Pergamon

Tetrahedron Letters 42 (2001) 2783–2785

TETRAHEDRON
LETTERS

An efficient cobalt catalyst for the neutral Diels–Alder reaction of acyclic 1,3-dienes with internal alkynes

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Received 20 February 2001

Abstract—The efficiently cobalt(I)-catalysed neutral Diels–Alder type reactions of internal alkynes with substituted 1,3-dienes is described. The regiochemistry for the dihydroaromatic products of reactions of isoprene with unsymmetrical reaction partners (2-alkynes and 1-trimethylsilyl-1-hexyne) is investigated. The dihydroaromatic reaction products are easily oxidised electrochemically to the corresponding functionalised durene and isodurene derivatives. © 2001 Elsevier Science Ltd. All rights reserved.

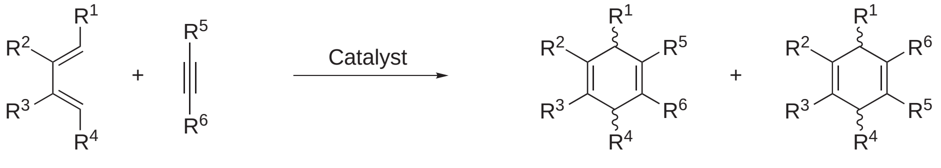
The transition metal-catalysed Diels–Alder reactions of 1,3-dienes with non-activated internal alkynes as dienophiles is of special interest for the preparation of 1,4-dihydroaromatic systems.[1] Whilst the thermal Diels–Alder reaction of simple olefins and alkynes proceeds only under drastic conditions, transition metal complexes can catalyse such reactions under much milder conditions. These catalysts are mostly cobalt-, rhodium-, nickel- or iron-based complexes[2] (Scheme 1).

As we reported earlier, the $CoBr_2(dppe)/ZnI_2/Bu_4NBH_4$ system serves as an excellent catalyst for the homo Diels–Alder reaction of norbornadiene with alkynes, as well as for the neutral Diels–Alder reaction of acyclic 1,3-dienes with terminal alkynes.[3]

Herein we wish to report the use of internal symmetrical and unsymmetrical alkynes as dienophiles in the neutral Diels–Alder reaction with symmetrical and unsymmetrical 1,3-dienes. The reaction of the symmetrical alkynes 3-hexyne (Table 1, entries 1–3,) and 1,4-dimethoxy-2-butyne (entries 4–6) with different 1,3-dienes furnished the corresponding products in excellent yields and under very mild conditions.

The reactions are generally complete within 2–4 h (GC analysis) when 2–3 mol% of the cobalt catalyst is employed. The dihydroaromatic products are easy to isolate via filtration through silica gel, but are somewhat sensitive towards oxidation, giving the corresponding aromatic compounds. The rate of the reactions with sterically more demanding dienes, such as 2-methyl-1,3-pentadiene, is somewhat diminished so that the reactions are complete within 12–16 h. This can be explained by the higher steric demand of the 1,3-pentadiene substrate while coordinated to the cobalt centre during the carbon–carbon bond formation process. Nonetheless, unfunctionalised as well as functionalised polysubstituted 1,4-cyclohexadiene derivatives can be generated in a simple and efficient way and these compounds can be used for further transformations.[5]

We then investigated the reactions of unsymmetrical alkynes with isoprene in order to determine the regioselectivity of the reactions (see Table 2). Whilst the regiochemistry of the reaction of isoprene with 2-hexyne (Table 2, entry 1) could not be influenced by the addition of cosolvents (benzene, toluene, THF, dioxane or diethyl ether afforded only slightly different regiose-



Scheme 1.

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PII: S0040-4039(01)00289-1

Table 1. Neutral Diels–Alder reactions with internal symmetrical alkynes[4]

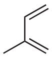
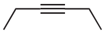
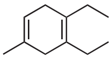
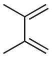
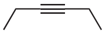
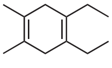
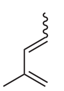
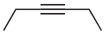
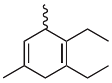
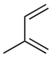
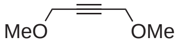
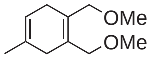
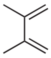
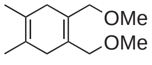
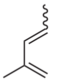
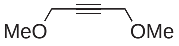
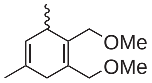
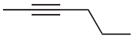
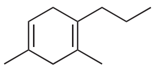
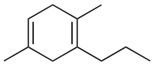
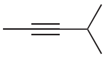
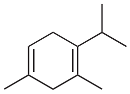
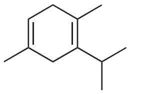
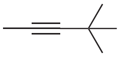
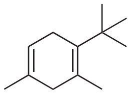
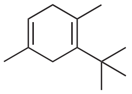
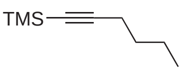
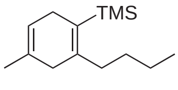
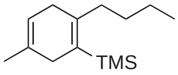
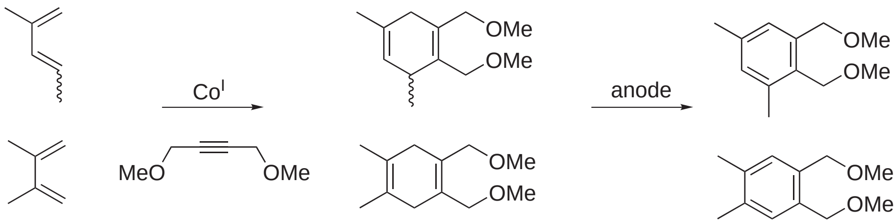
run	starting materials		product	yield [%]
1				99
2				98
3				84
4				98
5				94
6				87

Table 2. Results of neutral Diels–Alder reactions of isoprene with internal unsymmetrical alkynes[4]

entry	starting material	products		ratio	yield [%]
1				70:30	92
2				82:18	85
3				>98:<2	72
4				>98:<2	97

lectivities), the ratio of regioisomers[6] could be significantly influenced by using sterically more hindered alkynes. Complete regiocontrol was observed when *t*-butyl- and trimethylsilyl-functionalised alkynes were employed (entries 3 and 4). In these experiments the regioisomer with less steric hindrance was formed with good to excellent regioselectivity. Again, for these sterically more demanding alkynes the rate of the reaction is somewhat diminished; however, the reactions are still generally complete within 16 h when 2–3 mol% of cobalt catalyst is used.

The oxidation of these dihydroaromatic systems can be performed under very mild conditions in a quasi-divided electrochemical cell (2–3 F/mol) using a glassy carbon anode and a platinum wire cathode in dichloromethane (0.1 M tetrabutylammonium tetrafluoroborate as supporting electrolyte) to generate the corresponding aromatic compounds.[7] The electrochemical oxidation was preferred over aerobic oxidation because, by further electrochemical oxidation in the presence of nucleophiles, it opens up further possibilities for functionalisation of the generated arene com-



Scheme 2.

pounds.[8] The reactions can not only be performed sequentially as shown above but also in a one pot procedure. The goal for further investigations is the electrochemical generation of the reactive Co(I) species in combination with the electrochemical oxidation of the dihydroaromatic reaction products. The attractiveness in this approach lies in the easy synthesis of well-defined substituted arene derivatives, particularly durene and isodurene aromatic systems, which are difficult to obtain by other methods[9] (Scheme 2).

The synthesis of the dimethoxy derivatives of isodurene and durene (80 and 78% isolated yield over two steps, respectively) illustrates the usefulness of the key reaction in furnishing polysubstituted arenes with well-defined substitution and functionalisation patterns.

Acknowledgements

This work was supported by grants from the German Science Foundation.

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3. Hilt, G.; du Mesnil, F.-X. *Tetrahedron Lett.* **2000**, *41*, 6757–6761.
4. All products were characterised by ^{1}H and ^{13}C NMR, and MS; for a general experimental procedure see Ref. 3.
5. The conversion to arene–ruthenium complexes is currently under investigation in our laboratory.
6. The regiochemistry was determined by HMBC and HMQC NMR experiments. The ratios of regioisomers were determined by integration over quantitative ^{13}C NMR spectra of the crude reaction mixture and/or by gas chromatography.
7. Representative procedure for the electrochemical oxidation of the dihydroaromatic compounds:
   In a 50 mL beaker cell under nitrogen, 1,2-bis-methoxymethyl-4,5-dimethyl-cyclohexa-1,4-diene (368 mg, 1.88 mmol) was dissolved in dichloromethane (20 mL) containing Bu_4NBF_4 (0.1 M) as supporting electrolyte. The solution was electrolysed at a constant current (100 mA) on a glassy carbon anode (15 cm^2) and a platinum wire cathode until the starting material was consumed (GC analysis, generally 2–3 F/mol). The solvent was evaporated and the residue was filtered through a small amount of silica gel (pentane:diethyl ether = 10:1). The product 1,2-bis-methoxymethyl-4,5-dimethyl-benzene (304 mg, 1.56 mmol, 83%; 78% over the two steps) was obtained as a colourless oil after column chromatography on silica gel with pentane as eluent.
8. Hammerich, O. In *Organic Electrochemistry*; Lund, H.; Hammerich, O., Eds., 4th ed.; Dekker: New York, 2001; pp. 471–498.
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