ORGANIC
LETTERS

2010
Vol. 12, No. 7
1536−1539

Cobalt Catalysis at the Crossroads: Cobalt-Catalyzed Alder−Ene Reaction versus [2 + 2] Cycloaddition

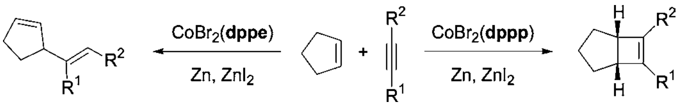
Gerhard Hilt,* Anna Paul, and Jonas Treutwein

*Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse,
35043 Marburg, Germany*

hilt@chemie.uni-marburg.de

Received February 2, 2010

ABSTRACT



The application of bidentate phosphine ligands in cobalt-catalyzed transformations of cyclic alkenes such as cyclopentene and cycloheptene with internal alkynes led to a chemoselective Alder−ene or a [2 + 2] cycloaddition reaction depending on the electronic nature of the alkyne and the bite angle of the ligand used.

The application of cobalt complexes in modern organic synthesis for the atom-economic formation of new carbon−carbon bonds is of great interest.[1] Cycloadditions are a prototype transformation, and several different types of such transformations have been described by us[2] and other groups[3] over the past decade. We recently reported the cobalt-catalyzed [2 + 2] cycloaddition of mono- and bicyclic alkenes with alkynes[4] and the Alder−ene reaction utilizing similar starting materials.[5] The [2 + 2] cycloaddition of cyclopentene with internal alkynes such as diphenyl acetylene was the first example of a transition-metal-catalyzed formation of a cyclobutene derivative utilizing a monocyclic alkene. Product **1** was obtained with an excellent yield of 91% utilizing cobalt bromide bis-1,2-diphenylphosphinopropane [CoBr$_2$(dppp)] as the catalyst (20 mol %) (Scheme 1). On the other hand, the Alder−ene product **2** was observed as the main product accompanied by **1** (**1**/**2** = 25:75) as an inseparable mixture when cobalt bromide 1,2-bis(diphenylphoshino)ethane [CoBr$_2$(dppe)] was applied.

---

(1) (a) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (b) Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318. (c) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547. (d) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (e) 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. (f) Welker, M. E. *Curr. Org. Chem.* **2001**, *5*, 785. (g) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (h) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (i) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(2) (a) Hilt, G.; Janikowski, J. *Org. Lett.* **2009**, *11*, 773. (b) Treutwein, J.; Hilt, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6811. (c) Hilt, G.; Paul, A.; Harms, K. *J. Org. Chem.* **2008**, *73*, 5187. (d) Hilt, G.; Janikowski, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5243. (e) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204. (f) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474. (g) Hilt, G.; Korn, T. J. *Tetrahedron Lett.* **2001**, *42*, 2783. (h) Hilt, G.; Hengst, C.; Hess, W. *Eur. J. Org. Chem.* **2008**, 2293.

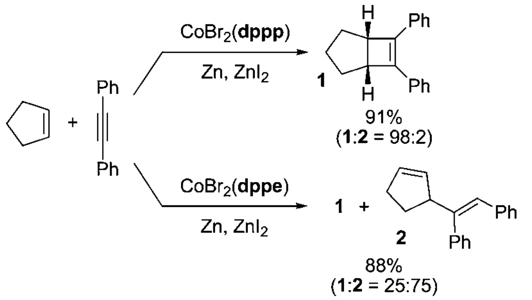
(3) (a) Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* **2005**, *7*, 2353. (b) Pardigon, O.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1977. (c) Pardigon, O.; Tenaglia, A.; Buono, G. *J. Org. Chem.* **1995**, *60*, 1868. (d) Tenaglia, A.; Pardigon, O.; Buono, G. *J. Org. Chem.* **1996**, *61*, 1129. (e) Pardigon, O.; Tenaglia, A.; Buono, G. *J. Mol. Catal. A: Chem.* **2003**, *196*, 157. (f) Ma, B.; Snyder, J. K. *Organometallics* **2002**, *21*, 4688. (g) Chen, Y.; Kiattansakul, R.; Ma, B.; Snyder, J. K. *J. Org. Chem.* **2001**, *66*, 6932. (h) Doszczak, L.; Tacke, R. *Organometallics* **2007**, *26*, 5722. (i) Doszczak, L.; Fey, P.; Tacke, R. *Synlett* **2007**, 753. (j) Goswami, A.; Ito, T.; Okamoto, S. *Adv. Synth. Catal.* **2007**, *349*, 2368. (k) Xu, B. H.; Wu, D.-H.; Li, Y.-Z.; Yan, H. *Organometallics* **2007**, *26*, 4344. (l) Field, L. D.; Ward, A. J. *J. Organomet. Chem.* **2003**, *681*, 91. (m) Yong, L.; Butenschön, H. *Chem. Commun.* **2002**, 2852. (n) Sugihara, T.; Wakabayashi, A.; Nagai, Y.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* **2002**, 576. (o) Montilla, F.; Aviles, T.; Casimiro, T.; Ricardo, A. A.; Nunes da Ponte, M. *J. Organomet. Chem.* **2001**, *632*, 113. (p) Field, L. D.; Ward, A. J.; Turner, P. *Aust. J. Chem.* **1999**, *52*, 1085. (q) Sigman, M. S.; Fatland, A. W.; Eaton, B. E. *J. Am. Chem. Soc.* **1998**, *120*, 5130. (r) Rhyoo, H.-Y.; Lee, B. Y.; Yu, H. K. B.; Chung, Y. K. *J. Mol. Catal.* **1994**, *92*, 41. (s) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (t) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (u) Chang, H. T.; Jeganmohan, M.; Cheng, C. H. *Org. Lett.* **2007**, *9*, 505. (v) Saino, N.; Amemiya, F.; Tanabe, E.; Kase, K.; Okamoto, S. *Org. Lett.* **2006**, *8*, 1439. (w) Wu, M. S.; Shanmugasundaram, M.; Cheng, C. H. *Chem. Commun.* **2003**, 718.

(4) Treutwein, J.; Hilt, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6811.

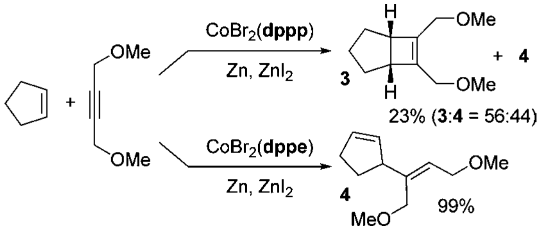
(5) Hilt, G.; Treutwein, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8500.

10.1021/ol100266u

Scheme 1. Cobalt-Catalyzed [2 + 2] Cycloaddition and Alder−Ene Reaction with Diphenyl Acetylene as Substrate



Scheme 2. Cobalt-Catalyzed [2 + 2] Cycloaddition and Alder−Ene Reaction with 1,4-Dimethoxybut-2-yne as Substrate



This situation became more interesting when we used 1,4-dimethoxybut-2-yne as substrate (Scheme 2). In these reactions, the chemoselectivity was altered significantly. Now, the [2 + 2] cycloaddition product **3** was obtained as a mixture of products **3** and **4** in 23% yield (**3**/**4** = 56:44) utilizing the [$CoBr_2$(dppp)] catalyst while product **4** was generated in 99% yields as the sole product utilizing the [$CoBr_2$(dppe)] complex.

Therefore, we propose that the chemoselectivity of the transformation is determined at the crossroad of a common intermediate. Early on in this investigation we realized that depending on the nature of the substituents on the alkyne and the bite angle of the bidentate phosphine ligands both pathways were possible. Therefore, we were interested in investigating which parameters controlled the chemoselectivity of these reactions.

To this end, we examined the dependency of the cobalt-catalyzed transformation of cyclopentene with 1,4-dimethoxybut-2-yne (Scheme 2) on the ligand system.

A rather low conversion was observed (~5%) for the test reaction using 1,2-bis(diphenylphosphino)benzene as ligand. Surprisingly, smaller bite angles as obtained with 1,2-bis(diphenylphosphino)methane (dppm) as well as larger bite angles obtained with 1,2-bis(diphenylphosphino)butane (dppb), 1,2-bis(diphenylphosphino)hexane (dpph), and BINAP led to no conversion of the starting materials. While 1,1′-bis(diphenylphosphino)ferrocene (dppf) gave about 33% conversion, the cyclotrimerization product of the alkyne was found to be the predominant product. As we demonstrated previously, the use of pyridine−imine ligands[2a,d,e] as well as diaryl sulfide ethane-type ligands[2h] led selectively to the cyclotrimerization product even if larger amounts of cyclopentene were applied. Other phosphine ligands utilized in this reaction (see Figure 1) gave no conversion of the starting materials and were disregarded for further investigation.

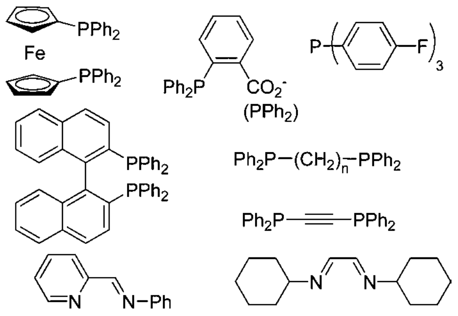
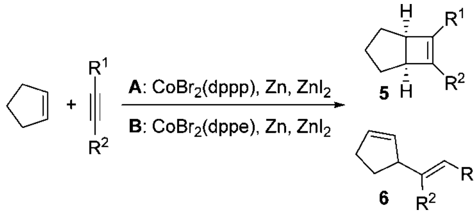


Figure 1. Other ligands tested in the reaction of cyclopentene with 1,4-dimethoxybut-2-yne.

Scheme 3. Cobalt-Catalyzed Alder−Ene Reaction or [2 + 2] Cycloaddition of Cyclopentene with Unsymmetrical Alkynes

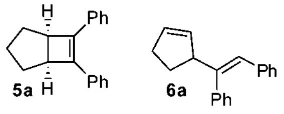
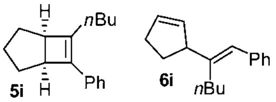
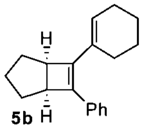
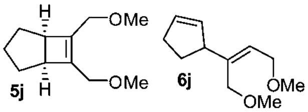
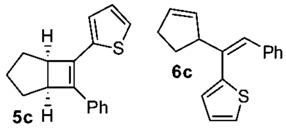
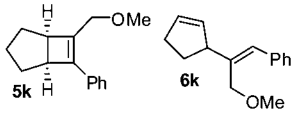
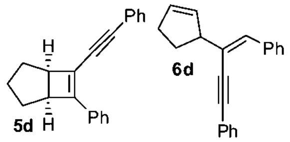
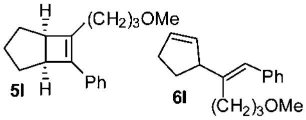
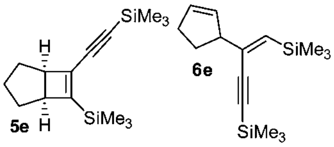
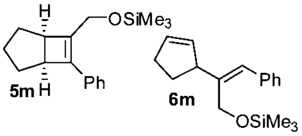
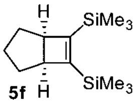
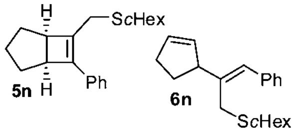
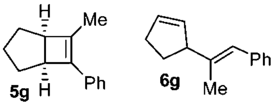
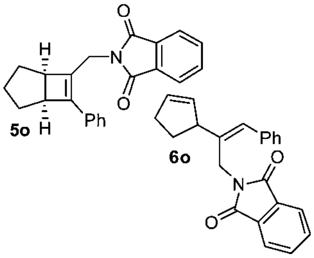
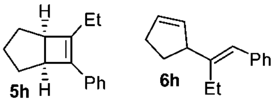


To investigate the chemoselectivity for both cobalt complexes the reaction between cyclopentene and symmetrical as well as unsymmetrical internal alkynes was performed (Scheme 3). The cycloaddition/Alder−ene ratios were determined via ^{1}H NMR spectroscopy or GC analysis and the results are presented in Table 1.

It turned out that in almost every case by applying the $CoBr_2$dppp complex the formation of the cycloaddition products of type **5** is favored while the cobalt dppe complex predominantly forms the Alder−ene adducts of type **6** as the major product. However, the nature of the alkyne also seems to have an effect on the selectivity of the reaction since alkynes which exclusively form the cyclobutene derivative with the cobalt dppp complex generate a mixture of both products when the cobalt dppe complex is used and vice versa. With diphenyl acetylene (Table 1, entry 1) or 2-(phenylethynyl)thiophene (entry 5) and the cobalt dppp complex the cyclobutenes **5a** and **5c** are obtained as the only product, whereas the 1,4-dienes **6a** and **6c** are formed as mixtures with cyclobutenes **5a** and **5c** when the cobalt dppe complex is used.

In the case of (cyclohexenylethynyl)benzene (entry 3), the conversion with the cobalt dppp as well as the cobalt dppe

Table 1. Results of the Cobalt-Catalyzed Reactions of Internal Alkynes with Cyclopentene[a]

entry	products of type **5** and **6**	yield[b] (**5**:**6**)	entry	products of type **5** and **6**	yield[b] (**5**:**6**)
1	 **5a** **6a**	**A** 91% (98:2)	17	 **5i** **6i**	**A** 87% (86:14)
2		**B** 88% (25:75)	18		**B** 62% (6:94)
3	 **5b**	**A** 99% (100:0)	19	 **5j** **6j**	**A** 23% (56:44)
4		**B** 26% (100:0)	20		**B** 99% (0:100)
5	 **5c** **6c**	**A** 93% (100:0)	21	 **5k** **6k**	**A** 34% (39:61)
6		**B** 83% (25:75[d])	22		**B** 32% (11:89)
7	 **5d** **6d**	**A** 64% (100:0)	23	 **5l** **6l**	**A** 83% (84:16)
8		**B** 62% (84:16)	24		**B** 76% (5:95)
9	 **5e** **6e**	**A** 68% (35:65)	25	 **5m** **6m**	**A** 70% (26:74)
10		**B** No conversion	26		**B** 59% (0:100)
11	 **5f**	**A** No conversion	27[c]	 **5n** **6n**	**A** 51% (62:38)
12		**B** No conversion	28[c]		**B** 65% (0:100)
13	 **5g** **6g**	**A** 98% (84:16)	29	 **5o** **6o**	**A** 74% (73:27)
14		**B** 60% (0:100)	30		**B** 52% (0:100)
15	 **5h** **6h**	**A** 78% (84:16)			
16		**B** 55% (0:100)			

[a] Catalyst system **A**: $CoBr_2$(dppp) (20 mol %), zinc dust (40 mol %), zinc iodide (40 mol %). Catalyst system **B**: $CoBr_2$(dppe) (20 mol %), zinc dust (40 mol %), zinc iodide (40 mol %). [b] The ratio of the regioisomers (**5**:**6**) is given in parentheses. [c] *c*Hex = cyclohexyl. [d] **6c** consists of a mixture of regioisomers, see text.

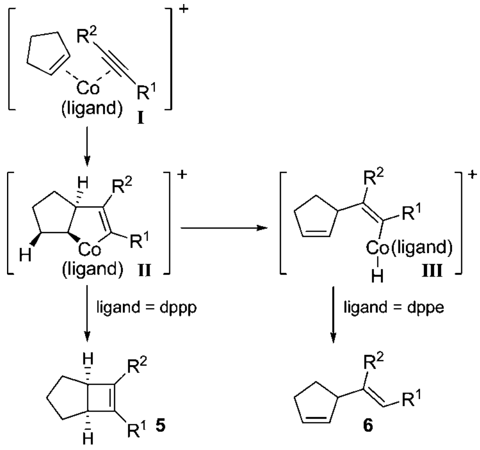
complex leads to the cyclobutene product **5b** without any traces of the 1,4-diene. In the cases when 1,3-diynes are used (entries 7 and 9), the type of substituent (phenyl or $SiMe_3$) on the diynes influences the chemoselectivity drastically. A rationale could be the better stabilization of intermediate **III** (see Scheme 4) by a silyl substituent. Alkynes bearing bulky substituents such as 1,2-bis(trimethylsilyl)acetylene were unreactive under these conditions (entries 11 and 12).

When alkyl−aryl-substituted alkynes are used, products of type **5** are predominantly formed utilizing catalyst system **A**. On the other hand, products of type **6** are generated with catalyst system **B**. Exceptions are those alkynes where an oxygen is in the propargylic position (entries 21 and 25) where the Alder−ene products **6k** and **6m** are formed predominantly by catalyst system **A** as well. In these cases, additional coordination of the oxygen functionalities might influence the reaction pathway. In contrast, sulfur and nitrogen in a propargylic position (entries 27 and 29) as well as oxygen functional groups further removed from the triple bond did not exhibit this effect on catalyst system **A** (entry 23).

As already noted above, we assume that the starting materials coordinate to the cobalt center (**I**) to begin with (Scheme 4). The common cobaltacylopentene intermediate **II** is obtained upon formal oxidative addition. At this stage, the interplay of substituents and ligands applied determine the chemoselectivity of the reaction.

With the dppp ligand, reductive elimination leads to the cyclobutene derivatives of type **5**. For the formation of the 1,4-dienes a β-hydride elimination leading to intermediate **III** takes

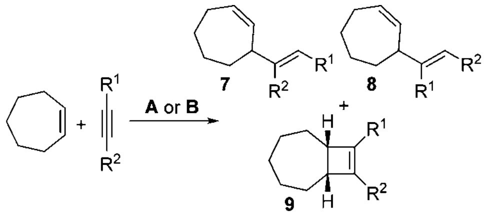
Scheme 4. Cobalt-Catalyzed Alder−Ene Reaction or [2 + 2] Cycloaddition of Cyclopentene with Unsymmetrical Alkynes



place and the Alder−ene products of type **6** are formed. This pathway is favored when the dppe ligand is utilized.

The first step of the catalytic cycle leading to cobaltacyclopentene **II** is decisive for the regioselectivity in the Alder−ene product (Scheme 5). Only when 2-(phenylethynyl)thiophene was used were both regioisomers of **6c** detected with a 79:21 ratio. In this case, the thiophene substituent in the main product is adjacent to the cyclopentenyl substituent. In all other cases, a single regioisomer is formed.

Scheme 5. Cobalt-Catalyzed Alder−Ene Reaction or [2 + 2] Cycloaddition of Cyclopentene with Unsymmetrical Alkynes



$R^1 = R^2 = Ph$	**A**: 37%, **7a**:**9a** = 67:33
$R^1 = R^2 = CH_2OMe$	**B**: 51%, **7b**:**9b** = 100:0
$R^1 = Ph$, R^2 = 2-thiophene	**A**: 61%, **7c**:**8c**:**9c** = 36:37:27
$R^1 = Ph$, $R^2 = nBu$	**A**: 56%, **7d**:**9d** = 78:22
$R^1 = Ph$, $R^2 = C{\equiv}CPh$	**A**: 39%, **7e**:**9e** = 69:31
$R^1 = Ph$, $R^2 = CH_2OMe$	**B**: 40%, **7f**:**9f** = 100:0
$R^1 = Ph$, $R^2 = CH_2$Phthalimide	**A**: 23%, **7g**:**9g** = 100:0

A: $CoBr_2$(dppp), Zn, ZnI_2 **B**: $CoBr_2$(dppe), Zn, ZnI_2

In addition to cyclopentene, we were also interested if other cyclic alkenes could be used in the cobalt catalyzed transformations. Therefore, 1,4-dimethoxybut-2-yne as a representative alkyne was reacted with cyclic alkenes. To our surprise, reactions with cyclohexene were unsuccessful whereas the conversions with cycloheptene gave the desired products. The results for the conversions of cycloheptene with alkynes are summarized in Scheme 5. The reactivity of cycloheptene is lower than cyclopentene so that the trimerization of the alkyne becomes predominant. Nevertheless, the Alder−ene products of type **7**/**8** are formed in acceptable yields while the corresponding products **9** of the [2 + 2] cycloaddition are always the minor component.

When mixtures were obtained, the separation of the products could only be realized for the products **7a**/**9a** and **7e**/**9e**. The general characteristics of the reaction of cycloheptene are similar to those with cyclopentene in terms of *E*/*Z* selectivity and regioselectivity. A mixture of the two regioisomers **7c** and **8c** was obtained only with 2-(phenylethynyl)thiophene as starting material. Concerning the chemoselectivities, changes can be identified with respect to the reactions with cyclopentene, indicating that the ring size of the alkene also plays an important role influencing whether reductive elimination or β-hydride elimination is the predominant reaction taking place. In the reactions of substrates with functional groups in the propargylic position only single Alder−ene isomers were detected.

In conclusion, we have demonstrated that the cobalt-catalyzed transformation of cyclopentene and, to a lesser extent, cycloheptene with internal alkynes leads to the desired adducts in acceptable to excellent yields. The chemoselectivity toward the Alder−ene or the [2 + 2] cycloaddition products is dependent on the alkyne substituents as well as on the diphosphine ligand used.

Acknowledgment. This work was partly supported by the BASF SE and the German Science Foundation. Their support 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.

OL100266U