Diels–Alder Reaction

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meta-Directing Cobalt-Catalyzed Diels–Alder Reactions[**]

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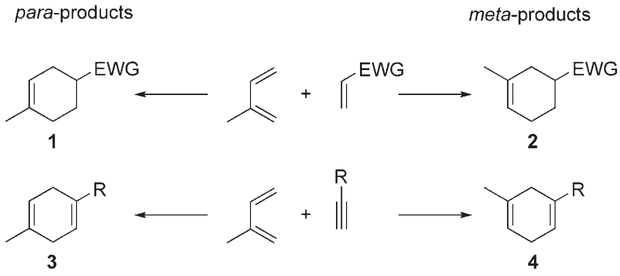
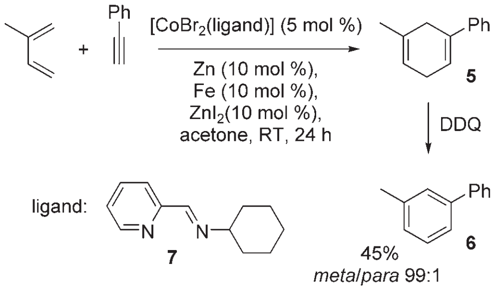
The Diels–Alder reaction has belonged to the arsenal of synthetic organic chemists for decades as can be seen in the large number of applications in natural-product synthesis and of biologically active compounds.[1] The usefulness of the Diels–Alder reaction is based on the cyclic transition state which allows the transfer of the stereochemical information in the starting material *E*- or *Z*-selectively into *cis*- or *trans*-configured products. Furthermore, the regiochemistry of the intermolecular Diels–Alder reaction can be predicted by the Woodward–Hoffmann rules and the therein implied *ortho*/*para* rules.[2] While the *ortho/para*-selectivity of the thermal Diels–Alder reaction allows access to *ortho*- or *para*-substituted products (such as **1**, Scheme 1) the intermolecular reaction is limited to the generation of *para*-substituted products when starting from isoprene, the *meta*-substituted products of type **2** (Scheme 1) can not be accessed. Only the thermal Diels–Alder reaction of alkenyl boron compounds, such as the vinyl-9-borabicyclo[3.3.1]nonane, with unsymmetrical 1,3-dienes, such as isoprene, poses an exception. In this case the regioselective *meta*-directing Diels–Alder reaction generates the product of type **2** in a ratio of *meta*:*para* = 90:10.[3]



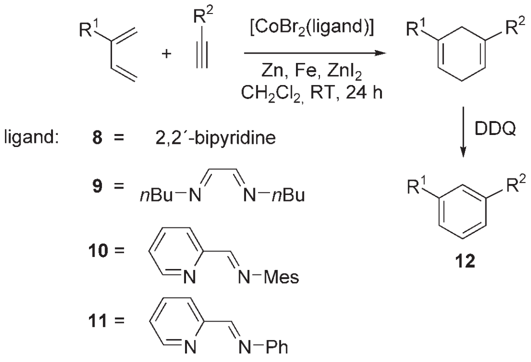
Scheme 1. *para*- and *meta*-Diels–Alder reaction products. EWG = electron-withdrawing group.

To our knowledge an analogous *meta*-directing Diels–Alder reaction to produce **4** starting from a 1,3-diene and an alkyne has not been described. Nevertheless, the *meta*-substituted dihydroaromatic systems **4** have been detected and isolated as side products in transition-metal-catalyzed cycloaddition reactions.[4] In these transition-metal-catalyzed reactions the *para*-substituted product **3** is formed as the major product.

In our investigations of cobalt-catalyzed cyclizations we reported the use of a simple cobalt catalyst system consisting of [$CoBr_2$dppe] (dppe = 1,2-bis(diphenylphosphino)ethane), ZnI_2, Zn, or Bu_4NBH_4 as reducing agent for the Diels–Alder reaction of unactivated starting materials under mild conditions for the production of the *para*-substituted Diels–Alder adducts **3**.[5] Recently, we also identified a simple cobalt catalyst system consisting of [$CoBr_2$(diimine)] (5 Mol %), ZnI_2, Zn, and Fe powder (each 10 Mol %) which performs the cobalt catalyzed Diels–Alder reaction between phenyl acetylene and isoprene, gives very good yields, and forms the *meta*-substituted isomer **5** in excellent regioselectivity. The corresponding aromatic product **6** was then generated by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and its identity determined by NMR spectroscopy. Among several ligands tested the best chemo- and regioselectivity was obtained for cobalt complexes with pyridine donor ligands, such as **7** (Scheme 2) or 2,2′-bipyridine (**8**, Scheme 3) or 1,10-phenanthroline.[6] Also symmetrical aliphatic diimine ligands (**9**) as well as mixed pyridine imine ligands (**10** and **11**) gave good results. In addition, by using a combination of zinc- and iron powder as the reducing agent, the formation of the [2+2+2]-cyclotrimerization product from the alkyne was completely suppressed. The *meta*-



Scheme 2. *meta*-Selective cobalt-catalyzed Diels–Alder reaction.



Scheme 3. Preparative application of the *meta*-selective cobalt-catalyzed Diels–Alder reaction. Mes = 2,4,6-trimethylphenyl, R^1, R^2: see Table 1

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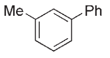
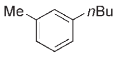
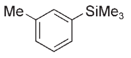
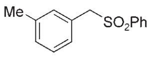
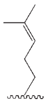
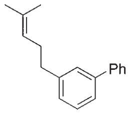
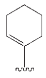
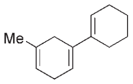
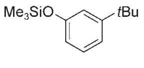
substituted product **6** could be isolated in an acceptable yield of 45 % and in an almost perfect regioselectivity of 99:1. We recognized that the yield was enhanced in dichloromethane compared to that in acetone. The substitution of the cyclohexyl substituent for aromatic substituents (phenyl- or mesityl-, **10** and **11**) also improved the yield whereas the regioselectivity under these conditions was slightly lower.

In a series of experiments with four selected cobalt complexes aromatic-, aliphatic-, olefinic-, and silyl-functionalized terminal alkynes were converted with isoprene, myrcene and 2-trimethylsilyloxy-1,3-butadiene in dichloromethane (Scheme 3).

Besides aryl-, alkenyl- and alkyl-substituted alkynes also silyl- and sulfone functionalized terminal alkynes, as well as the non-protected propargylic alcohol, could be successfully converted. The reaction times of the Diels–Alder reactions of the cobalt diimine type ligands are somewhat longer compared to the *para*-directing Diels–Alder reaction with the {Co(dppe)} complex. As the results in Table 1 illustrate the *meta*-substituted products are formed with a high level of regioselectivity and in good to excellent yields. While a single perfect ligand for all reactions was not identified among the four selected ligands, at least one diimine ligand was identified which gave good results for both yield and regioselectivity.

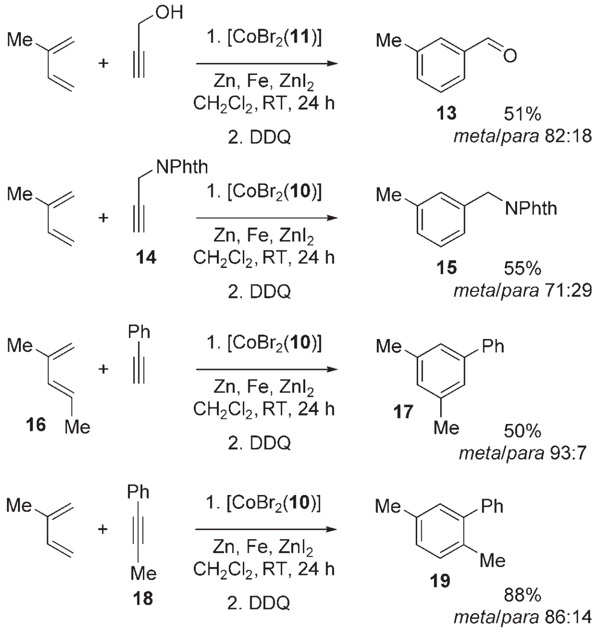
Table 1: Cobalt-catalyzed Diels–Alder reactions with ligands **8**–**11** (see Scheme 3).[a]

Entry	R^1	R^2	Product (**12**)	Yield (*meta*/*para*)
1	Me	Ph		**8**: 77 % (98:2)
2				**9: 90 % (97:3)**
3				**10**: 98 % (80:20)
4				**11**: 80 % (95:5)
5	Me	*n*Bu		**8: 85 % (92:8)**
6				**9**: 81 % (73:27)
7				**10**: 90 % (80:20)
8				**11**: 85 % (82:18)
9	Me	$SiMe_3$		**8**: 80 % (83:17)
10				**9**: 66 % (57:43)
11				**10: 80 % (93:7)**
12				**11**: 93 % (85:15)
13	Me	CH_2SO_2Ph		**8**: 47 % (95:5)
14				**9**: 57 % (90:10)
15				**10**: 61 % (69:31)
16				**11: 63 % (95:5)**
17		Ph		**8**: 67 % (97:3)
18				**9**: 75 % (96:4)
19				**10: 95 % (96:4)**
20				**11**: 53 % (95:5)
21	Me			**8**: 88 % (82:18)[c]
22				**9**: 88 % (85:15)[c]
23				**10**: 80 % (87:13)[c]
24				**11: 81 % (90:10)**[c]
25	$OSiMe_3$[b]	*t*Bu		**8**: 22 % (98:2)
26				**9: 80 % (99:1)**
27				**10**: 78 % (97:3)
28				**11**: 41 % (94:6)

[a] The best results in terms of yield and regioselectivity are highlighted in bold text. [b] For the work-up the silica gel should be deactivated by addition of triethylamine to the eluent. [c] The DDQ oxidation leads to decomposition of the product so that the dihydroaromatic compound was isolated in approximately 95 % purity.

For this new catalyst system we propose that the preformed cobalt(II) complexes are reduced in situ to the corresponding cobalt(I) complexes (neither the zinc powder nor the iron powder are sufficient reducing agents for a further reduction of the cobalt(I) species[7]). We can not rationalize the effect of the iron powder in preventing the formation of the [2+2+2]-cyclotrimerization side product.[8] When one component of the catalyst system is omitted, reduced chemoselectivities or reduced conversions are encountered. In some cases the formation of the 1,3,6-cyclooctatriene side product is observed. Nevertheless, the amount of the [4+2+2]-cycloaddition adduct is barely higher than 10 % (GC-analysis) and this by-product can easily be separated by column chromatography.[9]

Surprisingly the reaction of the unprotected propargylic alcohol (Scheme 4) with isoprene occurs in relatively good chemo- and regioselectivity. In contrast, the similar reaction with the $[CoBr_2(dppe)]$ catalyst could not be realized to date. Nevertheless, the subsequent DDQ oxidation generates the corresponding aldehyde so that in this conversion 2.2 equivalents of DDQ were used to obtain the product **13** in reasonable yields.[10]



Scheme 4. *meta*-Selective Diels–Alder reaction of a higher substituted 1,3-diene and of an internal alkyne; Phth = phthaloyl.

Using the cobalt catalysts system $[CoBr_2(dppe)]$, ZnI_2, Zn, the propargylic phthalimide **14** reacts with 1,3-dienes giving the cycloaddition products in rather low yields,[11] with the new cobalt diimine system (Scheme 4) **15** could be obtained in yields of up to 55 %, a significant increase. The regioselectivity in this case is diminished and a *meta*/*para* = ratio of 71:29 was observed.

To further illustrate the complementary regioselectivity of the new cobalt catalyst system to that of the *para*-selective [CoBr$_2$(dppe)] system the unsymmetrical 1,3-diene **16** was converted with phenyl acetylene under the new reaction conditions to give the corresponding regioisomeric *meta*-product **17** in good yield and excellent regioselectivity (93:7). Because the reactivity of the higher substituted 1,3-diene **16** is reduced the alkyne trimerization product is isolated in 45% yield. In addition, the cobalt diimine catalyst system also accepts internal unsymmetrical alkynes, such as the 1-phenyl-1-propyne (**18**), and the corresponding aromatic cycloaddition product (**19**) could be obtained in excellent yield (88%) and regioselectivity (86:14) after DDQ oxidation.

Herein we described the first broad application of the *meta*-selective Diels–Alder reaction of non-activated starting materials catalyzed by a new cobalt diimine catalyst system. The dihydroaromatic intermediates can be isolated, but for the determination of the regioisomers a DDQ oxidation was performed to obtain the aromatic products. As we could demonstrate by a variation of the ligands and the reaction conditions regioisomeric Diels–Alder products can be obtained from identical starting materials in good yields and excellent regioselectivities either in favor of the *para*-substituted product ({Co(dppe)} complex) or of the *meta*-substituted product ({Co(diimine)} complex).

Experimental Section

Representative procedure for the *meta*-selective cobalt-catalyzed Diels–Alder reaction (Table 1, entry 2): A solution of [CoBr$_2$(**9**)] (39 mg, 0.1 mmol, 5.0 Mol%), zinc iodide (64 mg, 0.2 mmol, 10.0 Mol%) zinc powder (13 mg, 0.2 mmol, 10.0 Mol%), and iron powder (11 mg, 0.2 mmol, 10.0 Mol%) were briefly heated to boiling in dry dichloromethane (1.0 mL) under nitrogen atmosphere. Then isoprene (136 mg, 2.0 mmol) and phenyl acetylene (204 mg, 2.0 mmol) were added and the suspension was stirred until the starting materials were completely consumed (GC control) at room temperature. Then the suspension was filtered over a small amount of silica gel (eluent: diethyl ether), the solvent was removed in vaccuo, taken up in benzene, and the dihydroaromatic product was oxidized by DDQ (545 mg, 2.4 mmol, 1.2 equiv). After 2 h at room temperature the solution was diluted with diethyl ether (50 mL) and washed with an aqueous sodium hydroxide (10%)/sodium thiosulfate (10%) solution. The solvent was removed in vaccuo and the residue was purified by column chromatography on silica gel (eluent: pentane:CH$_2$Cl$_2$ = 100:1).The product was obtained as colorless oil (305 mg, 0.18 mmol, 90%). The analytical data are in accordance with the literature.[12] The ratios of regioisomers were determined by integration of the GC and NMR signals.

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Keywords: 1,3-dienes · alkynes · cobalt · cycloaddition · regioselectivity

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[6] Cobalt complexes of the vitamin B$_{12}$-type, such as salen-, glyoximato-, or phthalocyanin cobalt complexes are not reactive in the Diels–Alder reaction.

[7] The redox potential of the [CoBr$_2$(**10**)] complex was determined in an electroanalytical investigation. The differential pulse voltamogramms showed a single-electron reduction [Co^{II}/Co^{I}; $E = -560$ mV; Ag/AgCl] within the potential window of the solvent (CH$_2$Cl$_2$; 0.1 M Bu$_4$NClO$_4$; $E > -1.60$ V). Therefore, a further reduction of the proposed cobalt(I) species seems improbable with the mild reducing agents zinc and iron powder.

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[9] The results for the optimization of the cobalt-catalyzed [4+2+2]-cycloaddition will be reported elsewhere.

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[11] The [CoBr$_2$(dppe)]-catalyzed reaction of the propargylic phthalimide **8** with 2,3-dimethyl-1,3-butadiene generated the cycloaddition products in 36% yield; see: G. Hilt, F. Galbiati, *Synlett* **2005**, 829.

[12] We thank Dr. L. Ackermann, LMU München, for providing the analytical data; see: L. Ackermann, R. Born, *Angew. Chem.* **2005**, *117*, 2497; *Angew. Chem. Int. Ed.* **2005**, *44*, 2444.