Cobalt(I)-Catalyzed Diels–Alder, 1,4-Hydrovinylation and 1,4-Hydrosilylation Reactions of Non-Activated Starting Materials on a Large Scale

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Abstract: The transformation of non-activated starting materials with a readily accessible and easy to handle catalyst system under ambient reaction conditions is of great value for the chemo- and regioselective generation of interesting building blocks in organic synthesis. Therefore, we present the large-scale application for the cobalt-catalyzed 1,4-hydrovinylation of 1,3-dienes with terminal alkenes (Scheme 1), the cobalt-catalyzed Diels–Alder reactions of various non-activated alkynes with 1,3-dienes and the cobalt-catalyzed 1,4-hydrosilylation of isoprene.

Key words: alkenes, alkynes, cobalt, Diels–Alder reaction, hydrovinylation, hydrosilylation

Introduction

The Diels–Alder reaction represents undoubtedly one of the most powerful strategies for complexity increasing reactions in organic synthesis. While the overwhelming number of reports are directed towards the Diels–Alder reaction with normal and inversed electron demand, the Diels–Alder reaction of non-activated starting materials with neutral electron demand is limited to few cases. Successful transformations of the later kind can be performed in the presence of low-valent transition metal catalysts. In these processes, it is believed that the starting materials coordinate to the transition metal centre and undergo the cycloaddition process in a stepwise fashion within the ligand sphere of the transition metal. Thereby interesting hydrocarbon derivatives can be generated under comparable mild reaction conditions. However, when a β-hydride elimination process is possible an alternative reaction pathway of the metallacycle opens to yield products of a formal 1,4-hydrovinylation process. Such alternative reaction pathways were observed when acyclic 1,3-dienes were converted with alkynes or alkenes respectively using a cobalt(I)-catalyst system (in the following abbreviated as CoI) generated from CoBr₂(dppe), ZnI₂ and Zn dust or Bu₂NBH₄ as reducing agent.

Cobalt(I)-Catalyzed 1,4-Hydrovinylation Reaction

The same cobalt-catalyst system that is under investigation in our group for the Diels–Alder reaction of non-activated starting materials, such as acyclic 1,3-dienes and alkynes (see below), is also capable of undergoing a 1,4-
hydrovinylation reaction under very mild reaction conditions, to generate functionalized as well as non-functionalized products with a 1,4-diene subunit. The cobalt-catalyzed 1,4-hydrovinylation process leads with very high selectivity to the branched products with an exo-chain double bond when electronically neutral terminal alkenes are used (Scheme 2). With unsymmetrical 1,3-dienes, such as isoprene, the regioisomeric products (1 and 2) are formed, with the carbon-carbon bond formation taking place predominantly at the lower substituted end of the 1,3-diene system (2).

On the other hand, acceptor substituted alkenes, such as n-butyric acrylate, produce in good yield the linear 1,4-hydrovinylation products (3 and 4) (Scheme 3), with the internal double bond with very high selectivity. Under these mild reaction conditions no traces of a thermal Diels–Alder product was observed. When unsymmetrical 1,3-dienes, such as isoprene, were used, predominantly the product where the carbon-carbon bond formation took place at the higher substituted end of the 1,3-diene are formed (4).

These reactions can be performed with as little as 1.0 mol% of catalyst on a 20 grams scale at ambient temperature within 16 hours reaction time with an excess of the 1,3-diene (1.8–2.0 equiv) to give complete conversion. After fractional distillation, the hydrovinylation products can be obtained in good yields directly from the crude reaction mixture.

The scope and limitations of the hydrovinylation reaction with this quite simple catalyst system are mostly directed by steric effects. The substitution pattern of the alkene is limited to terminal alkenes so far and some heteroatoms functionalities such as nitrogen containing functions are not appropriate starting materials. Besides acylates, however, allylic ethers, higher alkenoles, alkenes also allyl silanes, vinyl silanes and allylic boronic esters undergo the reaction in good to excellent yields. The 1,4-hydrovinylation reaction of these terminal alkenes can successfully be performed with mono- and disubstituted acyclic 1,3-dienes such as 1,3-pentadiene, isoprene, 2,3-dimethyl-1,3-butadiene and 2-methyl-1,3-pentadiene. The advantages of this catalyst system are the mild reaction conditions and Lewis-acid character of the ingredients, which allows the isolation of the products without recognisable double bond migrations.

Cobalt(I)-Catalysed Diels-Alder Reactions

The cobalt(I)-catalyst system that promotes the 1,4-hydrovinylation process is also capable to facilitating the Diels–Alder reaction of non-activated starting materials, such as the reaction of 1,3-dienes with terminal and internal alkynes. Compared to the above mentioned 1,4-hydrovinylation process, a β-hydride elimination on the cobaltacycle intermediate is not possible, so a reductive elimination pathway leads to the dihydroaromatic products as shown in Scheme 4. Until now, we are able to efficiently convert various non-activated terminal alkynes, enynes (synthesis of 5), internal alkynes (synthesis of 6) as well as various 1,3-diynes with non-activated 1,3-dienes and norbornadiene (Scheme 5, synthesis of 7). Thereby, new building blocks, such as 5, can be generated which can be used in follow-up chemical steps such as a thermal Diels–Alder reaction with reactive dienophiles.

With the very easy to handle catalyst system consisting of CoBr₂(dppe), ZnI₂ and Zn dust, the catalytic active species [Co(dppe)⁺] is generated efficiently, so that dihydroaromatic products are formed without a noticeable double bond migration. From unsymmetrical starting materials a good 1,4-regioselectivity (generally > 90:10) is observed and mostly sterical hindrance seems to control the stereochemical outcome of the reactions.

As can be anticipated from the representative reactions outlined in Schemes 4 and 5, interesting functional groups

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are accepted by the catalyst. Therefore, synthetically more interesting transformations of functionalized building blocks bearing oxygen, sulfur, nitrogen, silicon and boron containing functional groups can be realized with our catalyst system. As we have shown in several reports, the corresponding dihydroaromatic compounds formed can be useful synthetic platforms for the generation of complex molecules. For instance, the combination of a cobalt-catalyzed Diels–Alder reaction of alkynyl boronic esters (8) with isoprene, which proceeds with very good regioselectivity (>95:5), and a Suzuki-coupling reaction with a functionalized iodobenzene derivative can be used in a fast, efficient and high yielding manner for the synthesis of the tricyclic heterocycle 10.12 Both reactions can be performed on a 5 grams scale with 2–3 mol% of catalyst and the intermediate 10 is formed in good overall yield.

Scheme 6

Generally, the Suzuki-coupling of dihydroaromatic boronic esters such as 9 with functionalised iodobenzene derivatives generates products with a high functional group density (e.g. in 10: a protected benzylic alcohol, a 1,1-disubstituted alkene, a 1,3-diene subunit and a dihydroaromatic carbonyl), which can be used for various follow-up transformations. Currently we are exploring such building blocks for the fast and efficient synthesis of interesting carbon backbones or heterocyclic compounds.

Cobalt(I)-Catalysed Hydrosilylation

In addition to the above mentioned reactions which are promoted by the cobalt(I)-catalyst system, we also found good reactivity for the hydrosilylation of 1,3-diienes with a slightly modified catalyst system. As a typical transformation we present herein the hydrosilylation of isoprene with triethoxysilane (Scheme 7). This reaction is an easy applicable alternative to hydrosilylations catalyzed by rhodium, ruthenium, palladium and platinum complexes. Of special interest is the regiochemistry of the hydrosilylation reaction. With a catalyst generated from CoBr2, 2 equivalents P(n-Bu)3, ZnI2 and Zn dust the desired product with the new silicon–carbon bond formed at C–4 position of the isoprene system is obtained in 90% yield on a 10 grams scale as a single detectable isomer (>100:1) after fractional distillation from the crude reaction mixture (Scheme 7).

Scheme 7

This extremely good selectivity is in contrast to Rh-, Ru-, Pd- and Pt-catalyst systems, which produce predominantly the regiochemical isomer in variable ratios. Compared to the other catalyst systems the easy availability and the inexpensive nature of the ingredients are of advantage.

In this short overview, we have presented reactions of the catalyst systems for the easy to perform large scale preparation of dihydroaromatic compounds by a cobalt catalyzed cycloaddition, acyclic 1,4-dienes by a 1,4-hydrovinylation reaction and the synthesis of allylic silanes by a 1,4-hydrosilylation reaction. In these reactions the products are formed with a good to high degree of regioselectivity in good chemical yields and on a reasonable large scale so that the products can be used as an early platform for further synthetic transformations towards more complicated structures. In most cases the isolation can be performed directly from the reaction mixture by fractional distillation or by filtration through a small amount of silica gel. Thereafter, the products can generally be obtained in a pure enough form for further synthetic transformations.

Caution! The large-scale reactions sometimes result in an uncontrollable evolution of heat after a variable induction period and an irreversible loss of the material through one of the Schlenk flask necks. For larger scale reactions proper precautions such as extensive cooling or preferable a thick walled glass autoclave are advisable. When the cobalt-catalyzed reactions are performed on a smaller scale (<500 mg) generally no such problems are observed.

1,4-Hydrovinylation of Isoprene with Non-Activated Alkenes: 2-Butyl-5-methyl-1,4-hexadiene (1) and (4Z)-2-Butyl-4-methyl-1,4-hexadiene (2); General Procedure

A 250 mL Schlenk-flask was charged with anhyd ZnI2 (4.15 g, 13.0 mmol, 5.0 mol%) and CoBr2(dppp) (1.50 g, 2.43 mmol, 1.0 mol%) under N2 atmosphere. The materials were suspended in anhyd CH2Cl2 (30 mL) and isoprene (30.1 g, 441 mmol, 1.8 equiv.) and 1-hexene (21.1 g, 251 mmol) were added. To the stirred suspension NBu4BH4 (1.00 g, 3.89 mmol, 1.5 mol%) was added in portions over 15 min, while the color of the mixture changed to deep brown and the mixture was stirred for 3–4 h. The mixture was cooled to 0 °C overnight. The mixture was then filtered through a pad of silica (pentane–Et2O, 5:1, 500 mL)
and fractionally distilled with a 10 cm Vigreux column. The regioisomeric product mixture (regioisomeric ratio, 1,2 = 78:22) was obtained as a colorless liquid (33.8 g, 222 mmol, 88%); bp 62–64 °C at 40 mbar. 

IR (KBr): 3079 (m), 2959 (s), 2932 (s), 2873 (s), 1644 (m), 1466 (s), 1379 (s), 1363 (s), 890 (m), 816 (w) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 5.22–5.14 (m, 1 H, C=CH), 4.70 (br s, 2 H, C=CH₂), 2.69 (d, J = 7.3 Hz, 2 H, C=CH₂), 2.69 (t, J = 7.4 Hz, 2 H, C=CH₂), 1.73 (br s, 3 H, CH₃), 1.62 (br s, 3 H, CH₃), 1.48–1.25 (m, 4 H, CH₂), 0.91 (t, J = 7.1 Hz, 3 H, CH₃), 0.89 (t, J = 7.1 Hz, 3 H, CH₃), 0.89 (t, J = 7.1 Hz, 3 H, CH₃).

13C NMR (75 MHz, CDCl₃): δ = 149.7, 132.9, 122.3, 108.8, 36.1, 35.1, 30.2, 25.9, 22.7, 17.8, 14.2.

MS (EI): m/z (%) = 152 (13) [M⁺], 109 (31), 95 (100).

HRMS: m/z calcd for C₁₁H₂₀: 152.1565; found: 152.1571.

1H NMR (100 MHz, CDCl₃): δ = 6.90 (d, J = 15.6, 6.7 Hz, 1 H, MeO₂CCH=C), 5.77 (d, J = 15.6 Hz, 1 H, MeO₂CCH=C), 5.32 (q, J = 6.6 Hz, 1 H, C=CH₂), 4.08 (t, J = 6.8 Hz, 2 H, OCH₂), 2.91 (d, J = 6.6 Hz, 2 H, C=CH₂), 1.62 (s, 3 H, CH₃), 1.62–1.55 (m, 2 H, CH₂), 1.52 (d, J = 6.6 Hz, 3 H, C=CH₂), 1.35 (hex, J = 7.5 Hz, 2 H, C=CH₂), 0.89 (t, J = 7.5 Hz, 3 H, CH₃).

13C NMR (75 MHz, CDCl₃): δ = 166.8, 146.1, 131.7, 121.72, 121.67, 64.1, 34.5, 30.8, 23.5, 19.2, 13.7, 13.3.

MS (EI): m/z (%) = 100 (100), 79 (22), 140 (15), 196 (2) [M⁺].

HRMS: m/z calcd for C₁₁H₁₃O₂: 196.1463; found: 196.1452.

Cobalt(I)-Catalyzed Diels–Alder Reactions: 1-(1-Cyclohexen-1-yl)-4-methyl-1,4-cyclohexadiene (5): Typical Procedure

A 100 mL Schlenk-flask was charged with anhyd ZnI₂ (2.62 g, 8.21 mmol, 2.5 mol%) and zinc powder (2.29 mmol, 8.9 mol%) under N₂ atmosphere. The materials were suspended in anhyd CH₂Cl₂ (20 mL) and isoprene (15.0 g, 220 mmol, 1.4 equiv) and butyl acetate (20.2 g, 158 mmol) were added and the mixture was stirred at r.t. overnight. The mixture was then fractionally distilled and the regioisomeric product mixture (regioisomeric ratio 3:4 = 10:90) was obtained as a colorless liquid (27.9 g, 142 mmol, 90%); bp 57 °C at 0.1 mbar.

HR (KBr): 2961 (s), 2874 (s), 1723 (s), 1651 (s), 982 (s), 816 (s) cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 4.85–4.79 (m, 1 H, C=CH), 2.98 (s, 3 H, OCH₃), 2.97 (s, 3 H, OCH₃), 2.93–2.85 (m, 4 H, 2 × CH₂), 0.08 (s, 9 H, 3 × SiCH₃).

13C NMR (75 MHz, CDCl₃): δ = 147.8, 129.62, 129.55, 99.8, 70.8, 70.7, 57.14, 57.10, 33.4, 30.1, 0.0.

MS (ESI): m/z (%) = 257 (3) [M + H⁺], 279 (86) [M + Na⁺].


Trimethyl[1,4,5-metheno-3-[(trimethylsilyl)ethynyl]-1,3a,4,5,6,6a-hexahydro-2-pentalenyl]silane (7): Typical Procedure

A 100 mL Schlenk-flask was charged with CoBr₂(dppe) (406 mg, 0.688 mmol, 2.0 mol%), anhyd ZnI₂ (1.00 g, 3.13 mmol, 12.1 mol%) and zinc powder (170 mg, 2.29 mmol, 8.9 mol%) under N₂ atmosphere. Then norbornadiene (2.75 g, 29.9 mmol, 1.2 equiv) and 1,4-bis(trimethylsilyl)-1,3-buta diyne (5.01 g, 25.8 mmol) and anhyd CH₂Cl₂ (10 mL) were added. After stirring 30 min at r.t. the color changed to deep brown and an exothermic reaction was observed and the mixture was stirred at r.t. overnight. The mixture was then filtered through a pad of silica (pentane–Et₂O = 5:1, 500 mL). The product was purified by column chromatography with pentane as eluent to obtain the desired product in 96% yield (7.1 g, 24.8 mmol, Rf 0.70) as a colorless liquid.

[5-(Bis(methoxy methyl)-1,4- cyclohexadien-1-yl)oxy]trimethylsilane (6): Typical Procedure

In a sealed tube CoBr₂(dppe) (535 mg, 0.867 mmol, 2.2 mol%), ZnI₂ (1.40 g, 4.39 mmol, 11.0 mol%) and zinc powder (170 mg, 2.60 mmol, 6.5 mol%) were brought to reaction with 2-trimethylsilyloxy-1,3-buta diyne (6.13 g, 48.5 mmol, 1.2 equiv) and 1,4-dimethoxy-2-butyne (4.63 g, 40.1 mmol) in anhyd CH₂Cl₂ (15 mL) under N₂ atmosphere. After stirring 1 h at r.t. the color changed to deep brown and a very exothermic reaction occurred. The mixture was stirred at r.t. overnight. The mixture was then filtered through a pad of silica (Et₂O, 200 mL) and the product (9.44 g, 39.3 mmol, 97%) was obtained as an off-white liquid in good purity after removal of the solvent.

IR (KBr): 2959 (s), 2926 (s), 2894 (s), 2820 (s), 1700 (m), 1669 (m), 1253 (s), 1086 (s), 846 (s) cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 4.85–4.79 (m, 1 H, C=CH), 2.98 (s, 3 H, OCH₃), 2.97 (s, 3 H, OCH₃), 2.93–2.85 (m, 4 H, 2 × CH₂), 0.08 (s, 9 H, 3 × SiCH₃).

13C NMR (75 MHz, CDCl₃): δ = 147.8, 129.62, 129.55, 99.8, 70.8, 70.7, 57.14, 57.10, 33.4, 30.1, 0.0.

MS (ESI): m/z (%) = 257 (3) [M + H⁺], 279 (86) [M + Na⁺].


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(4) For a more detailed investigation upon sterical and electronic effects on the regiochemistry see: Hilt, G.; Lüers, S. Synthesis 2002, 609.


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(11) Very recently we identified a nitrogen containing functional group (phthalimide) which allows the cobalt-catalysed cycloaddition with 1,3-dienes with our catalyst system.

