Propargylic Phosphonium Salts in Cobalt-Catalysed Diels–Alder Reactions

Gerhard Hilt,* Christoph Hengst

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein Straße, 35043 Marburg, Germany
Fax +49(6421)2825677; E-mail: Hilt@chemie.uni-marburg.de

Received 5 September 2006

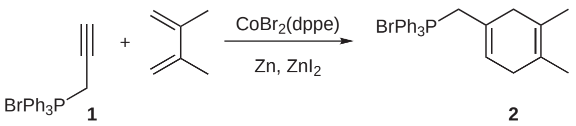
Abstract: A straight forward one-pot reaction sequence consisting of a cobalt-catalysed Diels–Alder reaction for the generation of a dihydroaromatic phosphonium salt and a subsequent Wittig olefination generates polysubstituted dihydrostilbene derivatives which can optionally be oxidised by DDQ to the corresponding stilbenes. Several aldehydes, 1,3-dienes and also homopropargylic phosphonium salts can be applied.

Key words: catalysis, cobalt, 1,4-diene, stilbene, Wittig olefination

The Diels–Alder reaction of non-activated 1,3-dienes and dienophiles is a well-established process if transition-metal catalysts are employed.[1] The transition-metal catalysts can either be added in their active forms or have to be activated in situ. In both cases, the catalysts should react under mild conditions and tolerate various functional groups, and exclude harsh activating conditions or reagents.

The generation of functionalised dihydroaromatic compounds by means of a cobalt-catalysed Diels–Alder reaction of non-activated 1,3-dienes and dienophiles has long been a focus of our research. Under these circumstances, we were able to report a rather simple cobalt-catalyst system, which is capable to convert various functionalised building blocks containing boron-, silicon-, nitrogen-, oxygen- or sulfur-functionalised 1,3-dienes or alkynes.[2]

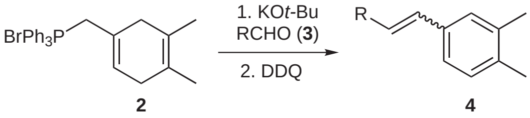
In an attempt to include phosphorus containing starting materials into the arsenal of building blocks suitable for a cobalt-catalysed Diels–Alder reaction we report herein the first use of propargylic phosphonium salts in such reactions (Scheme 1).



Scheme 1

The use of phosphorus-containing compounds like a propargylic phosphonium salt seems to be of much higher synthetic value in terms of possible follow-up chemistry as the use of alkynyl phosphines.[3] The envisaged cobalt-catalysed Diels–Alder reaction of a propargylic phosphonium salt such as **1** generates a dihydroaromatic allylic phosphonium salt intermediate **2** prone for further modifications such as an in situ Wittig olefination (Scheme 2).

The isolation of the phosphonium salt **2** was attempted; however, because of the other inorganic ingredients in the reaction mixture, **2** could not be obtained in pure form. In addition, a control of the conversion by means of ^{31}P NMR directly from the reaction mixture was not applicable because of paramagnetic cobalt catalyst components. The addition of a base and an aldehyde (**3**) then converted the phosphonium salt **2** in a Wittig olefination and subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) into an organic product **4** which could then be detected and isolated in the conventional manner. Therefore, we determined the optimal time for the cobalt-catalysed reaction before starting the Wittig olefination reaction. Accordingly, the best results for this protocol were obtained when the cobalt-catalysed Diels–Alder reaction was stirred for 30 minutes at room temperature after the characteristic colour change towards a deep brown colour.



Scheme 2

The reaction conditions for the cobalt-catalysed Diels–Alder reactions are very mild since the cobalt precatalyst (10–20 mol%) is stirred with 1.5–2.0 equivalents of dry zinc iodide and 40–60 mol% zinc dust at ambient temperature in dichloromethane. The amount of zinc iodide had to be increased compared to previous cobalt-catalysed Diels–Alder reactions because the bromide of the phosphonium salt retards the reactivity of the cobalt catalyst and has to be quenched by stoichiometric amounts of a Lewis acid.[4]

To determine the *E*/*Z* ratios of the in situ Wittig reactions, the Diels–Alder cyclisations were firstly conducted with the symmetrical 2,3-dimethyl-1,3-butadiene. Later, the unsymmetrical dienes isoprene and 2-methoxy-1,3-butadiene (entries 7, 8) were also used. In these latter cases besides the *E*/*Z* isomers, regioisomeric products from the cycloaddition process were also encountered. The separation and isolation of these regioisomers in pure form were not possible for most cases.[5] Therefore, the overall yields

SYNLETT 2006, No. 19, pp 3247–3250
Advanced online publication: 23.11.2006
DOI: 10.1055/s-2006-951544; Art ID: G25006ST
© Georg Thieme Verlag Stuttgart · New York

Downloaded by: Karolinska Institutet. Copyrighted material.

for the regio- and stereoisomers are given. The ratios were determined by integration of ^{1}H NMR signals and by GC analysis.

The Wittig-type reaction with aromatic aldehydes led to dihydroaromatic stilbenes, whereas the reaction with an aliphatic aldehyde led to a dihydroaromatic styrene product. The aldehyde was added in one portion and, after one hour stirring at ambient temperature, the dihydroaromatic products could be detected by GC-MS analysis.

Table 1 Results of the Cobalt-Catalysed Diels–Alder–Wittig Olefination–DDQ Oxidation Reaction Sequence

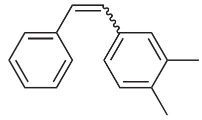
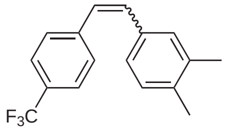
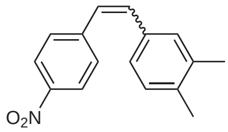
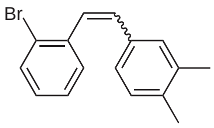
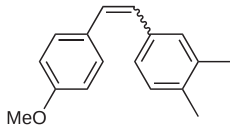
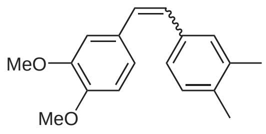
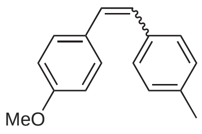
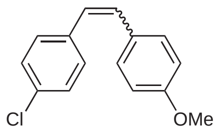
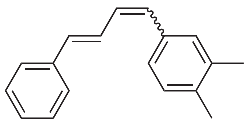
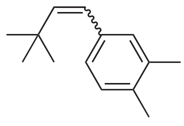
Entry	Product (**4**)	*E*/*Z* (1,3- vs. 1,4-)[a]	Yield (%)[b]
1	 **4a**	1.1:1.0	94
2	 **4b**	2.2:1.0	64
3	 **4c**	1.5:1.0	85
4	 **4d**	1.9:1.0	66
5	 **4e**	1.7:1.0	84
6	 **4f**	1.4:1.0	63
7	 **4g**	1.8:1.0 (1.0:2.8)	68
8	 **4h**	1.2:1.0 (1.0:4.8)	57
9	 **4i**	1.0:1.0	64
10	 **4j**	1.0:2.5	44

Table 1 Results of the Cobalt-Catalysed Diels–Alder–Wittig Olefination–DDQ Oxidation Reaction Sequence (continued)

[a] Ratio of Diels–Alder regioisomers determined from ^{1}H NMR integration.

[b] Combined yield of stereo- and regioisomers.

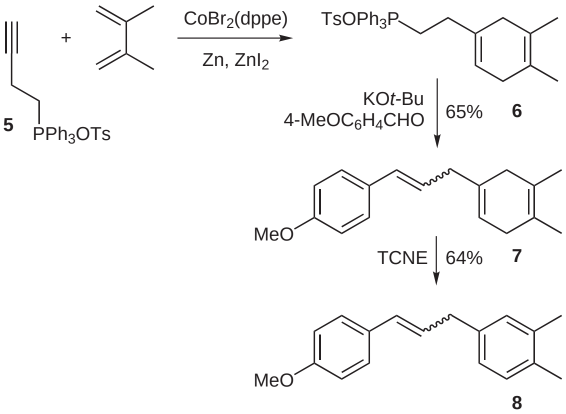
The dihydroaromatic compounds can be isolated following the regular work-up protocol for dihydroaromatic products but were preferably further oxidised by DDQ in benzene solution to generate the corresponding aromatic products **4**. The results of the cobalt-catalysed Diels–Alder–Wittig olefination–DDQ oxidation sequence are summarised in Table 1.[6] In general, the conversions of the proposed intermediate **2** with electron-deficient as well as electron-rich aromatic aldehydes **3** led to the desired products **4** in acceptable to excellent overall yields of up to 94% after three chemical transformations. The *E*/*Z* ratios observed in reactions with aromatic aldehydes slightly favour the *E*-configuration of the newly generated double bond. Therefore, the reactivity of dihydroaromatic phosphorus ylides seems to be in between the class of semi-stabilised and stabilised ylides, judged from the observed *E*/*Z* stereoselectivities.[7]

Of particular interest were mono- and higher-methoxylated benzaldehyde derivatives (entries 5–7) which led to interesting products.[8] The methoxy functionality can alternatively be introduced by the 1,3-diene building block (entry 8) which has a methoxy substituent in the 2-position. When the unsymmetrical 2-methoxy-1,3-butadiene is used also regioisomeric cycloadducts are observed. For the present examples the regioisomer with the 1,4-relation of the two substituents is preferred. As was illustrated earlier, the methoxy functionality can also be located in the 1-position of the 1,3-diene. In these cases an elimination of methanol occurs under the reaction conditions and the corresponding benzene derivative is formed removing the functionality from the product.[2f] If cinnamic aldehyde is used in the reaction sequence, a diaryl 1,3-butadiene product (**4i**) can be accessed.

On the other side, the application of aliphatic aldehydes gave only relatively poor results for pivalyl aldehyde (entry 10). Whereas, notable seems the preferred *Z*-configured product **4j** for the sterically bulky pivalyl aldehyde.

Downloaded by: Karolinska Institutet. Copyrighted material.

On the other hand a 1,3-diaryl substituted propene derivative **8** was generated from the homopropargylic phosphonium tosylate **5** via intermediate **6** (Scheme 3).



Scheme 3

The Diels–Alder–Wittig olefination sequence gave a reasonable amount of crude material **7** before DDQ oxidation (up to 65% yield). The oxidation process of **7** to form the aromatic product **8** revealed to be quite problematic resulting in polymerisation or many unidentified decomposition products. Therefore, an alternative and even milder oxidation methodology was applied to dehydrogenate the intermediate **7** and not initiate a decomposition process. For this purpose, TCNE (tetracyanoethylene) in dioxane was employed for the oxidation process. The desired aromatic product **8** was consequently isolated in 64% yield (*E*:*Z* = 1.0:1.2) starting from the crude dihydroaromatic material **7**. Because **7** does not obtain a 1,3-diene subunit such as the intermediates derived from propargylic phosphonium salts, a thermal Diels–Alder reaction does not occur.[9]

The first successful use of propargylic phosphonium salts in cobalt-catalysed Diels–Alder reactions broadens the usefulness of such cycloaddition reactions so that a strong increase in complexity starting from simple, mostly commercially available, educts can be realised. Therefore, the presented protocol provides a variable three-component access towards unsymmetrical polysubstituted dihydrostilbene derivatives, which can be easily oxidised by DDQ to the corresponding stilbenes.

References and Notes

(1) For selected examples of transition-metal-catalysed [4+2] cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) tom Dieck, H.; Diercks, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 778; *Angew. Chem.* **1983**, *95*, 801. (c) Bakhtiar, R.; Drader, J. J.; Jacobsen, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 8304. (d) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (e) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962. (f) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. (g) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. (h) Brunner, H.; Reimer, A. *Bull. Chem. Soc. Fr.* **1997**, *134*, 307. (i) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863.

(2) For cobalt-catalysed Diels–Alder reactions with functionalised building blocks, see: (a) Hilt, G.; Hess, W.; Harms, K. *Org. Lett.* **2006**, *8*, 3287. (b) Hilt, G.; Lüers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251. (c) Hilt, G.; Galbiati, F. *Synlett* **2005**, 829. (d) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624. (e) Hilt, G.; Smolko, K. I. *Angew. Chem. Int. Ed.* **2003**, *42*, 2795; *Angew. Chem.* **2003**, *115*, 2901. (f) Hilt, G.; Smolko, K. I.; Lotsch, B. V. *Synlett* **2002**, 1081.

(3) The alkynyl phosphine derivatives seem to coordinate to the cobalt catalyst via the phosphorus functionality, blocking the free coordination sites necessary for the Diels–Alder reaction. Higher catalyst loading did not restore the reactivity, as it did in the case of alkynyl sulfide derivatives (ref. 2d).

(4) The reduction of the amount of zinc iodide reduced the reactivity of the catalyst system considerably. The yields of dihydroaromatic intermediates or the final products **4** were not diminished by the considerable amount of inorganic components.

(5) The separation of the *E*/*Z* stereoisomers is possible after column chromatography.

(6) **General Procedure.**
Under an argon atmosphere, ZnI$_2$ (319 mg, 1.0 mmol, 2.0 equiv), zinc dust (20 mg, 0.3 mmol, 60 mol%) and CoBr$_2$ (dppe) (62 mg, 0.1 mmol, 20 mol%) were suspended in dry CH$_2$Cl$_2$ (10 mL). After formation of the active catalytic species, recognisable when the green suspension turned deep brown, prop-2-ynyl(triphenyl)phosphonium bromide (**1**, 191 mg, 0.5 mmol, 1.0 equiv) and 2,3-dimethyl-1,3-butadiene (0.75 mmol, 62 mg, 85 μL, 1.5 equiv) were added. The resulting mixture was stirred at r.t. for 30 min. After cooling the solution down in an ice bath, *t*-BuOK (281 mg, 2.5 mmol, 5.0 equiv) and 4-nitrobenzaldehyde (91 mg, 0.6 mmol, 1.2 equiv) were added at 0 °C. After the addition was completed, the reaction mixture was stirred one additional hour at ambient temperature and then filtered over a short pad of silica gel (eluent: pentane–MTBE, 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene (10 mL) and oxidised with DDQ (170 mg, 0.75 mmol, 1.5 equiv) at r.t. After 2 h the reaction mixture was washed twice with aq basic thiosulfate solution (10% NaOH, 10% Na$_2$S$_2$O$_3$, 2 × 10 mL). The aqueous phases were combined, extracted with MTBE (20 mL) and the combined organic phases were dried over MgSO$_4$. After evaporating the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (eluent: pentane–MTBE, 100:1) to give 108 mg (85%) of **4e** as a yellow solid.
E-isomer: ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.20 (d, 2 H, *J* = 8.8 Hz), 7.60 (d, 2 H, *J* = 8.8 Hz), 7.33 (s, 1 H), 7.29 (d, 1 H, *J* = 7.8 Hz), 7.22 (d, 1 H, *J* = 16.3 Hz), 7.16 (d, 1 H, *J* = 7.8 Hz), 7.08 (d, 1 H, *J* = 16.3 Hz), 2.31 (s, 3 H), 2.30 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$): δ = 146.5, 144.2, 137.8, 137.0, 133.8, 133.4, 130.1, 128.2, 126.6, 125.1, 124.6, 124.1, 19.8, 19.6.
Z-isomer: ^{1}H NMR (500 MHz, CDCl$_3$): δ = 8.07 (d, 2 H, *J* = 8.7 Hz), 7.40 (d, 2 H, *J* = 8.7 Hz), 7.01 (s, 1 H), 7.01 (d, 1 H, *J* = 7.0 Hz), 6.94 (d, 1 H, *J* = 7.8 Hz), 6.76 (d, 1 H, *J* = 12.2 Hz), 6.54 (d, 1 H, *J* = 12.2 Hz), 2.26 (s, 3 H), 2.20 (s, 3 H). ^{13}C NMR (125 MHz, CDCl$_3$): δ = 146.3, 144.5, 136.7, 136.5, 134.0, 133.5, 130.0, 129.7, 129.5, 127.0, 126.1, 123.4, 19.5, 19.5. IR (KBr): 3070, 2972, 1590, 1514,

Downloaded by: Karolinska Institutet. Copyrighted material.

1452, 1344, 1183, 1109, 972, 866, 834, 814, 750, 710, 690 cm^{-1}. MS (EI): m/z = 253 [M$^+$], 223, 207, 192, 178, 165, 91. HRMS (EI): m/z calcd for $C_{16}H_{15}NO_2$: 253.1103; found: 253.1106.

(7) For recent examples of Wittig reactions with allylic-type phosphonium salts, see: (a) Ackermann, M.; Berger, S. *Tetrahedron* **2005**, *61*, 6764. (b) Otero, M. P.; Torrado, A.; Pazos, Y. *J. Org. Chem.* **2002**, *67*, 5876. (c) Qing, F.-L.; Yue, X.-J. *Chin. J. Chem.* **2000**, *18*, 76. (d) Qing, F.-L.; Yue, X.-J. *Tetrahedron Lett.* **1997**, *38*, 8067.

(8) Investigations towards the synthesis of combretastatin derivatives are underway.

(9) Hilt, G.; Lüers, S.; Polborn, K. *Isr. J. Chem.* **2001**, *41*, 317.

Downloaded by: Karolinska Institutet. Copyrighted material.