Remarkable Activation of an Alkyne [2+2+2]-Cycloaddition Catalyst, 2-Iminomethylpyridine (dipimp)/$CoCl_2·6H_2O$/Zn, by a Phthalate Additive

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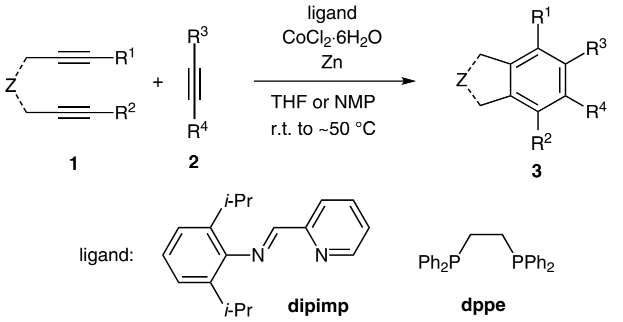
Received: 25.07.2012; Accepted after revision: 27.08.2012

Abstract: A catalyst for alkyne [2+2+2]-cycloaddition reactions, 2-(2,6-diisopropylphenyl)iminomethylpyridine (dipimp)/$CoCl_2·6H_2O$/Zn, can be effectively activated by addition of a catalytic amount of dialkyl phthalate to enable reactions that cannot proceed under unactivated conditions. The activation by adding phthalate was ligand- and solvent-dependent, and it was unique to dipimp and *N*-methyl-2-pyrrolidone (NMP). With use of diphosphine ligand instead of dipimp or with use of tetrahydrofuran (THF) instead of NMP, no activation by a phthalate additive was observed. This simple method of catalyst activation with use of inexpensive, commercially available compounds is highly practical and may find many applications.

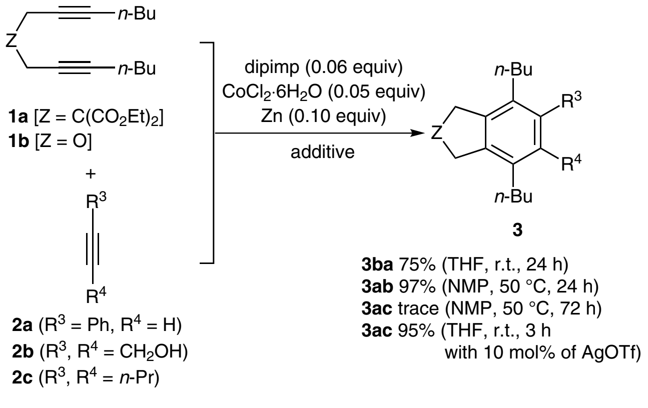
Key words: cycloaddition, homogeneous catalysis, alkynes, esters, ligands, phthalate, catalyst activation

The catalytic cycloaddition of alkynes in a [2+2+2] fashion provides a straightforward, atom-economical means of producing a variety of substituted benzenes.[1,2] We have recently developed a highly practical and user-friendly catalyst for alkyne cycloaddition, which can be generated on demand from stable, inexpensive cobalt salt and readily available ligand [2-(2,6-diisopropylpheny)imino-methylpyridine (dipimp) or 1,2-bis(diphenylphosphino)ethane (dppe)] by in situ reduction with commercial zinc powder (Scheme 1).[3–5] The new catalyst can perform cycloadditions of alkynes intramolecularly and intermolecularly to provide a variety of substituted benzenes, and it has been utilized in a controlled polymerization reaction to give linear polymers in a chain-growth fashion.[6]



Scheme 1 Cobalt-catalyzed alkyne cycloaddition

However, the synthesis of sterically demanding benzene derivatives with this catalyst sometimes requires a long reaction time, and unactivated simple aliphatic internal alkynes, such as 4-octyne, cannot be utilized as substrates **2**. For instance, the reaction of 1,6-diyne **1a** or **1b** with a terminal alkyne **2a** or an alkyne bearing a propargylic oxygen **2b** proceeded smoothly to yield the corresponding benzene derivatives in good yields, but the reaction with a simple aliphatic internal alkyne **2c** did not proceed at all with complete recovery of the substrates (Scheme 2).[3,5] To overcome this limitation, we have rationally designed and developed an efficient catalyst activation by addition of a catalytic amount of AgOTf, where an electron-deficient cationic Co(I) species could be generated. Although compound **3ac** could be prepared from **1a** and **2c** (2 equiv) in an excellent yield under mild reaction conditions with this activation,[7] it requires a rather expensive additive (AgOTf) compared with the intrinsic inexpensiveness of the initial catalyst system. Herein we report the finding that, instead of a silver salt, a catalytic amount of commercially available, low-cost 1,2-dicarbonyl compounds can act effectively as an activating agent for the catalysis. Specifically, dimethyl phthalate was found to be the optimum additive.



Scheme 2 Past results

In the course of our investigation on catalytic alkyne cycloadditions, we found that some carboxylic esters can activate the cycloaddition catalyst system (Table 1 and Figure 1). In the presence of dimethyl phthalate (**4a**) (15 mol%), the reaction of **1a** and **2c** (3 equiv) proceeded smoothly to provide **3ac** quantitatively in *N*-methyl-2-pyrrolidone (NMP) (run 2), while the absence of **4a** resulted in complete recovery of the substrates (run 1). The

SYNLETT 2012, 23, 2549–2553
Advanced online publication: 28.09.2012
DOI: 10.1055/s-0032-1317318; Art ID: ST-2012-U0625-L

amounts of the catalyst and additive could be reduced to 2 and 5 mol%, respectively, without loss of activity (run 3). It was found that this effect was ligand-dependent; either the absence of ligand or use of dppe instead of dipimp resulted in no production of **3ac** (runs 6 and 7). The solvent (NMP) was also important for this activation (run 2 vs. 5). Effects of other esters have been explored, and the results are shown in runs 8–20. Introducing a sterically demanding alkyl group to phthalate decreased the yield of **3ac** (runs 8 and 9). Aliphatic diesters **4e–g**, except for malonate **4d**, showed activation, with 1,6-dicarbonyl compound **4g** (adipate) being the most effective (runs 10–13). Similarly, the effect of 1,6-dicarbonyl compound **4k** was remarkable (run 17). However, without a ligand (dipimp), no activation with **4k** was observed (run 18). In addition, 1,4-diol **4j**, 1,4-diketone **4l**, and mellitic acid ester **4m** showed a certain degree of activation (runs 16, 19, 20). Interestingly, no activation effect was observed by the addition of terephthalate **4h** or benzoate **4i** (runs 14, 15). These results may suggest that the near presence of two oxygen functionalities of carbonyl or alcohol groups may be necessary for an effective activation of the catalysis. The activation could probably occur through coordination in a bidentate ligating fashion to the cobalt atom in an active catalytic species (*vide infra*).

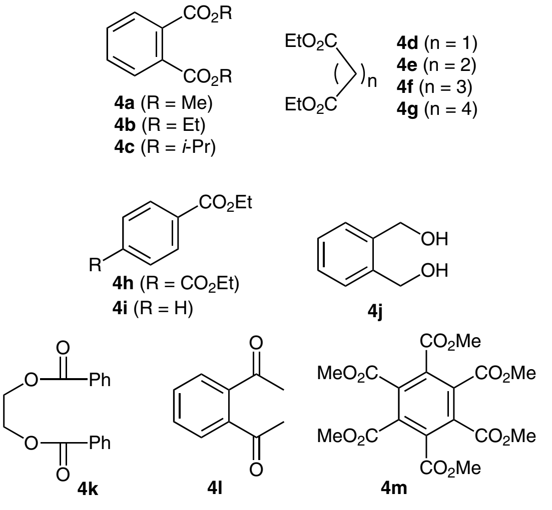


Figure 1 Dicarbonyl and diol additives

Table 2 summarizes the results of the reactions of other representative substrates. Runs 1–8 in Table 2 explore the generality and applicability of this activation by adding phthalate **4a** (15 mol%) (Scheme 3). Without an additive **4a**, production of **3cc** from **1c** and **2c** was slow because of its steric bulkiness (run 1), while addition of **4a** activated the catalysis to promote formation of **3cc** in 90% yield within 12 h. Similarly to the results of the reaction of **1a** and **2c** (runs 3 and 4), runs 5–8 show the effect of **4a** in achieving high yields of sterically demanding fully substituted benzenes **3ad** and **3dc**, products which could not be obtained under unactivated conditions.

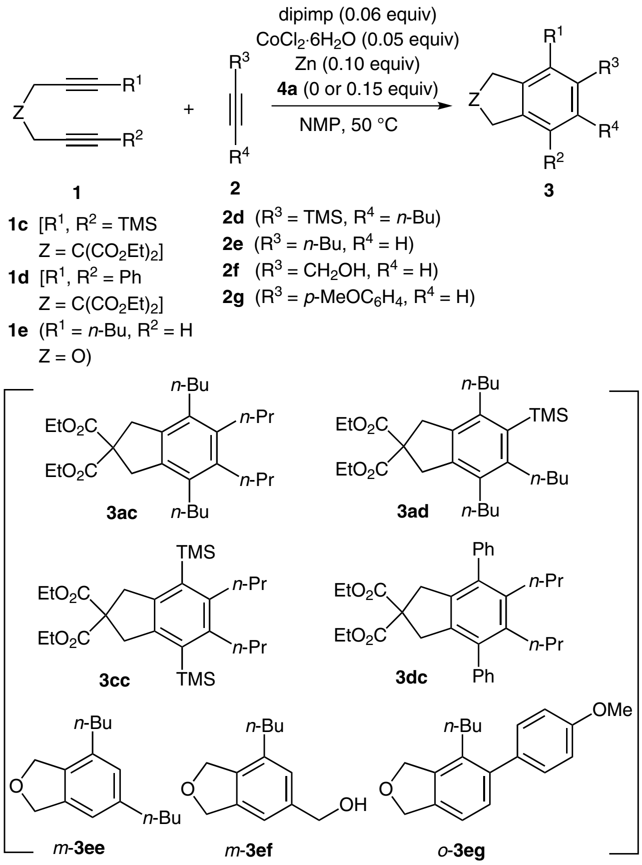
Table 1 Effect of Additives **4** in the Reaction of **1a** and **2c**[a]

Run	Ligand	Additive (0 or 15 mol%)	**3ac**[b]
1	dipimp	–	trace
2	dipimp	dimethyl phthalate (**4a**)	99%
3[c]	dipimp	**4a** [2% of catalyst]	91%
4[d]	dipimp	**4a** [1% of catalyst]	37%
5[e]	dipimp	**4a** [in THF]	11%
6	–	**4a**	trace
7	dppe	**4a**	trace
8	dipimp	diethyl phthalate (**4b**)	88%
9	dipimp	diisopropyl phthalate (**4c**)	15%
10	dipimp	diethyl malonate (**4d**)	trace
11	dipimp	diethyl succinate (**4e**)	14%
12	dipimp	diethyl glutarate (**4f**)	56%
13	dipimp	diethyl adipate (**4g**)	75%
14	dipimp	diethyl terephthalate (**4h**)	trace
15	dipimp	ethyl benzoate (**4i**)	trace
16	dipimp	1,2-phenylenedimethanol (**4j**)	43%
17	dipimp	ethane-1,2-diyl dibenzoate (**4k**)	86%
18	–	**4k**	trace
19	dipimp	1,1′-(1,2-phenylene)diethanone (**4l**)	22%
20	dipimp	hexamethyl benzene-1,2,3,4,5,6-hexacarboxylate (**4m**)	64%

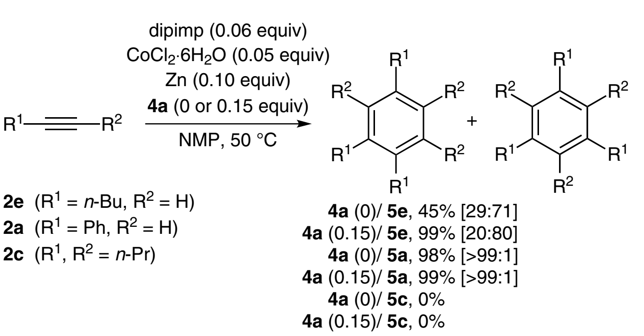
[a] Reaction conditions: **1a** (0.5 mmol), **2c** (1.5 mmol), dipimp or dppe (0 or 6 mol%), $CoCl_2·6H_2O$ (5 mol%), additive (0 or 15 mol%), Zn powder (10 mol%), NMP (2.0 mL), 50 °C, 24 h.
[b] Determined by ^1H NMR analysis using 4-*tert*-butyltoluene as an internal standard.
[c] **1a**/**2c**/$CoCl_2·6H_2O$/dipimp/**4a**/Zn (0.5/1.5/0.01/0.012/0.025/0.05 mmol) in NMP (0.8 mL).
[d] **1a**/**2c**/$CoCl_2·6H_2O$/dipimp/**4a**/Zn (0.5/1.5/0.005/0.006/0.025/0.05 mmol) in NMP (0.4 mL).
[e] The reaction was performed in THF instead of NMP.

As shown in runs 9–15 in Table 2, the regioselectivity of the partially intramolecular reaction of unsymmetrical diynes and alkynes was not greatly affected by the addition of phthalate **4a** as well as more sterically demanding **4c** (run 13). Similarly, in the fully intermolecular reactions of 1-alkynes such as **2a** and **2e**, the additive had very little impact on the regioselectivity (Scheme 4).

Although the cyclotrimerization of simple internal aliphatic alkynes such as **2c** unfortunately did not proceed at all even in the presence of **4a** (Scheme 4),[8] it can also be said that this may contribute to high yields of cross-adducts such as **3ac**, **3cc** and **3dc** from **2c** and 1,6-diynes by



Scheme 3 Partially intramolecular reactions



Scheme 4 Fully intermolecular reactions

a clean reaction without a competitive self-trimerization of **2c** (Scheme 3 and Table 2).

Scheme 5 illustrates the reaction of tetrayne **6** with 2-butyn-1,4-diol (6 equiv), a double cycloaddition to give biphenyl compound **7**. The reaction without additive **4a** (in THF) successfully gave **7** in 93% yield, but the reaction required as long as three days for completion.[4] The addition of phthalate **4a** activated the catalysis to enable high yields of **7** (98% yield) with a much reduced reaction time (3 h).

Table 2 Reaction in the Presence of Additive **4a**[a]

Run	**1**	**2**	**4a**[b]	h	**3** Yield[c] [*o*-/*m*-][d]
1	**1c**	**2c**	–	24	**3cc** (50%)[e]
2	**1c**	**2c**	+	≤12	**3cc** 90%
3	**1a**	**2c**	–	48	**3ac** trace
4	**1a**	**2c**	+	≤12	**3ac** 96%
5	**1a**	**2d**	–	≤12	**3ad** trace
6	**1a**	**2d**	+	≤12	**3ad** 91%
7	**1d**	**2c**	–	48	**3dc** trace
8	**1d**	**2c**	+	12	**3dc** 83%
9	**1e**	**2e**	–	12	**3ee** 68% [14:86]
10	**1e**	**2e**	+	12	**3ee** 70% [25:75]
11	**1e**	**2f**	–	12	**3ef** 80% [38:62]
12	**1e**	**2f**	+	12	**3ef** 77% [26:74]
13[f]	**1e**	**2f**	+	12	**3ef** 65% [34:66]
14	**1e**	**2g**	–	12	**3eg** 31% [>99:<1]
15	**1e**	**2g**	+	12	**3eg** 51% [>99:<1]

[a] **1**/**2**/$CoCl_2·6H_2O$/dipimp/**4a**/Zn (0.5/1.5/0.05/0.06/0 or 0.075/0.05 mmol) in NMP (2.0 mL) at 50 °C.

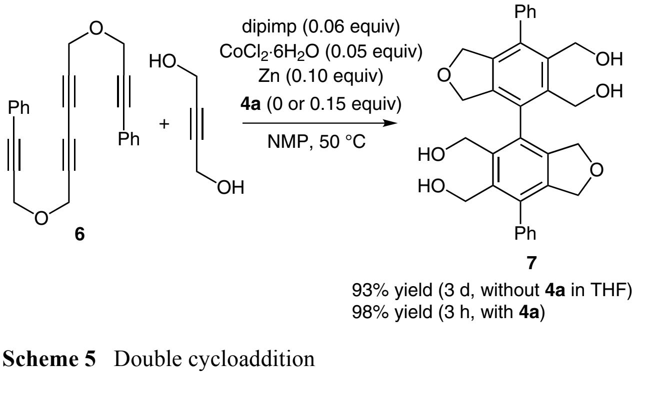
[b] +: 15 mol% of **4a**, –: no additive.

[c] Isolated yield.

[d] Determined by ^1H NMR analysis.

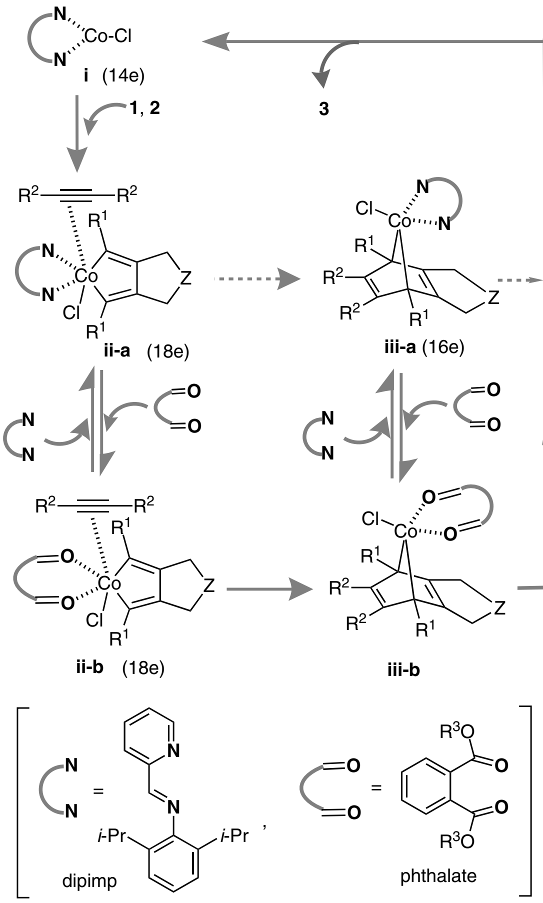
[e] ^1H NMR yield measured with use of 4-*tert*-butyltoluene as an internal standard.

[f] 15 mol% of **4c** was used instead of **4a**.



Scheme 5 Double cycloaddition

We postulate that the dipimp/$CoCl_2·6H_2O$/Zn-catalyzed benzene-formation reaction might proceed through a (dipimp)Co^ICl complex **i** generated by the reduction of (dipimp)$CoCl_2$ with zinc; this complex could react with diynes to provide cobaltacyclopentadiene intermediate **ii**, which is formally an 18-electron complex with coordination of a mono-alkyne substrate (Scheme 6). The aforementioned structure-activating efficiency relationship of (di)carbonyl additives suggests that phthalates such as **4a** may act as a bidentate-ligating agent. Based on these considerations, we propose that the phthalate-ligated complex (alkyne)–(phthalate)Co^{I}Cl (**ii-b**) may be present in the equilibrium with (alkyne)–(dipimp)Co^{I}Cl (**ii-a**) by the ligand-exchange reaction. The complex **ii-b** may have a more electron-deficient nature by coordination of weaker Lewis base and may be much more reactive than **ii-a**. Confirmation of the more detailed mechanism must await further study.



Scheme 6 Proposed mechanism

In summary, we found that the addition of a catalytic amount of dicarbonyl or diol compounds can greatly activate the alkyne [2+2+2]-cycloaddition catalyst, dipimp/$CoCl_2 \cdot 6H_2O$/Zn (in NMP), to enable a high yields of sterically demanding hexa-substituted benzenes from unactivated simple aliphatic internal alkynes. Among additives investigated, dimethyl phthalate was found to be the most effective. This simple method of catalyst activation with use of inexpensive, commercially available compounds is highly practical and may find application in the laboratory as well as in industry.

Typical Procedure for the Cycloaddition of Diynes 1 and Alkyne 2 Catalyzed by a dipimp/$CoCl_2 \cdot 6H_2O$/Zn Reagent with a Phthalate Activator: To a mixture of dimethyl phthalate (14.6 mg, 0.075 mmol), zinc powder (3.3 mg, 0.05 mmol), 1,6-diyne **1a** (174 mg, 0.5 mmol), and 4-octyne **2c** (0.23 mL, 1.5 mmol) in NMP (1.0 mL) was added a solution of $CoCl_2 \cdot 6H_2O$ (6.0 mg 0.025 mmol) and dipimp (8.0 mg, 0.03 mmol) in NMP (1.0 mL). The mixture was stirred at 50 °C. After addition of saturated aq NH_4Cl, the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered through a pad of Celite and concentrated in vacuo to give a crude mixture, which was analyzed by ^1H NMR. The residue was purified by column chromatography on silica gel to afford the substituted benzene **3ac** (220 mg, 96% yield).

Acknowledgement

We thank the Scientific Frontier Research Project of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan for financial support. We also thank the Japan Society for the Promotion of Science (JSPS) for a grant to Y.S.

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