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Regiocontrolled Cobalt-Catalyzed Diels−Alder Reactions of Silicon-Functionalized, Terminal, and Internal Alkynes

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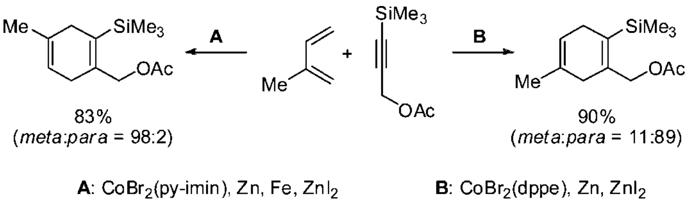
ABSTRACT

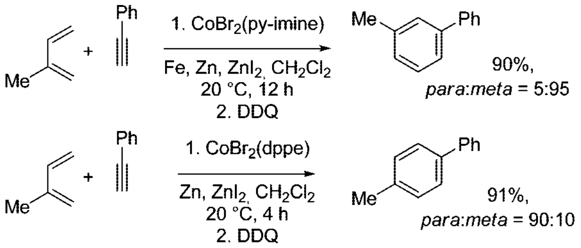


The efficient control of the regiochemistry of the Diels−Alder adducts which are formed in excellent yields from 1,3-dienes and alkynylsilanes can be realized utilizing cobalt complexes with a pyridine-imine ligand or a dppe ligand, respectively. The application of 2-trimethylsilyloxy-1,3-butadiene leads to a very interesting cyclohexenone derivative suitable for further transformations.

Silicon-functionalized building blocks are finding more and more applications in carbon−carbon bond formation processes. The interest arises not only from the low toxicity, ease of handling, and stability of the silicon-functionalized compounds but also from the increasing number of methodologies available for their synthesis and use in follow-up reactions.[1]

Consequently, simple and flexible approaches for the synthesis of silicon-functionalized compounds are needed to permit access to increasingly complicated structures. Among such new techniques are hydrosilylation and metal−silicon exchange reactions.[2] The use of silicon-functionalized building blocks in cycloadditions and, in particular, in Diels−Alder reactions is mostly limited to the use of silyloxy-functionalized dienes. Rarely are trialkylsilyl-functionalized 1,3-dienes and dienophiles used, mainly because of their

Scheme 1. Regioselective Cobalt-Catalyzed Diels−Alder Reactions



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[1] For selected reviews, see: (a) Welker, M. E. *Tetrahedron* **2008**, *64*, 11529. (b) Denmark, S. E.; Baird, J. D. *Chem.—Eur. J.* **2006**, *12*, 4954. (c) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727. (d) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 16, pp 3−216. (e) Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *1*, 211. (f) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531. (g) Hiyama, T.; Shirakawa, E. *Handb. Organopalladium Chem. Org. Synth.* **2002**, 285–309. (h) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58.

[2] For representative overviews, see: (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644. (b) Hosomi, A.; Miura, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 835. (c) Chandrasekhar, V.; Boomishankar, R.; Nagendran, S. *Chem. Rev.* **2004**, *104*, 5847. (d) Denmark, S. E.; Ober, M. H. *Aldrichim. Acta* **2003**, *36*, 75.

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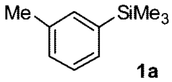
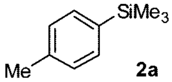
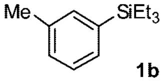
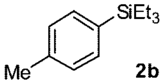
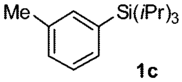
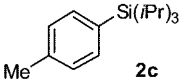
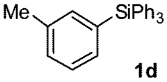
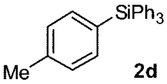
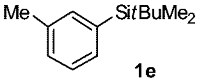
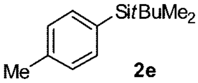
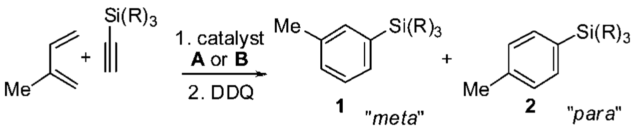
Table 1. Results of the Cobalt-Catalyzed Diels−Alder Reaction with Terminal Silyl-Functionalized Alkynes[a]

entry	alkyne	main product (**1**/**2**)	cat.	yield[b]
1	≡—SiMe$_3$	 **1a**	A	80% (93:7)
2	≡—SiMe$_3$	 **2a**	B	78% (4:93)
3	≡—SiEt$_3$	 **1b**	A	92% (92:8)
4	≡—SiEt$_3$	 **2b**	B	93% (7:93)
5	≡—Si(*i*Pr)$_3$	 **1c**	A	88% (94:6)
6	≡—Si(*i*Pr)$_3$	 **2c**	B	91% (7:93)
7	≡—SiPh$_3$	 **1d**	A	85% (95:5)
8	≡—SiPh$_3$	 **2d**	B	91% (8:92)
9	≡—Si*t*BuMe$_2$	 **1e**	A	78% (96:4)
10	≡—Si*t*BuMe$_2$	 **2e**	B	72% (6:94)

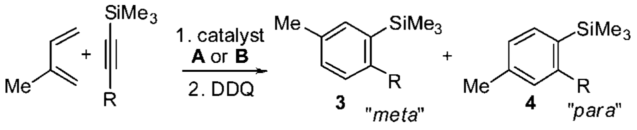
[a] Catalysts system **A**: CoBr$_2$(mesityl-pyridin-2-yl-methyleneamine) 10 mol %; iron powder 20 mol %; zinc dust 20 mol %; zinc iodide 20 mol %. Catalyst system **B**: CoBr$_2$(1,2-bis-diphenylphosphinoethane) 10 mol %; zinc dust 20 mol %; zinc iodide 20 mol %. [b] The ratio of the regioisomers (**1**:**2**) is given in parentheses.

moderate activation toward thermal Diels−Alder reactions with normal or inverse electron demand.[3] Accordingly, additional electron-withdrawing substituents are needed for the successful application in Diels−Alder reactions with normal electron demand. Cycloadditions can be efficiently catalyzed by transition-metal complexes even in the absence of such activating groups.[4] Nevertheless, to the best of our knowledge, only cobalt-catalyzed Diels−Alder reactions lead to the generation of both possible regioisomers from an alkyne and a 1,3-diene by simply altering the ligands of the cobalt complex (Scheme 1).[5]

Scheme 2. Application of the Two Cobalt-Catalyst Systems **A** and **B** for Regioselective Diels−Alder Reactions



Scheme 3. Application of the Two Cobalt-Catalyst Systems **A** and **B** for Regioselective Diels−Alder Reactions



The expansion of the substrate compatibility of the cobalt catalyst systems toward terminal as well as internal alkynes bearing silicon functionalities would greatly enhance the usefulness of the methodology for the generation of highly enriched regioisomers from simple starting materials. Therefore, terminal alkynes bearing different silyl functionalities were applied in the cobalt catalyzed Diels−Alder reaction to generate products **1** or **2** in a regiocontrolled fashion from identical starting materials. In the catalyst system **A** mesitylpyridin-2-ylmethyleneamine (abbreviated as py-imin) was utilized as the ligand in order to generate the 1,3-substituted products (**1**) predominantly, whereas in case **B** 1,2-bis(diphenylphosphino)ethane was used as the ligand (dppe) to generate the regioisomeric "*para*"-product (**2**) with a 1,4-substitution pattern of the methyl and the silyl group, respectively (Scheme 2). The results of this investigation are summarized in Table 1.

For easier determination of the regioselectivities the primary 1,4-cyclohexadiene products of the Diels−Alder reactions were oxidized with DDQ to the corresponding silyl-substituted benzene derivatives. The isolation of the

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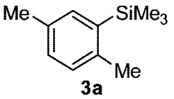
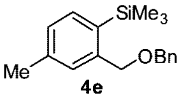
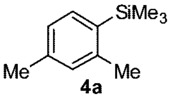
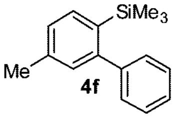
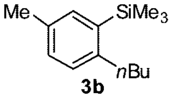
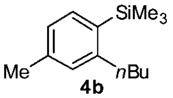
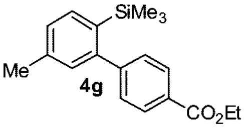
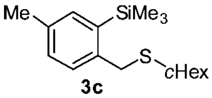
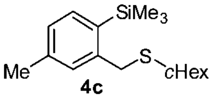
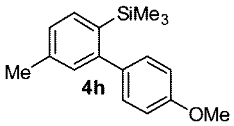
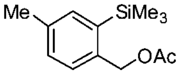
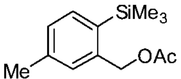
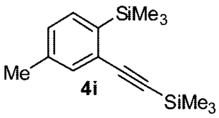
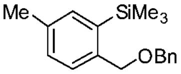
(3) For reviews for the application of silicon-functionalized building blocks, see: (a) Lin, L.; Liu, X.; Feng, X. *Synlett* **2007**, 2147. (b) Gandon, V.; Aubert, C.; Malacria, M. *Curr. Org. Chem.* **2005**, *9*, 1699. (c) Herczegh, P.; Kovacs, I.; Erdösi, G.; Varga, T.; Agocs, A.; Szilagyi, L.; Sztaricskai, F.; Berecibar, A.; Lukacs, G.; Olesker, A. *Pure Appl. Chem.* **1997**, *69*, 519. (d) Finguelli, F.; Taticchi, A. *Dienes in Diels-Alder Reactions*; Wiley: New York, 1990. (e) Petrizilka, M.; Graison, J. I. *Synthesis* **1981**, 753. (f) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415. (g) Batt, D. G.; Ganem, B. *Tetrahedron Lett.* **1978**, *18*, 3323. Gonzalez-Nogal, A. M.; Calle, M.; Cuadrado, P.; Valero, R. *Tetrahedron* **2006**, *63*, 224. (h) Coats, S. J.; Link, J. S.; Gauthier, D.; Hlasta, D. J. *Org. Lett.* **2005**, *7*, 1469. (i) Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983**, *24*, 23. (j) Sauer, J.; Heldmann, D. K.; Hetzenegger, J.; Krauthan, J.; Sichert, H.; Schuster, J. *Eur. J. Org. Chem.* **1998**, 2855. (k) Constable, E. C.; Housecroft, C. E.; Neuburger, M.; Reymann, S.; Schaffner, S. *Eur. J. Org. Chem.* **2008**, 1597.

(4) For reviews on cobalt-catalyzed cycloaddition processes, see: (a) Hilt, G. *Synthesis* **2008**, 3537. (b) Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318. (c) Malacria, M.; Aubert, C.; Renaud, J. L. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Lautens, M., Trost, B. M., Eds.; Thieme: Stuttgart, 2001; Vol. 1, p 439. (d) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (e) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (f) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(5) For selected examples see: (a) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204. (b) Hilt, G.; Hess, W.; Harms, K. *Org. Lett.* **2006**, *8*, 3287. (c) Hilt, G.; Smolko, K. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2795. (d) Hilt, G.; du Mesnil, F.-X. *Tetrahedron Lett.* **2000**, *41*, 6757.

Table 2. Results of the Cobalt-Catalyzed Diels−Alder Reaction with Terminal Silyl-Functionalized Alkynes

entry	R	main product (**3**/**4**)	cat.	yield[a]	entry	R	main product (**3**/**4**)	cat.	yield[a]
1	Me	 **3a**	A	87% (85:15)	10	CH_2OBn	 **4e**	B	85% (11:89)
2	Me	 **4a**	B	90% (5:95)	11	Ph	 **4f**	A	96% (18:82)
3	*n*Bu	 **3b**	A	72% (75:25)	12	Ph	**4f**	B	94% (9:91)
4	*n*Bu	 **4b**	B	86% (10:90)	13	4-$EtO_2CC_6H_4$	 **4g**	A	72% (18:82)
5	CH_2S*c*Hex[b]	 **3c**	A	92% (84:16)	14	4-$EtO_2CC_6H_4$	**4g**	B	76% (16:84)
6	CH_2S*c*Hex[b]	 **4c**	B	97% (17:83)	15	4-$MeOC_6H_4$	 **4h**	A	89% (18:82)
7	CH_2OAc	 **3d**	A	83% (98:2)	16	4-$MeOC_6H_4$	**4h**	B	93% (21:79)
8	CH_2OAc	 **4d**	B	90% (11:89)	17	-C≡C-$SiMe_3$	 **4i**	A	83% (28:72)
9	CH_2OBn	 **3e**	A	79% (89:11)	18	-C≡C-$SiMe_3$	**4i**	B	76% (10:90)

[a] Catalysts system **A**: $CoBr_2$(mesityl-pyridin-2-yl-methyleneamine) 10 mol %; iron powder 20 mol %; zinc dust 20 mol %; zinc iodide 20 mol %. Catalyst system **B**: $CoBr_2$(1,2-bis-diphenylphosphinoethane) 10 mol %; zinc dust 20 mol %; zinc iodide 20 mol %. The ratio of the regioisomers (**3**:**4**) is given in parentheses. [b] *c*Hex = cyclohexyl.

1,4-cyclohexadiene products can be accomplished as demonstrated on several occasions before under exclusion of air, and their follow-up chemistry has also been demonstrated.[6]

In most investigated reactions the yields for both cobalt-catalyst systems are good to excellent over the two steps. In terms of regioselectivity some very interesting results were obtained. Most important, the two catalyst systems were able to convert the terminal silyl-functionalized alkynes in very good yields and with high complementary regioselectivity to the desired *meta*-substituted products of type **1** (catalyst **A**) and to the *para*-substituted product of type **2** (catalyst **B**) respectively (entries 1−10).

The application of internal alkynes was then investigated in a series of experiments (Scheme 3) for the production of the two regioisomers **3** and **4**. The results are summarized in Table 2.

It was anticipated that the regioselectivity would be reduced if internal alkyl alkynyl silanes were applied. To our surprise in these cases the two catalyst systems **A** and **B** still gave good regioselectivities for both desired products.

When further functionalized internal alkynyl silanes were used (entries 4−10) the ratios of regioisomers formed by both catalyst **A** and **B** were also high. Only when the steric bulk of the substituent was enlarged to an aryl substituent the behavior changed (entries 11 and 12). While the results for catalyst system **B** were still good in terms of yield and with regioselectivity in favor of the *para*-substituted product, the results for catalyst system **A** changed dramatically. Although the yield of the Diels−Alder adduct is very high,

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(6) (a) Hilt, G.; Hess, W.; Harms, K. *Synthesis* **2008**, 75. (b) Hilt, G.; Galbiati, F. *Synthesis* **2006**, 3589. (c) Hilt, G.; Hess, W.; Schmidt, F. *Eur. J. Org. Chem.* **2005**, 2526. (d) Hilt, G.; Lüers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251.

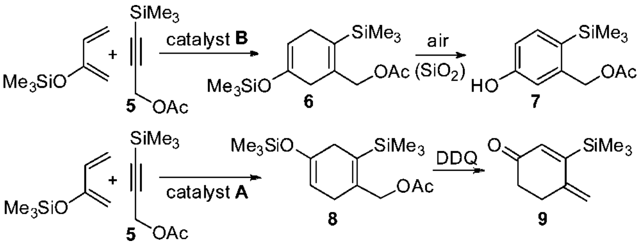
the product consists mainly of the *para*-substituted product **4f**. The effect of electronic factors was investigated by introduction of both electron-donating as well as electron-accepting substituents (entries 13−16). In these cases the major products were also *para*-substituted Diels−Alder adducts **4g** and **4h**. The electronic nature of the aryl-substituent had very little effect on the regioselectivities. Nevertheless, there seems to be a tendency for catalyst system **B** to favor the formation of the *meta*-substituted products of type **3** in the latter cases as well. The conclusion at this point in the investigation was that steric hindrance is mainly responsible for the observed regioselectivity in the cycloaddition for both catalyst systems **A** and **B**. The application of 1,4-bis-trimethylsilylbutadiyne as the dienophile led to very interesting results (entries 17 and 18). First, only one of the triple bonds was chemoselectively incorporated in the cycloaddition process which can be rationalized by the greater steric hindrance of the primary cycloaddition product compared to the starting materials used earlier (entries 11−16). Second, the yields for both catalyst systems **A** and **B** are very good. Third, although the ethynyl trimethylsilyl substituent can not be considered a very bulky substituent the results for both catalyst systems showed the preferential formation of the *para*-substituted product **4i**.

The determination of factors responsible for the regioselectivities observed with two such simple catalyst systems proved to be a challenging task for theoretical chemists.[7]

The application of 2-trimethylsilyloxy-1,3-butadiene as reactant with alkynyl silane **5** led to very interesting results. While the yields and regioselectivities for the reactions with catalyst system **A** and **B** are excellent in both cases, the surprise came when the DDQ oxidation of the intermediates was attempted (Scheme 4). The conversion of product **6** generated from catalyst **B** led to decomposition.

Alternatively, air was applied as oxidizing agent and the deprotected phenol derivative **7** was obtained after column chromatography on silica gel in good yield (81%). On the other hand, the attempted DDQ oxidation of intermediate **8** generated by catalyst **A**, and consequent workup of the product gave the unexpected unsaturated, silicon-functionalized ketone **9** in 80% yield as a single regioisomer.[8] Most importantly, the products **7** and **9** are generated from rather simple starting materials in an atom economic and highly regioselective cobalt-catalyzed Diels−Alder reaction (air oxidation for the formation of **7**) and are promising polyfunctionalized building blocks for further manipulation.

Scheme 4. 2-Trimethylsilyloxy-1,3-butadiene in Regioselective Cobalt-Catalyzed Diels−Alder Reactions



In conclusion, we have demonstrated that the regiochemistry of the Diels−Alder reaction of alkynylsilanes can be efficiently controlled by complementary cobalt catalysts for the preferential formation of the *meta*-substituted product by application of a cobalt-pyridine-imine complex and of the *para*-substituted product utilizing a cobalt-bis(diphenylphospino)ethane complex. The cycloaddition products have a high functional density and could be valuable intermediates in the synthesis of complex molecules.

Acknowledgment. This work is dedicated to Prof. Ryoji Noyori on the occasion of his 70th birthday. Financial support by the German Science Foundation is gratefully acknowledged.

Supporting Information Available: Experimental procedures and full characterization of the compounds **1**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802837M

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[7] Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, *130*, 8952.

[8] Oku, A.; Kinugasa, M.; Kamada, T. *Chem. Lett.* **1993**, *22*, 165.