) and a 2,3disubstituted 1,3-diene (**2**), this 1,4-hydrobutadienylation is accomplished in a stereo- and regioselective fashion (Scheme 1).^[6]



Scheme 1. 1,4-Hydrobutadienylation.

During the screening process for suitable catalysts, we identified a cobalt complex that led to isomerization of the initial 1:1 ratio of the 1,3-butadiene derivative (E/Z)-4, which was generated by a stereo-unspecific Wittig olefination of octanal. In the absence of 2, the E/Z mixture of 4 is converted selectively into (Z)-4a by utilizing a catalyst system comprising [CoBr₂(py-imine)], zinc powder, and ZnI₂ within 17 h reaction time in good yield (Scheme 2). This isomerization

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- [**] Financial support from the Deutsche Forschungsgemeinschaft is gratefully acknowledged. We thank Prof. R. W. Hoffmann and Prof. M. T. Reetz for helpful discussions.
- Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107512.



Scheme 2. Double-bond isomerization for the stereoselective generation of (*Z*)-4a.

reaction could be expanded to a number of other 1,3-dienes. The results of this investigation are summarized in Table 1.

The isomerization reaction tolerates aliphatic and aromatic substituted 1,3-dienes as well as an additional isolated terminal double bond (Table 1, entry 4). Esters, ethers, and silyloxy functional groups were accepted as substrates as well

Table 1: Results of the cobalt-catalyzed isomerization to Z-1,3-dienes.^[a]



[[]a] [CoBr₂(py-imine)] (5–10 mol%), zinc powder (10–20 mol%), zinc iodide (10–20 mol%), 5–120 h, CH_2Cl_2 , ambient temperature. TBS = *tert*-butyldimethylsilyl.

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(Table 1, entries 3 and 8–10). The relatively high volatility of many of the products led to diminished yields when the solvent was removed after workup. Also, in some cases polymer-type side-products were obtained after prolonged reaction times. Noteworthy is that the deprotected product **4h** was previously used as an intermediate in the synthesis of a pheromone^[7a] and can be found in different species in form of corresponding esters.^[7b,c]

We also identified a modified cobalt catalyst system comprising $[CoBr_2(dpppMe_2)]$, zinc powder, and ZnI_2 , which migrated diene double bonds inward by only one position (Scheme 3). Thereby, product **6a** was generated exclusively as the 2Z, 4E isomer by a 1,5-hydrogen shift.^[8]



Scheme 3. Double-bond migration for the stereoselective generation of (2Z,4E)-**6**a.

Remarkably, no further isomerization of the double bonds in **6a** along the chain or the E,E isomer was observed. The cobalt catalyst system converts both isomers (Z)-**4a** and (E)-**4a** into 2Z,4E-configured isomer **6a** in a stereoconvergent fashion under mild reaction conditions. The scope of the reaction was expanded towards several 1,3-dienes, and the results of this investigation are summarized in Table 2.

Table 2: Results of the cobalt-catalyzed isomerization to (2Z,4E)-2,4-dienes.^[a]

Entry	Product	Yield [%]
1	Me6aMe	67
2	Me 6b Me	67
3	6c Me	61
4	Me 6d Me	58 ^[b]
5	Me 6e Me	43 ^[b,c]
6	6f Me	89
7	TBSO 6g Me	67
8	TBSO 6h Me	78

[a] $[CoBr_2(dpppMe_2)]$ (5–20 mol%), zinc powder (10–40 mol%), zinc iodide (10–40 mol%), 18–72 h, CH₂Cl₂, ambient temperature. [b] Both 1,3-diene units were isomerized. [c] Increased amounts of polymeric side-products were formed.

For this isomerization reaction, aliphatic and aromatic substituents and protected alcohols were tolerated. The terminal double bond in 6c remains unchanged, indicating the high chemoselectivity of the catalyst system for the isomerization of 1,3-dienes. The mild reaction conditions also allowed the selective synthesis of 6f without additional isomerization towards the corresponding conjugated product. In contrast, we were not able to generate 1-phenyl-2,4pentadiene selectively by a Wittig olefination to investigate the cobalt-catalyzed isomerization with this derivative. Under the reaction conditions of the Wittig olefination (in analogy to Scheme 2) of phenyl acetaldehyde, the double bonds spontaneously migrated towards the conjugated system. Accordingly, the cobalt-catalyzed isomerization reaction is wellsuited to generate 1,3-dienes with benzyl-CH₂ or aryl-CH₂ substituents, thus avoiding isomerization towards the undesired aryl-diene conjugated products.

Of note, some long-chained 2Z,4E-configured dienes have been found in nature, mostly as pheromones or as part of more complex natural products, such as product **6a** or a compound related to product **6g**.^[9] Accordingly, applications of this new method in natural product synthesis can be envisaged.

The isomerization reactions described herein are unprecedented because thermodynamically less-favored isomers are formed. Therefore, both reactions cannot be the result of a transformation in its thermodynamic equilibrium. The formation of the Z double bond in 4 and 6 must therefore be a result of kinetic effects.

Control experiments have shown that the reaction does proceed in the dark but does not proceed when any of the cobalt catalyst components is absent. The yields remain unchanged when varying amounts of zinc powder and zinc iodide were used. Furthermore, the isolated isomers (*Z*)-**4a** or (2Z,4E)-**6a** could not be converted into the isomers (*E*)-**4a** or (2E,4E)-**6a** at elevated temperatures (up to 50 °C in a sealed tube) when retreated with the catalyst systems [CoBr₂(pyimine)] or [CoBr₂(dpppMe₂)], respectively, with Zn and ZnI₂.

We are well aware that the findings are in apparent conflict with the concept of microscopic reversibility of reactions in equilibrium, but these are the facts. When pure (E)-4b was used under the reaction conditions, apart from the desired (Z)-4b, only polymerization side-products were observed. Therefore, the E isomers are either isomerized or polymerized under the applied reaction conditions. Accordingly, we propose that both isomerization reactions must proceed by coordination of the 1,3-diene to the cobalt center and that the decomplexation of the Z-configured products is kinetically irreversible. In the case of the [CoBr₂(py-imine)]catalyzed reaction, it seems plausible that the s-cis conformation of the complexed 1,3-diene in complex 7b results in a kinetically less-stable complex, leading to the decomplexation of (Z)-4 (Scheme 4). The free diene (Z)-4 will also adopt the more favorable s-trans conformation, leading to the accumulation of the product.

Nevertheless, the exact process for the isomerization from **7a** to **7b** remain undetermined and a detailed quantum chemical investigation concerning the coordination mode of the 1,3-diene to the catalyst (s-cis versus s-trans),^[10] the

Angew. Chem. Int. Ed. 2012, 51, 1270-1273



Scheme 4. Rationale for the accumulation of product (Z)-4.

possibility of cobalt hydrides as catalytically active species and the steric factors responsible for the preferential formation of the Z double bonds is underway.

On the other hand, the isomerization process leading to products of type 6 utilizing the bidentate dpppMe₂ ligand is much more easily rationalized (Scheme 5). The free coordi-



Scheme 5. Rationale for the formation of the 2Z,4E-configured products of type **6**.

nation site on the cobalt center in the cobaltacycle **8b** allows the β -hydride elimination from the adjacent CH₂ group for the formation of the σ -bonded cobalt hydride intermediate **9**.^[11,12] A reductive elimination regenerates the active catalyst and furnishes the 2*Z*-configured double bond in (2*Z*,4*E*)-**6**. The overall reaction is a formal 1,5-hydogen shift, and the 4*E*configured double bond is formed exclusively for steric reasons, whereas the 2*Z*-configured double bond is predetermined in the cobaltacycle **8b**. The irreversible decomplexation of the product (2*Z*,4*E*)-**6** is in accordance with the observation that no conversion of 1,4-disubstituted 1,3-diene derivatives could be accomplished with cobalt catalyst systems in our laboratory to date.

In conclusion, we have presented a new isomerization of double bonds by applying a tridentate ligand system for the selective formation of Z-configured 1,3-dienes. The double bond migration and isomerization initiated by a bidentate phosphine ligand system led to the stereoconvergent synthesis of 2Z,4*E*-configured products. These reactions are the first examples of a transition-metal-catalyzed isomerization to the thermodynamically less stable isomers. Especially the 2Z,4*E*-

configured 2,4-diene subunit can be found in several natural products, and with our method a new approach for the synthesis of such structures seems possible.

Experimental Section

Representative procedure 1 (Table 1, entry 1): [CoBr₂(py-imine)] (20 mg, 0.05 mmol, 5 mol%), anhydrous zinc iodide (32 mg, 0.10 mmol, 10 mol%), and zinc powder (6.5 mg, 0.10 mmol, 10 mol%) were suspended under argon atmosphere in anhydrous dichloromethane (1 mL), and undeca-1,3-diene (152 mg, 1.0 mmol, 1 equiv) was added. The reaction mixture was stirred for 17 h at ambient temperature and after addition of n-pentane (1 mL) filtered over silica gel. The solvent was removed and the residue was purified by column chromatography on silica gel (eluent: n-pentane). The product (Z)-undeca-1,3-diene was obtained as colorless, pungent oil (114 mg, 0.75 mmol, 75%). ¹H NMR (CDCl₃, 300 MHz): $\delta = 6.72-$ 6.58 (m, 1 H), 6.00 (t, J = 10.9 Hz, 1 H), 5.51-5.41 (m, 1 H), 5.18 (dd, J = 16.9, 2.0 Hz, 1 H), 5.08 (d, J = 10.2 Hz, 1 H), 2.23–2.14 (m, 2 H), 1.41–1.22 (m, 10H), 0.89 ppm (t, J = 6.7 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ = 133.0, 132.4, 129.1, 116.6, 31.8, 29.6, 29.2, 29.2, 27.7, 22.6, 14.1 ppm. IR (film: $\tilde{\nu} = 3086, 3009, 2957, 2926, 2855, 1807, 1644, 1593,$ 1465, 1435, 1378, 996, 961, 901, 784, 723, 655, 611, 413 cm⁻¹. MS (EI): m/z (%) = 152 ([M^+], 18), 95 (16), 81 (42), 67 (73), 54 (100). HRMS (EI): m/z (%) calculated for C₁₁H₂₀: 152.1565; found: 152.1559.

Representative procedure 2 (Table 2, entry 1): [CoBr₂-(dpppMe₂)] (66 mg, 0.10 mmol, 10 mol%), anhydrous zinc iodide (64 mg, 0.20 mmol, 20 mol%), and zinc powder (13 mg, 0.20 mmol, 20 mol%) were suspended under argon atmosphere in anhydrous dichloromethane (1 mL), and undeca-1,3-diene (152 mg, 1.0 mmol, 1 equiv) was added. The reaction mixture was stirred at ambient temperature for 72 h and after addition of n-pentane (1 mL) filtered over silica gel. The solvent was removed and the residue was purified by column chromatography over silica gel (eluent: n-pentane). The product (2Z,4E)-undeca-2,4-diene was obtained as colorless, pungent oil (102 mg, 0.67 mmol, 67 %). ¹H NMR (CDCl₃, 300 MHz): $\delta = 6.33$ (ddq, J = 15.1, 10.9, 1.2 Hz, 1 H), 5.98 (dt, J = 10.9, 1.4 Hz, 1 H), 5.67 (dt, J = 15.0, 7.0 Hz, 1 H), 5.43–5.31 (m, 1 H), 2.11 (dt, J = 7.1, 7.0 Hz, 2 H), 1.74 (dd, J = 7.1, 1.6 Hz, 3 H), 1.44–1.22 (m, 8 H), 0.89 (t, J =6.7 Hz, 3 H). ¹³C NMR (CDCl₃, 75 MHz): $\delta = 134.6, 129.6, 125.3, 32.9,$ 31.8, 29.4, 28.9, 22.6, 14.1, 13.2. IR (film): $\tilde{\nu} = 3020, 2958, 2926, 2855,$ 1654, 1614, 1458, 1409, 1377, 980, 944, 920, 833, 710, 609, 425 cm⁻¹. MS (EI): m/z (%) = 152 ([M^+], 29), 95 (11), 81 (64), 68 (100), 53 (10). HRMS (EI): m/z (%) = calculated for C₁₁H₂₀: 152.1565; found: 152.1550.

Received: October 25, 2011 Published online: December 15, 2011

Keywords: cobalt · dienes · double-bond migration · isomerization · stereoselectivity

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