Regioselective Cobalt-Catalysed Hydrovinylation for the Synthesis of Non-Conjugated Enones and 1,4-Diketones

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Abstract: The highly regioselective cobalt-catalysed 1,4-hydrovinylation of terminal alkenes with 2-trimethylsilyloxy-1,3-butadiene generates in a stereospecific fashion unsaturated *E*-configured silyl enol ether intermediates that are suitable for diastereoselective Mukaiyama-aldol reactions with bulky aliphatic aldehydes. The acidic hydrolysis of the enol ethers to γ , δ unsaturated ketones followed by ozonolysis can be used for the synthesis of various 1,4-diketones and polycarbonyl derivatives. The 1,4-diketones and polycarbonyl derivatives were successfully tested for the synthesis of some mono- and bis-pyrrole derivatives. The γ , δ -unsaturated ketones are useful building blocks (e.g., in natural product synthesis) and can be generated in a one-pot procedure.

Keywords: catalysis; cobalt; diketones; 1,4-hydrovinylation; γ , δ -unsaturated ketones

Introduction

The synthesis of acyclic compounds with unsaturated functional groups at distinct positions and with a predictable geometry has steadily gained importance in modern organic synthesis. Especially atom economic carbon-carbon bond forming reactions are of increasing interest.^[1] Among these transformations, the 1,2-hydrovinylation of alkenes^[2] and the 1,4-hydrovinylation of substituted 1,3-butadienes with terminal alkenes proved to be relevant for the construction of linear carbon skeletons.^[3] More recently, the application of the 1,4-hydrovinylation reaction in the synthesis of 1,4-dienes and 1,3-dicarbonyl derivatives^[4] has been investigated in more detail thus far.^[5] For the

Scheme 1. 1,4-Hydrovinylation products utilising unsymmetrical components.

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application of unsymmetrical 1,3-dienes the control of the regioselectivity of the 1,4-hydrovinylation process is of great interest and the problem has only partially been solved.^[6] Moreover, the control of the regioselectivity concerning the carbon-carbon bond formation at the terminal alkene either toward linear products (1/3) or branched products (2/4)^[7] was addressed recently with a new ligand design with excellent results (Scheme 1).^[8]

Herein, we specifically report the regioselective cobalt-catalysed 1,4-hydrovinylation utilizing 2-trime-thylsilyloxy-1,3-butadiene ($\mathbf{5}$) as diene component which led to the exclusive generation of the branched silyloxy-functionalized 1,4-diene product of type $\mathbf{2}$ (Scheme 1).

Results and Discussion

Synthesis of Non-Conjugated Enones

The 1,4-hydrovinylation of **5** catalysed by a catalyst system comprising $\text{CoBr}_2(\text{dppe})$, zinc powder and zinc iodide in dichloromethane at ambient temperatures is different from earlier reported hydrovinylation reactions in several distinctive aspects.

First, the process is highly regioselective for the exclusive formation of intermediates of type 6 where





Scheme 2. Regioselective cobalt-catalysed 1,4-hydrovinylation of **5** with terminal alkenes.

the carbon-carbon bond formation took place at the internal carbon of the terminal alkene $(C-\beta)$ and at C-4 of **5** (Scheme 2). The high degree of regioselectivity is based on the steric demand of the trimethylsilyloxy substituent as well as the enhanced electron density of the 1,3-diene caused by this substituent which favours the formation of products of type **2**. Second, the reaction mechanism *via* cobaltacyclic intermediates^[9] dictates the exclusive formation of the *E*-geometry of the silyl enol ether subunit in **6** (see Scheme S1, Supporting Information), which is of high synthetic value for follow-up transformations (*vide infra*). Third, the *in situ* hydrolysis of **6** led to the selective formation of the γ , δ -unsaturated ketone **7** in good to excellent yields without any isomerisation of the methylene double bond toward α , β -unsaturated methyl ketones.

The scope of this 1,4-hydrovinylation reaction utilizing the specific diene 5 was investigated by applying a wide range of terminal alkenes. The *in situ* hydrolysis of the corresponding intermediates of type 6led to the desired products (7) in a straightforward one-pot procedure. The results of this investigation are summarized in Table 1.

The scope of the reaction sequence is relatively broad based on the rather mild reaction conditions of the cobalt-catalysed transformation tolerating several functional groups. Aliphatic, aromatic, heteroaromatic, ester, ether and phthalimide functional groups as well as an unprotected secondary alcohol and α,ω dienes are well accepted for the alkene component.

Table 1. Results of the cobalt-catalysed 1,4-hydrovinylation of 5 with terminal alkenes.^[a]

Entry		Product 7	Yield [%]
1	7a	MeMe	99
2	7b	Me	99
3	7c	Me Me	50
4	7d		68
5	7e	O Me	82
6	7f	O Me	77
7	7g		74
8	7h	OH Me	60

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Table 1. (Continued)

Entry		Product 7	Yield [%]
9	7i	S Me	84
10	7j	MeO MeO O	95
11	7k	Me Me	74
12	71	Me Me	77
13	7m	Me Me	77
14	7n	Me Me	67 ^[b]
15	8	Me	66

[a] Reaction conditions: 1) CoBr₂(dppe) (10 mol%), zinc powder (20 mol%), zinc iodide (20 mol%), terminal alkene (1.0 equiv.), 5 (1.2-1.5 equiv.) 13–24 h; 2) HCl (c=2 mol/L). [b]

Deprotection of the TMS group with KF/TBABr.

Notably, in all cases the 1,4-hydrovinylation products of type 2 (=6 in Scheme 2) were obtained as the exclusive regioisomer. Interestingly, the hydrolysis of intermediate 6n under acidic conditions led to the heterocycle 8 in good yield whereas the desired unsaturated ketone 7n was generated when KF/TBABr was used for the deprotection of 6n.

Mukaiyama-Aldol Reaction

Inspired by the encouraging results reported by Heathcock,^[10] the prototype silyl enol ether **6b** was then applied in situ in Mukaiyama-aldol reactions with various aldehydes initiated by $BF_3 \cdot OEt_2$ as Lewis acid additive (Scheme 3).

While the application of aliphatic aldehydes gave good yields and good syn-diastereoselectivities were obtained for the formation of 9a-9d, the corresponding reaction with an aromatic aldehyde, such as 3-nitrobenzaldehyde for the formation of 9e, was far less selective. Product 9e was isolated as a *syn:anti*=66:34 mixture in 72% yield. In this case, instead of 6b 1-(allyloxy)-4-bromobenzene was used as alkene component in order to obtain a crystalline product suitable for X-ray analysis.



- ^[a] Reaction conditions: aldehyde (1.0 equiv.), **6b** (1.2 equiv.), $BF_3 \cdot OEt_2$ (1.0 equiv.).
- ^[b] The corresponding silyl enol ether of 1-(allyloxy)-4-bromobenzene was used instead of 6b.
- ^[C] The *syn/anti* ratios were determined by ¹H NMR spectroscopy.^[13]

Scheme 3. BF₃-initiated Mukaiyama-aldol reaction of silyl enol ether **6b** with various aldehydes.



Scheme 4. Copper(II)-initiated dimerisation of the enolate of methyl ketone 7b.

Copper(II)-Initiated Dimerisation

In addition to the Mukaiyama-aldol transformation of the enol ether, we were also interested in the application of the methyl ketones in an oxidative dimerisation reaction. In a proof-of-principle transformation, adopting the protocol of Saegusa,^[11] the unsaturated ketone **7b** was deprotonated with LDA at low temperature and addition of anhydrous CuCl₂/DMF led to the oxidative dimerisation to the desired 1,4-diketone **10** which was isolated in 59% yield (Scheme 4).

Synthesis of 1,4-Diketones

Then, the application of the γ , δ -unsaturated ketones for the synthesis of 1,4-diketones and higher polyketones was investigated. In light of our previous investigations for the synthesis of 1,3-diketones (**12**) *via* a cobalt-catalysed 1,4-hydrovinylation reaction of 2,3dimethyl-1,3-butadiene^[4a] (Scheme 5), the herein presented protocol adds another dimension for the diverse synthesis of poly-functionalised building blocks.

Applying diene **5** in the cobalt-catalysed 1,4-hydrovinylation reaction leads *via* hydrolysis and ozonolysis to the corresponding 1,4-diketone products **11**. Notably, the key step for both approaches is the cobalt-cat-



Scheme 5. Cobalt-catalysed 1,4-hydrovinylation for the synthesis of 1,3- as well as 1,4-diketone derivatives.

 Table 2. Results of the ozonolysis of selected unsaturated ketones 7 and diketone 10 to 1,4-diketones 11 and higher polycarbonyl compounds.^[a]



^[a] *Reaction conditions:* O₃, PPh₃ (2.0 equiv.).

^[b] Generated from 10.

alysed 1,4-hydrovinylation with simple 1,3-butadiene derivatives. Accordingly, the same cobalt-catalysed reaction leads to both types of diketones **11** and **12** based on the choice of the 1,3-diene.

The results for the straightforward synthesis of 1,4diketones of type **11** and higher polycarbonyl compounds by ozonolysis of the γ , δ -unsaturated ketones 7 are summarised in Table 2.

The scope of this approach is mostly limited by the restrictions of the ozonolysis reaction. Electron-rich aromatic substituents are not compatible with the reaction conditions. Noteworthy, product **11a** is a direct precursor of dihydrojasmone which is reported to be an ingredient of perfumes.^[12] Nevertheless, we were able to generate a number of very interesting 1,4-diketones which are currently under investigation for the synthesis of pyrrole derivatives and other follow-up transformations.

Finally, the simple 1,4-dicarbonyl derivative **11b** was converted with allylamine to the corresponding pyrrole derivative **13** which was isolated in excellent 92% yield (Scheme 6).^[13] Especially the tetraketone derivatives generated in this study are of interest for the synthesis of bis-pyrrole derivatives with variable linker units in between the two pyrrole rings (**11h**–**11k**). Probably, the most interesting starting material in this series is **11k** (and **11h**) because it could lead to a bis-pyrrole adduct **14** as well as to a mono-pyrrole adduct **15** in the case where the inner two carbonyl groups would form the heterocycle. Accordingly, **11k** was reacted with five equivalents of allylamine and the desired bis-pyrrole product **14** was isolated in



Scheme 6. Synthesis of pyrroles from selected di- and tetracarbonyl derivatives.

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62% yield whereas the mono-pyrrole adduct **15** was obtained in 32% yield.

Conclusions

We have demonstrated that the cobalt-catalysed 1,4hydrovinylation reaction of 2-trimethylsilyloxy-1,3-butadiene is a highly regioselective carbon-carbon bond formation process leading to well-defined silyl enol ether intermediates. The follow-up reactions of these silyl enol ether intermediates with aldehydes in a Mukaiyama-type aldol reaction as well as the oxidative copper-induced coupling of the corresponding enolates to bis-unsaturated diketones were briefly investigated. The ozonolysis of the γ , δ -unsaturated ketones toward 1,4-diketones and polyketones opens the way toward the synthesis of more complex structures in the future such as bis-pyrrole adducts which are currently under investigation.

Experimental Section

General Remarks

NMR spectra were recorded on a Bruker Avance 300 or DRX 500 (¹H: 300 MHz or 500 MHz, $^{13}\mathrm{C}$: 75 MHz or 125 MHz) spectrometer using residual CHCl₃ as internal standard ($\delta = 7.26$ ppm). Mass and GC/mass spectra were measured on a Hewlett Packard 6890 GC-System including a Hewlett Packard 5973 Mass Selective Detector. For (high resolution) mass spectra a Finnigan MAT 95S and a Finnigan LTQ (ESI, HR-MS) spectrometer were used. Analytical thin layer chromatography was performed on Merck silica gel 60 F254. For column chromatography Merck silica gel 60 (230-400 mesh) was used. All reactions were carried out under an inert atmosphere (nitrogen or argon) using standard Schlenk techniques. Dichloromethane was dried over phosphorus pentoxide, tetrahydrofuran and diethyl ether over sodium. The pyrrole derivatives 13, 14 and 15 were synthesised adopting a procedure described by Trost.^[13]

1,4-Hydrovinylation with 2-Trimethylsilyloxy-1,3butadiene and Deprotection with HCl

In a flame-dried Schlenk tube fitted with a Teflon screw cap $CoBr_2(dppe)$ (0.1 mmol, 10 mol%), anhydrous zinc iodide (0.2 mmol, 20 mol%) and zinc powder (0.2 mmol, 20 mol%) were suspended in 1 mL of anhydrous dichloromethane under an argon atmosphere. Then 1.0 equivalent of the terminal alkene (1.0 mmol) and 2-trimethylsilyloxy-1,3-buta-diene (1.2–1.5 mmol) were added and the mixture was stirred at room temperature until complete conversion of the starting materials was monitored by GC/MS analysis (13–24 h). Then 5 mL of pentane were added to the suspension and the reaction mixture was filtered over a short pad of silica gel (diethyl ether). The solvent was removed under reduced pressure. The residue was redissolved in 5 mL diethyl ether, 10 mL aqueous HCl (c=2 mol/L) were added

and the solution was strongly stirred until complete deprotection was monitored by GC/MS analysis (3–24 h). The aqueous layer was separated and extracted with diethyl ether (2×10 mL). The combined organic layers were washed with brine and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel.

Mukaiyama-Aldol Reaction

In a flame-dried Schlenk tube fitted with a Teflon screw cap CoBr₂(dppe) (0.12 mmol, 10 mol%), anhydrous zinc iodide (0.24 mmol, 20 mol%) and zinc powder (0.24 mmol, 20 mol%) were suspended in 1 mL of anhydrous dichloromethane under an argon atmosphere. Then 1.2 equivalents of the terminal alkene (1.2 mmol) and 2-trimethylsilyloxy-1,3-butadiene (1.4-1.8 mmol) were added and the mixture was stirred at room temperature until complete conversion of the starting materials was monitored by GC/MS (13-24 h). Then 5 mL of pentane were added to the suspension and the reaction mixture was filtered over a short pad of silica gel (pentane:diethyl ether=1:1). The solvent was removed under reduced pressure and the silyl enol ether was added to a stirring solution of 1.0 equivalent of freshly distilled aldehyde (1.0 mmol) in 4 mL of anhydrous dichloromethane according to a procedure described by Heathcock.^[10] The solution was cooled to -78°C and 1.0 equivalent of BF₃·OEt₂ (1.0 mmol) was added dropwise. After 4 h the reaction was quenched by injecting 2.5 mL of saturated aqueous NaHCO₃. The reaction mixture was allowed to warm to room temperature and stirred overnight. The aqueous layer was separated and extracted with diethyl ether $(3 \times 30 \text{ mL})$. The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure.

The ratio of isomers was determined by ¹H NMR of the crude product. If this was not possible due to high complexity of the spectrum, the ratio was determined by ¹H NMR after purification by column chromatography on silica gel. In most cases, except for **9e**, the pure major isomer (*syn*-isomer) could be isolated. The stereochemical assignment (*syn* or *anti*) was made by ¹H NMR, using the well-accepted $J_{anti} > J_{syn}$ relationship.^[14] The coupling constants were determined by analysis of the proton signal adjacent to the hydroxy group *CHOH*. For a better resolution of the coupling constants the NMR probe was treated with D₂O.

Cu(II)-Initiated Dimerisation

According to a procedure reported by Saegusa^[11a] a solution of 1.1 equivalents of diisopropylamine (5.0 mmol) in 5 mL anhydrous tetrahydrofuran was treated with 1.1 equivalents of *n*-butyllithium (5.0 mmol) at -78 °C. After 20 min 1.0 equivalent of 5-benzylhex-5-en-2-one (**7b**) (4.5 mmol) was added dropwise. After additional stirring for 30 min 1.5 equivalents of anhydrous CuCl₂ (7.0 mmol) in anhydrous dimethylformamide (7 mL) were added in one batch. The dark green solution was stirred for 30 min at -78 °C and then allowed to warm to room temperature. The reaction was quenched by addition of an aqueous solution of NH₄Cl (5 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (pentane:diethyl ether=4:1). The product **10** was obtained as a yellow oil; yield: 501 mg (1.34 mmol, 59%).

Ozonolysis

A 10-mL Schlenk tube, fitted with a glass tube to admit ozone, was charged with 1.0 equivalent of the enone and 3– 6 mL of dichloromethane. The reaction mixture was cooled to -78 °C and ozone in a stream of oxygen was bubbled through the solution. The ozone addition was stopped when the solution turned blue. The excess of ozone was removed by passing oxygen through the solution. Then 2.0 equivalents of triphenylphosphine were added and the solution was allowed to warm to room temperature. After stirring for 1 h the solvent was removed under reduced pressure. The residue was absorbed on silica gel and purified by flash column chromatography.

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