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A simple cobalt catalyst system for the efficient and regioselective cyclotrimerisation of alkynes†

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Received (in Cambridge, UK) 25th November 2004, Accepted 5th January 2005
First published as an Advance Article on the web 26th January 2005
DOI: 10.1039/b417832g

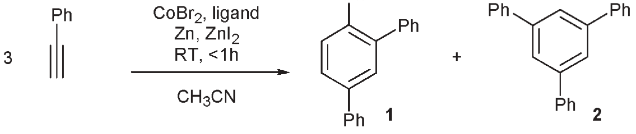
The intermolecular cyclotrimerisation of terminal and internal alkynes can be catalysed by simple cobalt complexes such as a $CoBr_2$(diimine) under mild reaction conditions when treated with zinc and zinc iodide with high regioselectivity in excellent yields.

The synthesis of polysubstituted aromatic compounds from simple alkynes by a regioselective trimerisation process has long been of great interest. Several elaborated catalyst systems involving palladium, cobalt, nickel, rhodium or other transition metals have been described.[1] Furthermore, approaches with permanently or intermediately tethered building blocks have been published.[2]

Based on a cobalt catalyst suitable for initiating a Diels–Alder reaction of non-activated starting materials[3] we report herein an easy to handle and inexpensive catalyst system for the [2 + 2 + 2]-cyclotrimerisation of terminal and internal alkynes. This reaction can be catalysed by cobalt diimine complexes which were activated *in situ* with a combination of zinc and zinc iodide in acetonitrile. Thereby highly reactive catalyst systems for the cyclotrimerisation of phenylacetylene to the unsymmetrical 1,2,4-substituted benzene derivative **1** (Scheme 1) were identified. Among several solvents tested, the best regioselectivity was observed in acetonitrile for the trimerisation reaction to obtain **1** and **2** in almost quantitative yield and in excellent regioselectivity (up to 97 : 3).

Quite surprising was the observation that in the absence of a diimine ligand anhydrous $CoBr_2$ catalysed the reaction in acetonitrile as well. In this case, the desired product **1** was generated in excellent yield (99%) and in good regioselectivity (95 : 5). However, the reactivity (0.5 h reaction time) of this $CoBr_2$/Zn/ZnI_2/CH_3CN system was lower than in the reactions conducted with the diimine ligands. Table 1 summarises some of the most reactive and regioselective cobalt complexes which were tested with phenylacetylene as substrate.

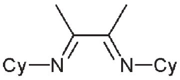
While electron-poor triphenyl phosphine as ligand is counterproductive under the conditions used,[4] conversion with the more electron-rich tricyclohexyl phosphine ligand leads in acetonitrile to a faster reaction, a better yield and higher regioselectivity. In terms of reactivity and selectivity the best results were obtained with diimine ligands. Since many modifications of this rather simple ligand type can be envisaged, we identified the dicyclohexyldiimine ligand (entry 5) as the ligand of choice. This system combines high reactivity with excellent yield and selectivity. The overall trend for lower regioselectivity and lower yields in THF as solvent can be found for all ligand systems tested. However, only in the case of the dicyclohexyldiimine ligand the regioselectivity was reversed and further small changes on the ligand system (entry 6) favoured the unsymmetrical product **1**.



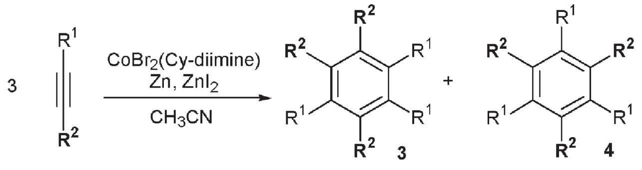
Scheme 1

Then the synthetic usefulness of this catalyst system consisting of cobalt dicyclohexyldiimine complex, Zn and ZnI_2 in acetonitrile was tested with terminal and internal alkynes (Scheme 2, Table 2). In all cases the unsymmetrical product **3** was found to be the major regioisomer.[5]

Table 1 [2 + 2 + 2]-Cyclotrimerisation reactions of phenylacetylene with cobalt complexes activated by Zn and ZnI_2

Entry	Ligand	Regioselectivity **1** : **2**	Time/h	Yield[a]
1	None	95 : 5	0.5	99%
2	2 PPh_3	93 : 7	1	57%
3	2 PCy_3	96 : 4	0.5	91%
4		94 : 6	0.5	96%
5		95 : 5	0.25	99%
6		96 : 4	0.5	94%
7		97 : 3	0.5	90%
8		96 : 4	0.5	85%

[a] Conditions: cobalt complex (5 mol%), zinc dust (10 mol%), ZnI_2 (10 mol%), 1.0 ml CH_3CN, phenylacetylene (204 mg, 2.0 mmol); Cy: cyclohexyl; Mes: (2,4,6-trimethylphenyl).



Scheme 2

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† Electronic supplementary information (ESI) available: Experimental details. See http://www.rsc.org/suppdata/cc/b4/b417832g/
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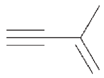
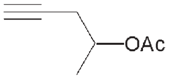
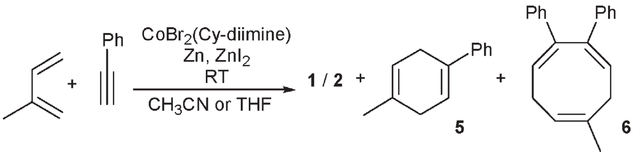
Table 2 [2 + 2 + 2]-Cyclotrimerisation of terminal and internal alkynes

Entry	Alkyne	Time/h	Ratio **3** : **4**	Yield[a]
1	≡—*n*Bu	1	92 : 8	90%
2	Ph—≡—Ph	15		83%[b,c]
3	Et—≡—Et	15		92%[c]
4	Me—≡—Ph	15	96 : 4	98%[c]
5	Me—≡—Et	15	78 : 22	99%[c]
6	≡—SiMe$_3$	0.25	75 : 25	88%
7		0.25	93 : 7	69%
8		15	94 : 6	98%
9	≡—CO$_2$Me	0.25	86 : 14	96%

[a] Conditions: CoBr$_2$(Cy-diimine) (5 mol%), zinc dust (10 mol%), ZnI$_2$ (10 mol%), 1.0 ml CH$_3$CN, alkyne (2.0 mmol); [b] precipitated from reaction mixture; [c] Reaction was performed at 80 °C.

While very mild reaction conditions could be applied for terminal alkynes (20 °C) obtaining the desired products in good to excellent yields in a short reaction time, the conversions with internal alkynes were conducted at 80 °C and stirred overnight. The terminal alkyl, alkenyl and aryl substituted alkynes gave the unsymmetrical product **3** in good to excellent regioselectivities. Only in the case of TMS-acetylene (entry 6) the regioselectivity was rather low. However, when internal unsymmetrical alkynes were used (entry 4 and 5) the regioselectivities were also high. Particularly, in entry 5 the unsymmetrical product was formed in an excellent 78 : 22 ratio taking into account that the catalyst system had to differentiate between a methyl and an ethyl substituent at 80 °C. Although the cyclotrimerisation reactions were conducted in acetonitrile as solvent the formation of pyridine derivatives could not be detected. This change in chemoselectivity is in contrast to other simple cobalt salts used previously for the synthesis of pyridine derivatives.[6]

The substantial change in reactivity of the cobalt complexes with respect to the previously described applications in Diels–Alder reactions with non-activated starting materials could be shown in a competitive experiment. When the CoBr$_2$(Cy-diimine) complex was reacted in acetonitrile at 20 °C with phenyl acetylene in the presence of an unhindered and reactive 1,3-diene such as isoprene the cyclotrimerisation products **1/2** were formed in 85% isolated yield accompanied by a small amount (4%) of the dihydroaromatic Diels–Alder adduct **5** (Scheme 3).



Scheme 3

However, in THF as solvent not only the products **1/2** and **5** were isolated in 25% and 47% yield, but also a regioisomerically pure 2 : 1 adduct (23%) which was identified as the cyclooctatriene derivative **6**.

In summary we have shown that the [2 + 2 + 2]-cyclotrimerisation of alkynes can be efficiently catalysed by a simple cobalt complex when properly activated in the right solvent to give either the symmetrical or the unsymmetrical regioisomer in good to excellent regio- and chemoselectivity and in high yields.

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