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The first cobalt catalyzed [2 + 2 + 2] alkyne cyclotrimerization in aqueous medium at room temperature†

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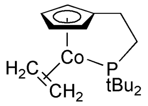
Chelate complex 1 (5 mol%) was found to catalyze the [2 + 2 + 2] cyclization of terminal alkynes in good yields in a 80/20 mixture of water and ethanol at room temperature without further activation.

The transition metal facilitated cyclotrimerization of alkynes and the co-cyclization of alkynes and alkenes as well as of alkynes and nitriles leading to arenes, cyclohexadienes, and pyridine derivatives has been recognized as a valuable tool for organic synthesis during the last three decades.[1–6] For the cyclization of alkynes and nitriles a number of catalysts have been used, the most prominent ones being cyclopentadienylcobalt(I) and palladium(0) complexes.[1] Although the reaction has widely been explored, still new catalysts and new reaction conditions are reported. For example, most recently Sugihara has shown 1–2 mol% of methylidynetricobalt nonacarbonyl to catalyze the cyclization of terminal as well as internal alkynes to the respective benzene derivatives in toluene at reflux.[7] In some newer publications the reaction is reported to take place in aqueous solutions. Heller and co-workers found that co-cyclizations of alkynes and nitriles in the presence of cyclopentadienylcobalt(I) cyclooctadiene derivatives as catalysts result in the formation of pyridines in water at room temperature under irradiation with visible light.[8–14] Dinjus and co-workers as well as Parsons and co-workers reported the reaction to take place in supercritical water.[15,16] More recently Eaton and co-workers reported thermal alkyne cyclotrimerization and alkyne nitrile co-cyclization in aqueous solvents at elevated temperatures.[17–19] These reactions take place with cyclopentadienylcobalt(I) catalysts bearing hydrophilic side chains at the cyclopentadienyl ligand. Many of the applied alkynes also have hydrophilic functional groups such as hydroxy, ketone, ester, amine, or carboxylic acid functions. In the cases of pyridine formation the respective nitriles are hydrophilic. The reactions were usually performed in 70:30 mixtures of water and methanol at 85 °C for 24 h. Clearly these reports mark some progress in the field, as the solvent system applied has obvious advantages in the light of environmental issues and industrial waste disposal.

Cyclopentadienyl complexes bearing pendant ligands such as phosphane moieties are gaining increased attention.[20] We have investigated the chemistry of di-*tert*-butylphosphanylethylcyclopentadienylcobalt(I) chelate **1** for some time.[21–29] Treatment of **1** with alkynes in THF at low temperature gave alkyne complexes.[27] The isolation of the phenylethyne complex required a temperature below 0 °C; terminal alkynes such as ethyne and 3,3-dimethyl-1-butyne rearranged to the corresponding vinylidene complexes.[27,29] In some cases at higher temperatures a co-dimerization of alkynes or *tert*-butylphosphaethyne was observed leading to the respective cyclobutadiene or diphosphete complexes.[21,26,28]



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Here we report on [2+2+2] cyclization reactions of terminal alkynes in water/ethanol (80:20) at room temperature using **1** as a catalyst. While **1** is sensitive to air, the complex is stable in water. Using 10 mol% of **1** the cyclotrimerization of phenylethyne was complete after 8 h at room temperature giving regioisomers **2** and **3** (66:34) in 86% yield. Using 5 mol% of **1** caused a slight decrease in yield to 84%, whereas using only 2 mol% of **1** caused a substantial decrease to 74% (Table 1). Thus, 5 mol% of catalyst **1** are regarded as sufficient.

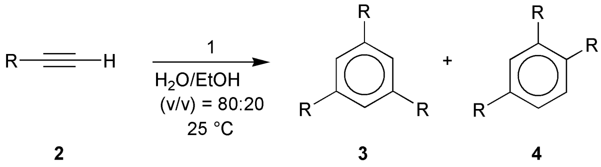

Table 1 Influence of catalyst amount on the **3**:**4** ratio and on the yield (R = Ph).

1 [mol %]	**3**:**4**[a]	Yield [%]
10	66:34	86
5	69:31	84
2	75:25	74

[a] Determined by GC.

The reaction was tested with a number of other alkynes. Results are summarized in Table 2.

The results demonstrate that the alkyne cyclotrimerization is possible using **1** as the catalyst in water/ethanol (80:20) at ambient temperature with no photochemical activation being necessary. The reaction works in good yield even with alkynes lacking hydrophilic functional groups (entries 1, 2, 3, 6, 7). In all cases the symmetric product **3** prevails over **4**, presumably for steric reasons.

Experiments using internal instead of terminal alkynes revealed that the yields are, most likely due to steric inter-

Table 2 Alkyne cyclotrimerization using 5 mol% of **1** in water/ethanol (80:20) at 25 °C.[30]

Entry	2	R	**3**:**4**[a]	Yield [%]
1	**a**	Ph	69:31	84
2	**b**	*n*-Bu	65:35	86
3	**c**	*t*-Bu	73:27	74
4	**d**	$HOCH_2$	61:39	89
5	**e**	EtO_2C	59:41	71
6	**f**	$Cl(CH_2)_3$	76:24	77
7	**g**	*n*-Dec[b]	77:23	91
8	**h**	*p*-Tol	57:43	81

[a] Determined by GC. [b] *n*-Dec = *n*-Decyl.

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b207978j/

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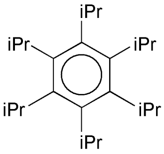
actions, somewhat smaller. In addition, a temperature of 60 °C was necessary for conversion. Thus, cyclotrimerization of 2,5-dimethyl-3-hexyne gave hexaisopropylbenzene (**5**) in 51% yield, and the reaction of diphenylethyne resulted in a 47% yield of hexaphenylbenzene (**6**).



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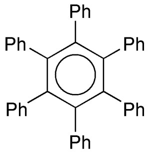

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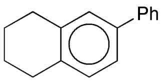

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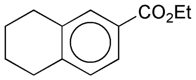

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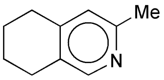

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Next, some co-cyclization experiments were performed, in which 1,7-octadiyne was treated with phenylethyne and with ethyl propionate. Under the usual reaction conditions[30] **7** and **8** were formed in 44% and 40% yield, respectively. As the co-cyclization of alkynes and nitriles has been used for the synthesis of pyridines, 1,7-octadiyne was then treated with acetonitrile giving tetrahydroisoquinoline **9** in 64% yield.

A closer examination of the reaction revealed that the reaction mixture is not homogeneous. Upon stirring after addition of the alkyne and the catalyst apparently an emulsion is formed, the reaction presumably taking place in the micelles. Upon alkyne consumption the formed cyclization product precipitates from the mixture.

We have shown that cobalt chelate **1** serves as a catalyst for the alkyne trimerization in water/ethanol (80:20) at room temperature. The use of this medium has obvious advantages over usual organic solvents in terms of organic solvent consumption, waste disposal and safety issues.

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30 *Typical experimental procedure:* To a 20 mL Schlenk flask, 16.2 mg (0.05 mmol) of ethene cobalt complex **1**, 102 mg (0.11 ml, 1.00 mmol) of phenylactylene (**2a**) and 5 ml of degassed water/ethanol (80:20) was added under argon. The reaction mixture was stirred at room temperature (25 °C) for 7 h. Then the reaction mixture was extracted with petroleum ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate 40:1) and gave 86 mg (28.1 mmol, 84%) of **3a**/**4a**.