Homogeneous Catalysis

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Cobalt-Catalyzed Alder–Ene Reaction**

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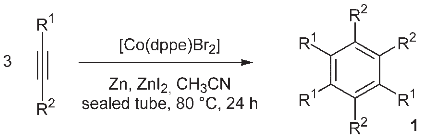
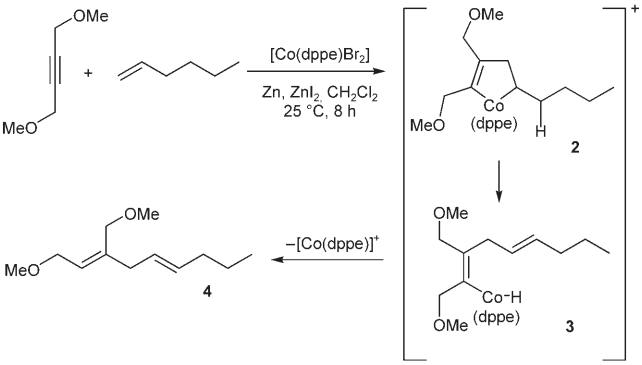
A valuable preparative synthetic method is characterized by a broad scope of substrates and high chemo- and regioselectivity in combination with an excellent yield. Many prominent transition-metal-catalyzed reactions, such as the Grubbs olefin metathesis[1] or the Sharpless epoxidation or bishydroxylation[2] fulfill these criteria.

Recently we reported the cyclotrimerization of alkynes with simple cobalt–diimine complexes.[3] During this work we found that cobalt–diphosphine complexes, such as [Co(dppe)Br_2], which we successfully applied in the cobalt-catalyzed Diels–Alder reaction of non-activated starting materials, did not efficiently catalyze the cyclotrimerization of terminal alkynes to form the aromatic product **1** (Scheme 1). The transformation of internal alkynes to the corresponding aromatic products could only be realized in acceptable yields at elevated temperatures and prolonged reaction times.



Scheme 1. Cobalt-catalyzed cyclotrimerization.[6]

Clearly, these results indicate that the starting materials coordinate to the cobalt center and that the desired cyclotrimerization proceeds; however, with internal alkynes the C–C coupling step is relatively slow. Therefore, under milder reaction conditions the coordination of alkynes should still be possible while the reaction rate for the cyclotrimerization should be further reduced. Additional substrates could then be added leading to alternative reaction pathways and new products. Thus, in addition to the internal alkynes, terminal alkenes were added to the catalyst. The outcome of this reaction was a formal intermolecular Alder–ene reaction[4] (Scheme 2) to afford the 1,4-diene **4**. This reaction is mechanistically related to the transformations undertaken by Trost with the $[CpRu]^+$ ($Cp = C_5H_5$) fragment.[5] Therefore, the cobalt-catalyzed reaction could also involve the coordination of the two starting materials in the coordination sphere of the cobalt center to form the cobaltacycle **2** (Scheme 2). A β-hydride elimination to **3** and a reductive elimination complete the stepwise formal Alder–ene reaction under very mild reaction conditions.



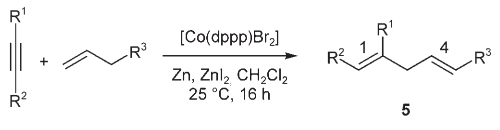
Scheme 2. Mechanism of the cobalt-catalyzed Alder–ene reaction.

Over the course of the investigation we realized that the transformation with a cobalt–dppm complex was very slow. Good results had already been obtained with a cobalt–dppe[6] complex, whereas the best results to date were with a cobalt–dppp[6] catalyst system. When a longer carbon chain was used in the diphosphine ligand, such as dppb,[6] the activity of the cobalt complex was reduced considerably, thus for further investigations the dppp ligand was used.

Some questions arise for this atom-economic interconnection of two simple starting materials: a) is the cobalt catalyzed Alder–ene reaction applicable to terminal alkynes? b) can unsymmetrical alkynes be transformed regioselectively? c) can the stereochemistry of the two newly formed double bonds in the 1,4-diene be controlled by the catalyst? and d) are a wide variety of functional groups accepted by the cobalt catalyst?

The first question could be answered easily: terminal alkynes prefer the formation of the cyclotrimerization product of type **1** ($R^2 = H$) and are unsuitable starting materials for the cobalt-catalyzed Alder–ene reaction.

However, the transformation of internal alkynes naturally leads to higher substituted 1,4-dienes which are the more valuable targets in the first place. The results of the investigation concerning the cobalt-catalyzed Alder–ene reaction of symmetrical and unsymmetrical internal alkynes (Scheme 3) are summarized in Table 1.



Scheme 3. 1,4-Diene syntheses by a cobalt-catalyzed Alder–ene reaction.

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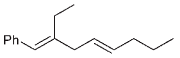
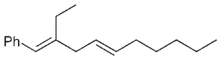
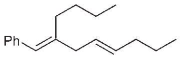
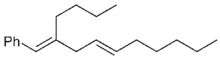
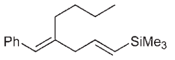
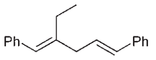
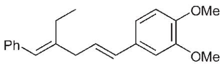
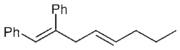
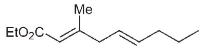
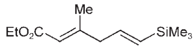
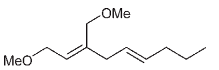
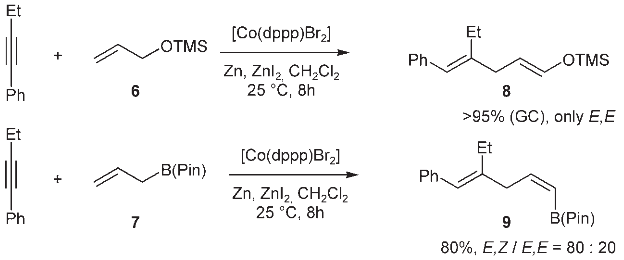
Table 1: Results of the formal cobalt-catalyzed Alder–ene reactions (see Scheme 3).

Entry	R^1	R^2	R^3	Product (**5**)	Yield [%] (E/Z)[a]
1	Et	Ph	*n*Pr		89 (89:11)
2	Et	Ph	*n*Pen		84 (89:11)
3	*n*Bu	Ph	*n*Pr		90 (88:12)
4	*n*Bu	Ph	*n*Pen		99 (88:12)
5	*n*Bu	Ph	$SiMe_3$		20 (95:5)
6	Ph	Et	Ph		85 (90:10)
7	Ph	Et	Ar[b]		95 (89:11)
8	Ph	Ph	*n*Pr		< 5[c]
9[d]	Me	CO_2Et	*n*Pr		88 (90:10)
10[d]	Me	CO_2Et	$SiMe_3$		100 (>99:1)
11[d]	CH_2OMe	CH_2OMe	*n*Pr		74 (69:31)

[a] The E/Z ratio is given for the double bond 4, see Scheme 3. [b] Ar = 3,4-dimethoxyphenyl. [c] Detected by GCMS analysis. [d] $[Co(dppe)Br_2]$ was used as catalyst.

Fortunately internal unsymmetrical alkynes are converted very regioselectively into 1,4-dienes where the newly formed carbon–carbon single bond in the case of phenyl-alkyl-alkynes (entries 1–7) is exclusively generated at the sterically less-hindered side of the former alkynes. The cobalt-catalyzed formal Alder–ene reaction leads exclusively to the formation of the products where the substituents R^1 and R^2 of the alkyne have the *Z*-configuration in the 1,4-diene. The stereochemistry of double bond 1 (see Scheme 3) is therefore uniform. However, the steric demand of two phenyl groups, such as in tolane (Table 1, entry 8), prohibits an efficient catalysis. For allyl silane (Table 1, entries 5 and 10) the reactivity is also somewhat reduced. Nevertheless, the desired product from phenyl butyne can be isolated in moderate yield and when ethyl butynoate is used the product is formed in quantitative yield, with exclusive regioselectivity with respect to double bond 1, and in excellent stereoselectivity for both newly formed carbon–carbon double bonds. Also, in the case of the alkyl-substituted reactants (R^3 = alkyl) the configuration of double bond 4 (see Scheme 3) is controlled in good to excellent selectivities by the [Co(dppp)] catalyst system. Additional functional groups, such as esters and ethers, are also accepted (Table 1, entries 9–11) so that products with excellent regioselectivity and, in some cases, very good stereoselectivity regarding double bonds 1 and 4 are generated in good yields.

The postulated reaction mechanism involves a double-bond shift in the alkene moiety so that the allyl silane is transformed into a vinyl silane. These processes were also exploited by Trost in the ruthenium-catalyzed reaction for the synthesis of γ,δ-unsaturated ketones from allylic alcohols.[5] Under the assumption that the [Co(dppp)] system exhibits a similar tolerance toward functional groups as has been shown for the [Co(dppe)] complex in the cobalt-catalyzed Diels–Alder reaction,[7] many different allylic-substituted functional groups can be envisaged as reactants in this Alder–ene reaction. To test this assumption allyl silyl ether **6** and allyl boronic ester **7** (Pin = pinacol) were tested so that after the double-bond shift the corresponding silyl enol ether **8** and the vinyl boronic ester **9** were generated (Scheme 4).[8]



Scheme 4. Conversion of functionalized alkenes. Pin = pinacol, TMS = trimethylsilyl.

The conversion of **6** and **7** into the products **8** and **9** was detected by GC and GCMS. The products were obtained in good yields considering the problems encountered during separation of product **9** from the accompanying cyclotrimerization product by column chromatography. Surprisingly, the double bond 4 in **9** was formed predominantly in the *Z*-configuration. Utilizing Suzuki coupling conditions, 1,4-dienes with an *E*,*Z* configuration become accessible. The products are obtained in good chemo-, regio-, and stereoselectivities so that they can be used for follow-up reactions.[9]

In conclusion we were able to establish an intermolecular cobalt-catalyzed Alder–ene reaction which connects two simple starting materials in an atom-economic fashion with a high degree of chemo- and regioselectivity for the generation of 1,4-dienes. The stereochemistry of the double bond 1 is controlled completely and that of the double bond 4 is controlled to a useful level. The use of functionalized alkynes and allyl components should lead to compounds that are valuable for further synthetic reactions.

Experimental Section

Representative Procedure for the intermolecular cobalt-catalyzed Alder–ene reaction (Table 1, entry 10): Allyl trimethylsilane (159 μL, 1.00 mmol) and ethyl 2-butynoate (175 μL, 1.50 mmol) were added to a suspension of $[Co(dppe)Br_2]$ (63 mg, 0.1 mmol, 10 mol%), zinc iodide (64 mg, 0.2 mmol, 20 mol%), and zinc powder (13 mg, 0.2 mmol, 20 mol%) in anhydrous dichloromethane (1 mL) under nitrogen atmosphere. The suspension was stirred for 16 h at ambient temperature until complete conversion was detected by GC analysis. The suspension was then filtered over a plug of silica gel (eluent: methyl *tert*-butyl ether (MTBE)) the solvent was removed under reduced pressure and the resulting material purified by column chromatography on silica gel (eluent: pentane/MTBE 20:1, R_f =

0.37). The product was obtained as a colorless oil (226 mg, 1.00 mmol, 100 %). ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 6.24$ (dt, $J = 14.0$, 7.4 Hz, 1H), 5.71–5.66 (m, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 2.95 (d, $J = 7.4$ Hz, 2H), 2.16 (d, $J = 1.3$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 0.13 ppm (s, 9H). ^{13}C NMR (CDCl$_3$, 75 MHz): $\delta = 166.7$, 157.8, 143.4, 132.7, 116.4, 59.5, 44.0, 19.0, 14.3, 0.1 ppm. IR: $\tilde{\nu} = 2957$, 2904, 1719, 1651, 1605, 1446, 1383, 1368, 1350, 1282, 1250, 1218, 1144, 1051, 839, 764, 691 cm^{-1}. MS (EI): m/z: 226 (M^+, 2), 211(12), 193(3), 181(35), 165(100), 108(38), 103(43), 91(12), 80(20), 73(75), 59(20). HRMS: calcd: m/z 226.1389; found: m/z 226.1382. The ratios of the stereoisomers were obtained by integration of GC- and NMR signals.

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Keywords: Alder-ene reaction · alkenes · alkynes · cobalt · stereoselectivity

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[6] dppm = 1,1-bis(diphenylphosphanyl)methane; dppe = 1,2-bis(diphenylphosphanyl)ethane; dppp = 1,3-bis(diphenylphosphanyl)propane; dppb = 1,4-bis(diphenylphosphanyl)butane.

[7] Selected references for functionalized building blocks: boron: G. Hilt, K. I. Smolko, *Angew. Chem.* **2003**, *115*, 2901; *Angew. Chem. Int. Ed.* **2003**, *42*, 2795; silicon: G. Hilt, K. I. Smolko, *Synthesis* **2002**, 686; nitrogen: G. Hilt, F. Galbiati, *Synlett* **2005**, 829; phosphorus: G. Hilt, C. Hengst, *Synlett* **2006**, 3247; oxygen: G. Hilt, K. I. Smolko, B. V. Lotsch, *Synlett* **2002**, 1081; sulfur: G. Hilt, S. Lüers, K. Harms, *J. Org. Chem.* **2004**, *69*, 624.

[8] Products **8** and **9** could be detected and characterized by GCMS analysis. After column chromatography of **8** the corresponding aldehyde could be obtained in 79 % yield. See also: B. M. Trost, J.-P. Surivet, F. D. Toste, *J. Am. Chem. Soc.* **2001**, *123*, 2897; B. M. Trost, A. F. Indolese, T. J. J. Müller, B. Treptow, *J. Am. Chem. Soc.* **1995**, *117*, 615.

[9] Selected examples for the ruthenium-catalyzed Alder–ene reaction and their application in total synthesis of natural products, see: B. M. Trost, G. D. Probst, A. Schoop, *J. Am. Chem. Soc.* **1998**, *120*, 9228; B. M. Trost, J. L. Gunzner, *J. Am. Chem. Soc.* **2001**, *123*, 9449; B. M. Trost, S. T. Wrobleski, J. D. Chrisholm, P. E. Harrington, M. Jung, *J. Am. Chem. Soc.* **2005**, *127*, 13589.