

Gaining Absolute Control of the Regiochemistry in the Cobalt-Catalyzed 1,4-Hydrovinylation Reaction

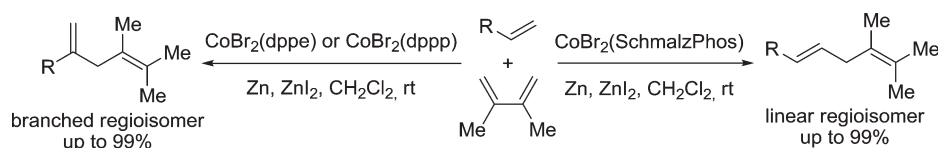
Marion Arndt,[†] Mehmet Dindaroğlu,[‡] Hans-Günther Schmalz,[‡] and Gerhard Hilt^{*,†}

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Str., 35043 Marburg, Germany, and Department für Chemie, Universität zu Köln, Greinstr. 4, 50939 Cologne, Germany

hilt@chemie.uni-marburg.de

Received October 7, 2011

ABSTRACT



The absolute control of the regiochemistry of a cobalt-catalyzed 1,4-hydrovinylation reaction is achieved by alternation of the ligands applied. While the dppe/dppp ligands led to the formation of the branched product, the herein described application of the SchmalzPhos ligand generates the corresponding linear product in both excellent yields and regioselectivities. The catalyst system exhibits a high tolerance toward functional groups, and the very mild reaction conditions allow the synthesis of 1,4-dienes without isomerization into conjugated systems.

The control of the regiochemistry of organic transformations is a great challenge for organic chemists in academia as well as in industry.¹ Regiocontrol can be achieved in many cases by employing selectively functionalized starting materials, e.g. in transition metal catalyzed cross-coupling reactions where the sites of the halide and metal groups determine the product constitution. In atom economic transformations of olefins, for instance in cobalt-catalyzed cycloaddition reactions, good levels of regioselectivity can often be achieved by a proper choice of ligands.² In certain cases it is even possible to selectively synthesize two different products from the same starting material.

The recent application of cobalt catalysis in the synthesis of acyclic 1,4-dienes (and some follow-up products) through

a formal 1,4-hydrovinylation³ inspired us to search for alternative ligands eventually inducing the formation of the regioisomeric hydrovinylation products. Our first generation of catalyst system **A** [CoBr₂(dppe), Zn, ZnI₂] applied in the 1,4-hydrovinylation of a terminal alkene (**1**) with

(3) (a) Hilt, G.; Roesner, S. *Synthesis* **2011**, 662. (b) Arndt, M.; Reinhold, A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 5203. (c) Hilt, G.; Arndt, M.; Weske, D. F. *Synthesis* **2010**, 1321. (d) Kersten, L.; Roesner, S.; Hilt, G. *Org. Lett.* **2010**, *12*, 4920. (e) Hilt, G.; Lüers, S.; Schmidt, F. *Synthesis* **2004**, 634. (f) Hilt, G.; Lüers, S. *Synthesis* **2002**, 609. (g) Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 387. For 1,2-hydrovinylation reactions, see: (h) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295. (i) Saha, B.; Smith, C. R.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2008**, *130*, 9000. (j) Shirakura, M.; Sugimoto, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (k) Saha, B.; RajanBabu, T. V. *J. Org. Chem.* **2007**, *72*, 2357. (l) Lassauque, N.; Franciò, G.; Leitner, W. *Adv. Synth. Catal.* **2009**, *351*, 3133. (m) Lassauque, N.; Franciò, G.; Leitner, W. *Eur. J. Org. Chem.* **2009**, 3199. (n) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414.

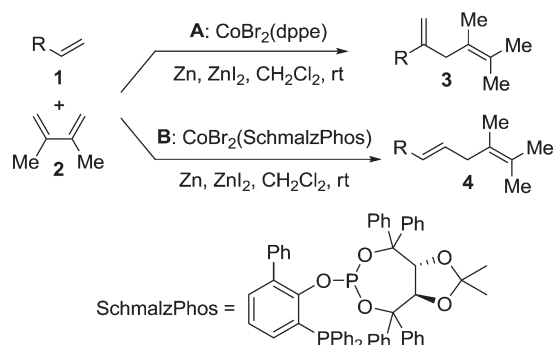
(4) For a very recent application of the SchmalzPhos ligand, see: (a) Bohn, M. A.; Schmidt, A.; Hilt, G.; Dindaroğlu, M.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2011**, *50*, 9689. See also: (b) Kranich, R.; Eis, K.; Geis, O.; Mühle, S.; Bats, J. W.; Schmalz, H.-G. *Chem.—Eur. J.* **2000**, *6*, 2874. (c) Blume, F.; Zemolka, S.; Fey, T.; Kranich, R.; Schmalz, H.-G. *Adv. Synth. Catal.* **2002**, *344*, 868. (d) Robert, T.; Velder, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7718. (e) Lölsberg, W.; Ye, S.; Schmalz, H.-G. *Adv. Synth. Catal.* **2010**, *352*, 2023. (f) Robert, T.; Abiri, Z.; Wassenaar, J.; Sande, A. J.; Romanski, S.; Neudörfl, J.-M.; Schmalz, H.-G.; Reek, J. N. H. *Organometallics* **2010**, *29*, 478. (g) Robert, T.; Abiri, Z.; Sande, A. J.; Schmalz, H.-G.; Reek, J. N. H. *Tetrahedron: Asymmetry* **2010**, *21*, 2671. (h) Velder, J.; Robert, T.; Weidner, I.; Neudörfl, J.-M.; Lex, J.; Schmalz, H.-G. *Adv. Synth. Catal.* **2008**, *350*, 1309.

[†] Philipps-Universität Marburg.[‡] Universität zu Köln.

(1) (a) Kumar, R. R.; Kagan, H. B. *Adv. Synth. Catal.* **2010**, *352*, 231. (b) Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365. (c) Bausch, C. C.; Patman, R. L.; Breit, B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5687. (d) Webster, R.; Boyer, A.; Fleming, M. J.; Lautens, M. *Org. Lett.* **2010**, *12*, 5418. (e) Wu, B.; Parquette, J. R.; RajanBabu, T. V. *Science* **2009**, *326*, 1662. (f) Jana, C. K.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6542. (g) Gansäuer, A.; Fan, C. A.; Keller, F.; Karbaum, P. *Chem.—Eur. J.* **2007**, *13*, 8084. (h) Pineschi, M.; Del Moro, F.; Crotti, P.; Di Bussolo, V.; Macchia, F. *J. Org. Chem.* **2004**, *69*, 2099. (i) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078.

(2) (a) Hilt, G.; Janikowski, J. *Org. Lett.* **2009**, *11*, 773. (b) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204.

Scheme 1. Regiodivergent Cobalt-Catalyzed 1,4-Hydrovinylation Reaction of Terminal Alkenes (**1**) with **2**



2,3-dimethyl-1,3-butadiene (**2**) afforded the branched products of type **3** in excellent yield and with outstanding levels of regioselectivity (Scheme 1).^{3g}

We herein present a second generation cobalt-based precatalyst system **B** [$\text{CoBr}_2(\text{SchmalzPhos})$, Zn, ZnI_2] which leads to the regioisomeric products of type **4** in excellent yields and regioselectivities under otherwise identical reaction conditions.⁴

The two complementary catalyst systems differentiate the two olefinic positions (CH-bonds) of **1** for the selective formation of the new carbon–carbon bond in the absence of any other activating or directing group. The starting materials **1** and **2** are used in a near-equimolar ratio (1.2 equiv of DMB) thus avoiding an excess of one component. The products of type **4** can be isolated in many cases after simple filtration through a small plug of silica gel in high purity. The results of several reactions of **2** (as the 1,3-diene) with different terminal alkenes of type **1** are summarized in Table 1.

The reaction of **2** with unfunctionalized terminal alkenes such as 1-octene or vinylcyclohexane afforded predominantly the linear 1,4-hydrovinylation products of type **4**. While 1-octene gave excellent results, the sterically more congested vinyl cyclohexane led to a diminished yield and only a moderate regioselectivity.

Our initial suspicion that secondary carbons next to the double bond were causing the reduced yield and regioselectivity could not be generalized because product **4n** was isolated in good to excellent yields and exclusive regioselectivity. Also, the silyl- and boron-functionalized alkenes **4c** and **4d**, which represent new building blocks for allylation reactions, as well as the allylbenzene **4e** and the γ,δ -unsaturated ketone **4f** could efficiently be prepared through the cobalt-catalyzed hydrovinylation (entries 3–6). Prop-2-en-1-ol (entry 7) as well as the three protected allylic alcohol derivatives (entries 8–10) gave the linear 1,4-hydrovinylation products **4g–4j**, exclusively in good yields as single regioisomers. In contrast to prop-2-en-1-ol, the secondary alcohol 3-buten-2-ol (entry 11) gave the desired product **4k** accompanied with small amounts of the branched regioisomer **3k**. Two more aspects are worth mentioning. First, with ethyl acrylate as a substrate the

Table 1. Results of the Cobalt-Catalyzed 1,4-Hydrovinylation of Terminal Alkenes with **2** Using the $\text{CoBr}_2(\text{SchmalzPhos})$ Precatalyst **B**^a

entry	product 4	yield ratio (4:3) ^b
1		99% (98:2)
2		74% (72:28)
3		98% (97:3)
4		93% (>99:1)
5		99% (98:2)
6		98% (>99:1)
7		97% (>99:1)
8		96% (>99:1)
9		78% ^{c,d} (>99:1)
10		69% ^c (>99:1)
11		85% (85:15)
12		99% ^{c,d} (>99:1)
13		99% (>99:1)
14		76% (>99:1)

^a Alkene (1.0 equiv), 2,3-dimethyl-1,3-butadiene (1.2 equiv), $\text{CoBr}_2(\text{SchmalzPhos})$ (5 mol %), Zn (10 mol %), ZnI_2 (10 mol %), dichloromethane, rt, 14–30 h. ^b Ratio determined by GC. ^c Twice the amount of the catalyst system (footnote a) was used. ^d Reaction mixture was heated up to 40 °C.

product **4m** was obtained as a single regioisomer not only with the SchmalzPhos-derived catalyst **B** (entry 13) but also with catalyst **A** (based on $\text{CoBr}_2(\text{dppe})$). Second, the reaction of styrene with DMB using catalyst **B** afforded the product **4n** in 76% yield after 16 h (entry 14) which compares well with the result obtained by Ritter utilizing an iron-based catalyst system.⁵ However, using catalyst **A** the reaction of styrene with DMB gave a mixture of regioisomers (**3n:4n** = 37:63) after up to 14 days of reaction time.⁶ Thus, the change of the ligand at the cobalt center from dppe to SchmalzPhos led in almost all cases to the formation of the linear hydrovinylation products. This reflects the absolute control of the site of the carbon–carbon bond formation in the reaction of terminal alkenes of type **1** with DMB (**2**).

We next investigated the 1,4-hydrovinylation of unsymmetrical 1,3-dienes employing isoprene (**5**) and 2-trimethylsilyloxy-1,3-butadiene (**10**), respectively. As indicated in Scheme 2 up to four 1,4-hydrovinylation products (**6–9**) could in principle arise from the reaction of terminal alkenes (**1**) with **5**. With 2-trimethylsilyloxy-1,3-butadiene (**10**) the methyl- and ethyl ketones **11–14** represent the four possible products after fluoride-mediated cleavage of the silyl enoethers formed as primary hydrovinylation products. Previous studies had shown that the 1,4-hydrovinylation of isoprene (**5**) using catalysts derived from either $\text{CoBr}_2(\text{dppe})$ or $\text{CoBr}_2(\text{dppp})$ exclusively affords the branched isomers **8** and **9** (**8:9** = >90:10)^{3g} and the method was successfully applied in the synthesis of the aglycone of moenomycin A.⁷

The outcome of various experiments (according to Scheme 2) employing the 1,3-dienes **5** and **10**, respectively, and $\text{CoBr}_2(\text{SchmalzPhos})$ as a precatalyst is summarized in Table 2.

Most importantly it must be noted that the linear hydrovinylation products of type **6/7** and **11**, respectively, were again predominantly formed in all reactions.

Scheme 2. The Regioselectivity Challenge in Cobalt-Catalyzed 1,4-Hydrovinylation Reactions of Terminal Alkenes (**1**) with Unsymmetrical 2-Substituted 1,3-Dienes (**5** and **10**)

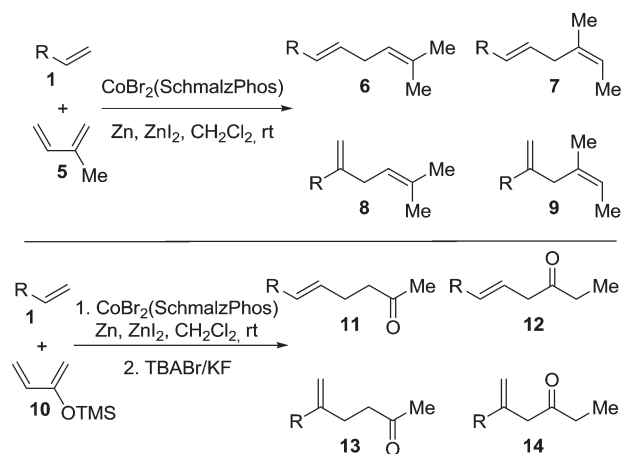


Table 2. Results of the Cobalt-Catalyzed 1,4-Hydrovinylation of Unsymmetrical 1,3-Dienes with Terminal Alkenes Utilizing the $\text{CoBr}_2(\text{SchmalzPhos})$ Catalyst Precursor^d

entry	main product	yield ratio: 6:7:8:9 ^b
1		97% ^c (54:40:3:3)
2		94% (75:24:<1:<1) ^d
3		81% (27:68:2:3)
4		90% (37:56:3:4) ^d
entry	main product ^a	yield ratio: 11:12:13:14 ^b
5		46% (93:<1:6:<1)
6		74% ^{c,e} (71:19:1:9) ^d
7		92% (88:7:4:1) ^d

^a Alkene (1.0 equiv), isoprene (1.2 equiv), 2-trimethyl-silyloxy-1,3-butadiene (1.2–1.5 equiv), $\text{CoBr}_2(\text{SchmalzPhos})$ (5–10 mol %), Zn (10–20 mol %), ZnI_2 (10–20 mol %), dichloromethane, rt, 14–21 h.
^b Ratio determined by GC. ^c Reaction mixture was heated up to 40 °C.
^d Ratio determined by integration of suitable ¹H NMR signals. ^e $\text{CoBr}_2(\text{SchmalzPhos})$ (15 mol %), Zn (30 mol %), and ZnI_2 (30 mol %) were used.

Interestingly, some complementary results were obtained with **5** and **10**. In the reaction of **5** an ester functionalized olefin afforded the main product **6a** together with isomer **7a** in a ratio of 54:40 in favor of **6a**. The product **6b** seems to be favored when no additional functional group is present in the starting material (entry 2). Other functional groups such as an acetate or an imide moiety invert the regioselectivity with respect to the 1,3-diene component (leading to the predominant formation of products of type **7**) while the regioselectivity concerning the terminal alkene is still very good to generate the linear hydrovinylation products of type **6/7** over the branched products **8/9** in good ratios (entries 3, 4). The OTMS-group in **10** seems to act primarily as a passive volume and directs the regioselectivity stronger than the methyl group in **5** toward the formation of products of type **11** (entries 5–7). While an alkyl-substituted olefin **1** gives rise to the γ,δ -unsaturated ketone **11e** with a good degree of

- (5) Moreau, B.; Wu, J. Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337.
 (6) Hilt, G.; Danz, M.; Treutwein, J. *Org. Lett.* **2009**, *11*, 3322.
 (7) Hilt, G.; Treutwein, J. *Chem. Commun.* **2009**, 1395.

regioselectivity, the products **11f** and **11g** are formed as major regioisomers in combined yields of 74% and 92%.

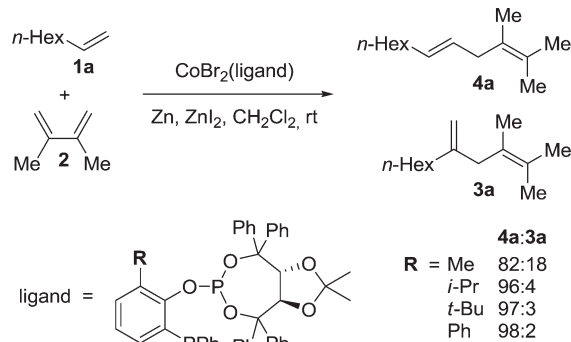
The change from the simple diphosphine ligand dppe to the phosphine-phosphite ligand SchmalzPhos led in many cases to a complete alteration of regioselectivity in the 1,4-hydrovinylation reaction with respect to the terminal alkene component (Table 1).

Strong similarities can be identified regarding the cobalt-catalyzed Diels–Alder reaction where the $\text{CoBr}_2(\text{dppe})$ complex led to the 1,4-substitution pattern⁸ while cobalt diimine- and pyridine-imine-type complexes led to the 1,3-substituted products.² Quantum-chemical calculations revealed that the steric hindrance of the ligands is the crucial factor for the regioselectivity of the carbon–carbon bond formation process of the Diels–Alder reaction.⁹ In the case of the 1,4-hydrovinylation the SchmalzPhos ligand is sterically more demanding than the dppe ligand. Accordingly, we reason that the significant change in regioselectivity of the hydrovinylation reaction is also determined by steric factors. The steric influence was investigated with four different SchmalzPhos-type ligands for the 1,4-hydrovinylation of DMB with 1-octene (Scheme 3).

The increasing steric hindrance of substituent R in the SchmalzPhos-type ligand led to an increasing regioselectivity in favor of product **4a**. These results indicate that the flexibility of coordinated starting materials on the cobalt center is efficiently reduced by the steric bulk of the SchmalzPhos-type ligand and that electronic factors are less relevant for determining the regioselectivity of the hydrovinylation process.

In conclusion, we have greatly expanded the scope of the 1,4-hydrovinylation as an atom-economic carbon–carbon bond formation process. In particular, we have demonstrated that the choice of ligand at the catalytic cobalt center is crucial for the regioselectivity. The application of

Scheme 3. Regioselectivity of Cobalt-Catalyzed 1,4-Hydrovinylation Reactions of **1a** with **2** Utilizing Different SchmalzPhos-type Ligands



SchmalzPhos led to excellent yields and regioselectivities complementary to those obtained with the previously described cobalt dppe/dppp catalyst systems. The control of the regioselectivity concerning the terminal alkene component is virtually complete whereas the regioselectivity for the unsymmetrical 1,3-diene component is good but still has potential for further improvement. The high compatibility toward many functional groups of the cobalt-catalyzed 1,4-hydrovinylation has been demonstrated, and we are looking forward to addressing the synthesis of linear 1,4-dienes which are part of natural products in the future. The inspiring results for the application of the SchmalzPhos ligand in hydrovinylation reactions of unsymmetrical 1,3-dienes opens up possibilities toward this goal.

Acknowledgment. This work was supported by the German Science Foundation which is gratefully acknowledged.

Supporting Information Available. Experimental procedures and full characterization of the compounds obtained in pure form. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(8) (a) Auvinet, A.-L.; Harrity, J. P. A.; Hilt, G. *J. Org. Chem.* **2010**, 75, 3893. (b) Hilt, G.; Danz, M. *Synthesis* **2008**, 2257. (c) Hilt, G.; Hengst, C. *J. Org. Chem.* **2007**, 72, 7337. (d) Hilt, G.; Hengst, C. *Synlett* **2006**, 3247. (e) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, 69, 624. (f) Hilt, G.; Smolko, K. I. *Angew. Chem., Int. Ed.* **2003**, 42, 2795. (g) Hilt, G.; Smolko, K. I.; Lotsch, B. V. *Synlett* **2002**, 1081.

(9) Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, 130, 8952.