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# A Highly Practical *Instant* Catalyst for Cyclotrimerization of Alkynes to Substituted Benzenes

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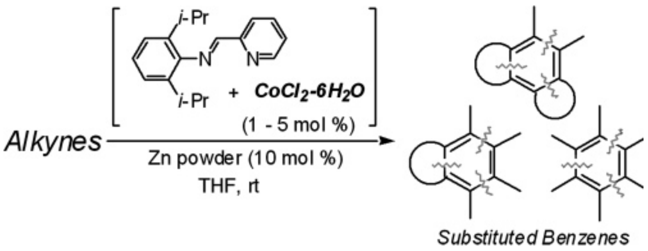
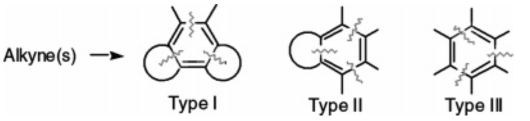
## ABSTRACT



**A 2-(2,6-diisopropylphenyl)iminomethylpyridine (1a)/$CoCl_2 \cdot 6H_2O$/Zn reagent has been developed as an effective *instant* catalyst for the intra- and intermolecular cyclotrimerization of alkynes to substituted benzenes, making the method extremely practical since the reagent, 1a/$CoCl_2 \cdot 6H_2O$/Zn, is inexpensive and easy to handle and the reaction is less sensitive to moisture and is reasonably general.**

Cyclotrimerization of alkynes,[1,2] which can be classified into three types, i.e., an intramolecular reaction (type I, Scheme 1) and two intermolecular reactions (types II and III), continues to attract considerable attention by virtue of its intrinsic atom economy,[3] as well as the importance of substituted and annulated benzenes as synthetic intermediates. After the pioneering work of Reppe,[1] complexes of many transition metals have been developed as effective catalysts or precursors for the transformation.

**Scheme 1**



Among them, CpCoL complexes (Cp = cyclopentadienyl) involving $CpCo(CO)_2$, CpCo(alkene)$_2$, and $CpCo(PPh_3)_2$ have been used most widely,[4] where the nature of ligand L influences the starting behavior of the catalyst: too effective stabilization retards initiation of the catalyst, while, with too weak stabilizing ligand(s), the complex tends to undergo decomposition reactions. To avoid the difficulty and waste associated with isolation and initiation of the catalyst, efforts

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(1) Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann.* **1948**, *560*, 104.

(2) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 741. Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 1129. Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. Malacria, M.; Aubert, C.; Renaud, J. L. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Lautens, M., Trost, B. M., Eds.; Georg Thieme Verlag: Stuttgart, 2001; Vol. 1, pp 439−530.

(3) Trost, B. M. *Science* **1991**, *254*, 1471. Trost. B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(4) Chang, C. A.; Francisco, C. G.; Gadek, T. R.; King, J. J. A.; Sternberg, E. D.; Vollhardt, K. P. C. In *Organic Synthesis Today and Tomorrow*; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon Press: Oxford, 1981; pp 71−83. Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 536. Vollhardt, K. P. C. *Pure Appl. Chem.* **1985**, *57*, 1819. Vollhardt, K. P. C. *Pure Appl. Chem.* **1993**, *65*, 153. Eickmeier, C.; Holmes, D.; Junga, H.; Matzger, A. J.; Scherhag, F.; Shim, M.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 800. Aubert, C.; Buisine, O.; Petit, M.; Slowinski, F.; Malacria, M. *Pure Appl. Chem.* **1999**, *71*, 1463. Slowinski, F.; Aubert, C.; Malacria, *J. Org. Chem.* **2003**, *68*, 378 and references cited therein.

10.1021/ol0602295 CCC: $33.50

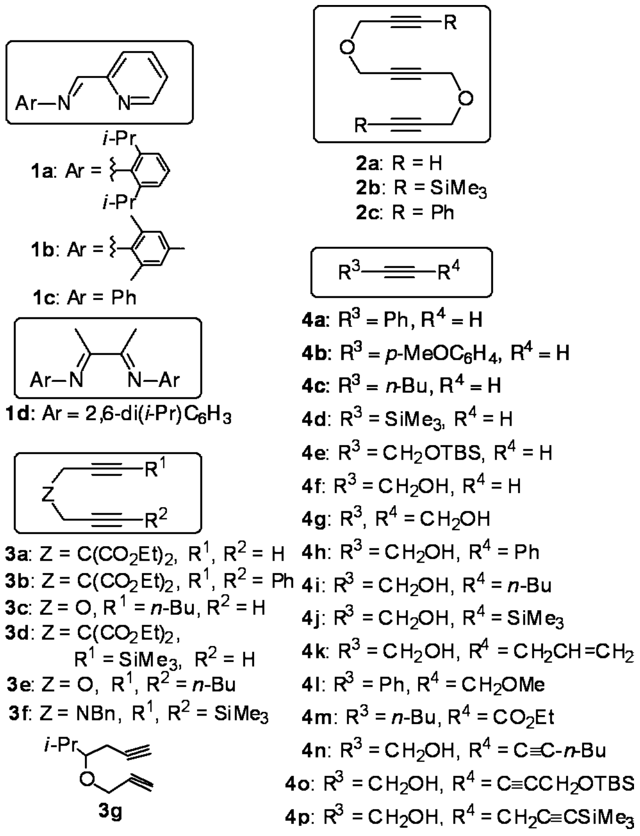

**Figure 1.**

have recently been made to generate an active catalyst in situ by reduction of cobalt (II) halides in the presence of substrate(s). This "instant" protocol requires a weak and minimal amount of stabilizing ligand(s), and therefore, the catalyst can be initiated under milder conditions and can be expected to exhibit high reactivity. Regarding such concept, Boennemann et al. reported a $CoCl_2\cdot6H_2O/NaBH_4$ reagent as a catalyst system for intermolecular reaction (type III).[5] $CoCl_2/Mn$ and $CoI_2/PPh_3/Mn$ have been developed as a catalyst system for the intramolecular reaction (type I) by Chiusoli et al.[6] and Malacria et al.,[7] respectively. We have introduced a $CoCl_2$/imidazolium carbene/Zn reagent for the reaction of type I.[8] Most recently, Hilt et al. have described that a $CoBr_2/2PR_3$, disulfide, or diimine/$Zn/ZnI_2$ reagent can effectively catalyze intermolecular cyclotrimerization of alkynes.[9] However, it is somewhat surprising that no reaction has been investigated for partially intramolecular reactions (type II),[10,11] which are synthetically useful as can be seen in applications to synthesis of complex molecules[2,4] and have often been used as a benchmark reaction to evaluate the synthetic potential of the method.

In this context, we wished to focus our investigation on utilization of a stable cobalt salt, $CoCl_2\cdot6H_2O$, for the instant generation of a catalyst, aiming to develop a user-friendly and environmentally benign method at low cost. We introduced 2-(2,6-diisopropylphenyl)iminomethylpyridine (**1a**)[12] as a ligand into a $CoCl_2\cdot6H_2O$/Zn system and found that this inexpensive, easily handled combination reagent, **1a**/$CoCl_2$-$6H_2O$/Zn, is an effective catalyst to perform the reaction of types I−III with unique chemo- and regioselectivity (see Figure 1 for the ligands and substrates employed in the present study).

The results in Table 1 show the feasibility of a **1a**/$CoCl_2\cdot6H_2O$/Zn reagent for the partially intramolecular reactions of type II. Thus, to a mixture of diyne **3a** and alkyne **4a** (1.3 equiv) and zinc dust (10 mol %) in THF was added a solution of a ligand and $CoCl_2\cdot6H_2O$ in THF.[13] After being stirred for 5 min at 35−40 °C, the mixture was stirred at room temperature (∼25 °C). As revealed in Table 1, although the reaction without a ligand and that with $PPh_3$, TMEDA, 2,2′-bipyridinyl, or 1,2-diimine **1d** did not afford benzene derivative **5aa** at all (entries 1, 2, 5, 6, and 7), the reaction with dppe (entry 3) or 2-iminomethylpyridine **1a** (entry 8) proceeded smoothly to provide **5aa** quantitatively. The results of the reactions with use of 2-iminomethylpyridines as a ligand (entries 8−18) revealed the following characteristics: Use of less bulky ligand **1b** instead of **1a** was not effective (entry 13).[14] Interestingly, use of 2 equiv of **1a** to $CoCl_2\cdot6H_2O$ did not work (entry 9).[15] The amount of catalyst precursor could be reduced to 1 mol %, although a higher temperature (∼40 °C) was applied to complete the reaction in a reasonable amount of time (entry 10). Anhydrous $CoCl_2$ could be used as well as its hydrate (entry 11). The reaction is less sensitive to moisture so that it could proceed in aqueous THF [THF/$H_2O$ = 40/1 (v/v)] (entry 12). The reaction with arylacetylene such as **4a** and **4b** proceeded

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(5) Boennemann, H.; Brinkmann, R.; Schenkluhn, H. *Synthesis* **1974**, 575.

(6) Chiusoli, G. P.; Costa, M.; Reverberi, S.; Terenghi, M. G. *Transition Met. Chem.* **1989**, *14*, 238. Chiusoli, G. P.; Terenghi, G. *Transition Met. Chem.* **1984**, *9*, 360.

(7) Slowinski, F.; Aubert, C.; Malacria, M. *Adv. Synth. Catal.* **2001**, *343*, 64.

(8) Saino, N.; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065.

(9) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474. Hilt, G.; Hess, W.; Vogler, T.; Hengst, C. *J. Organomet. Chem.* **2005**, *690*, 5170.

(10) For the related *instant* procedures for Co-catalyzed Diels−Alder, homo-Diels−Alder, pyridine formation, and allene−diyne−[2 + 2 + 2] cycloaddition reactions, see: $Co(acac)_n$/dppe/$Et_2AlCl$: Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863. Lyons, J. E.; Myers, H. K.; Schneider, A. *J. Chem. Soc., Chem. Commun.* **1978**, 636. $CoX_2$(dppe)/Zn/$ZnI_2$: Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* **2005**, *7*, 2353. Hilt, G.; Galbiati, F. *Synlett* **2005**, 829. Hilt, G.; Lueers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624. $CoX_2(PR_3)_2$/Zn: Wu, M.-S.; Rayabarapu, D. K.; Cheng, C.-H. *Tetrahedron* **2004**, *60*, 10005. Wu, M.-S.; Shanmugasundaram, M.; Cheng, C.-H. *Chem. Commun.* **2003**, 718. Pardigon, O.; Tenaglia, A.; Buono, G. *J. Org. Chem.* **1995**, *60*, 1868. Duan, I. F.; Cheng, C. H.; Shaw, J. S.; Cheng, S. S.; Liou, K. F. *J. Chem. Soc., Chem. Commun.* **1991**, 1347.

(11) A $NiBr_2$(dppe)/Zn system has been reported for the alkyne-cyclotrimerization: Turek, P.; Kotora, M.; Tislerová, I.; Hocek, M.; Votruba, I.; Císarová, I. *J. Org. Chem.* **2004**, *69*, 9224 and cited therein.

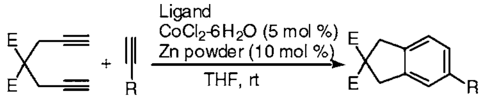
(12) Prepared from commercially available 2,6-diisopropylaniline and pyridine-2-carboxaldehyde. For the results of the reactions with related ligands other than **1a**, see the Supporting Information.

(13) The solution prepared by simply mixing **1** and $CoCl_2\cdot6H_2O$ in THF could be stored at room temperature for more than 1 month under Ar.

(14) Probably generated less hindered species, **1b**·CoCl or **1c**·CoCl, by reduction with Zn would be unstable and may decompose and/or precipitate via the reactions such as dimerization and disproportionation.

(15) Presumably due to generation of stable $(\mathbf{1a})_2CoCl$ (formal 18-electron complex), which would not form a metallacyclopentadiene intermediate.

**Table 1.** Type II Reactions with Various Ligands[a]



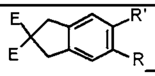
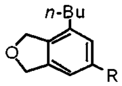
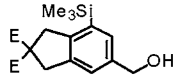
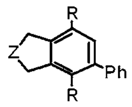
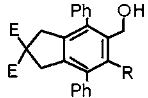
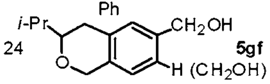
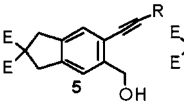
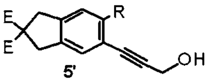
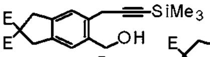
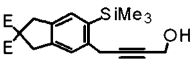
**3a** **4**
[E = $CO_2Et$]

**5aa**: R = Ph
**5ab**: R = *p*-$MeOC_6H_4$
**5ac**: R = *n*-Bu
**5ad**: R = $SiMe_3$
**5af**: R = $CH_2OH$

| entry | ligand (mol %) | **4** (equiv) | conditions | yield, %[b] |
|---|---|---|---|---|
| 1 | none | **4a** (1.3) | 24 h | **5aa** trace |
| 2 | $PPh_3$ (10) | **4a** (1.3) | 24 h | **5aa** trace |
| 3 | $Ph_2P(CH_2)_2PPh_2$ [dppe] (6) | **4a** (1.3) | 24 h | **5aa** ~100 |
| 4 | $Ph_2P(CH_2)_4PPh_2$ [dppb] (6) | **4a** (1.3) | 24 h | **5aa** 17 |
| 5 | $Me_2N(CH_2)_2NMe_2$ [TMEDA] (6) | **4a** (1.3) | 24 h | **5aa** trace |
| 6 | 2,2'-bipyridinyl (6) | **4a** (1.3) | 24 h | **5aa** trace |
| 7 | **1d** (6) | **4a** (1.3) | 24 h | **5aa** trace |
| 8 | **1a** (6) | **4a** (1.3) | 4 h | **5aa** ~100 (91)[c] |
| 9 | **1a** (12) | **4a** (1.3) | 24 h | **5aa** trace |
| 10 | **1a** (1.2) | **4a** (1.3) | $CoCl_2$-$6H_2O$ (1.0 mol %), 40 °C, 24 h | **5aa** (89)[c] |
| 11 | **1a** (6) | **4a** (1.3) | anhydrous $CoCl_2$, 4 h | **5aa** (90)[c] |
| 12 | **1a** (6) | **4a** (1.3) | in THF/$H_2O$ (40/1), 4 h | **5aa** (92)[c] |
| 13 | **1b** (6) | **4a** (1.3) | 24 h | **5aa** trace |
| 14 | **1a** (6) | **4b** (1.3) | 4 h | **5ab** (92)[c] |
| 15 | **1a** (6) | **4c** (1.0) | 4 h | **5ac** (37)[c] |
| 16 | **1a** (6) | **4c** (3.0) | 4 h | **5ac** (63)[c] |
| 17 | **1a** (6) | **4d** (3.0) | 4 h | **5ad** (83)[c] |
| 18 | **1a** (6) | **4f** (3.0) | 4 h | **5af** (96)[c] |

[a] Conditions: **3a** (1.0 mmol), **4** (1.3 or 3.0 mmol), ligand, $CoCl_2 \cdot 6H_2O$ or $CoCl_2$ (5 mol %), Zn dust (10 mol %), solvent(s) (4 mL). Reactions were performed at room temperature (~25 °C) after 5 min of stirring at 35−40 °C. [b] Unless otherwise indicated, $^1H$ NMR yield. [c] Isolated yield.

**Table 2.** Representative Examples of Type II Reaction[a]

| entry | 3 | **4** (equiv) | t, h | product(s) | | | yield[b] (ratio)[c] |
|---|---|---|---|---|---|---|---|
| | | | |  (E = $CO_2Et$) | R | R' | |
| 1 | **3a** | **4g** (3) | 8 | **5ag** | $CH_2OH$ | $CH_2OH$ | 83% |
| 2 | **3a** | **4h** (3) | 4 | **5ah** | Ph | $CH_2OH$ | 91% |
| 3 | **3a** | **4i** (3) | 12 | **5ai** | *n*-Bu | $CH_2OH$ | 80% |
| 4 | **3a** | **4j** (3) | 12 | **5aj** | $SiMe_3$ | $CH_2OH$ | 98% |
| 5 | **3a** | **4k** (3) | 8 | **5ak** | $CH_2CH=CH_2$ | $CH_2OH$ | 73% |
| 6 | **3a** | **4l** (3) | 8 | **5al** | Ph | $CH_2OMe$ | 87% |
| 7 | **3a** | **4m** (3) | 8 | **5am** | *n*-Bu | $CO_2Et$ | 94% |
| | | | |  | R | | |
| 8 | **3c** | **4c** (3) | 4 | **5cc** | *n*-Bu | | 52% (76:24)[d] |
| 9 | **3c** | **4f** (3) | 4 | **5cf** | $CH_2OH$ | | 74% (71:29)[d] |
| 10 | **3c** | **4b** (1.3) | 2 | **5cb** | *p*-$MeOC_6H_4$ | | 48% (1:99)[e] |
| 11 | **3d** | **4f** (3) | 8 |  **5df** | | | 83% (85 : 15)[d] |
| | | | |  | Z | R | |
| 12 | **3b** | **4a** (1.3) | 8 | **5ba** | $C(CO_2Et)_2$ | Ph | 99% |
| 13 | **3e** | **4a** (1.3) | 24 | **5ea** | O | *n*-Bu | 75% |
| 14 | **3f** | **4a** (1.3) | 2 | **5fa** | BnN | $SiMe_3$ | 98% |
| | | | |  | | | |
| 15 | **3b** | **4g** (1.3) | 8 | **5bg** | R = $CH_2OH$ | | 90% |
| 16 | **3b** | **4h** (1.3) | 8 | **5bh** | R = Ph | | 95% |
| 17 | **3g** | **4f** (3) | 24 |  **5gf** | | | 68% (1 : 1) |
| | | | |  **5**  **5'** | | | |
| 18 | **3a** | **4n** (1.3) | 24 | R = *n*-Bu | **5an**:**5'an** = 87:13 | | 85% |
| 19 | **3a** | **4o** (1.3) | 24 | R = $CH_2OTBS$ | **5ao**:**5'ao** = 82:18 | | 94% |
| 20 | **3a** | **4p** (1.3) | 24 |  **5**  **5'** | **5ap**:**5'ap** = 82 : 18 | | 80% |

[a] Conditions: **3** (1.0 mmol), **4** (1.3 or 3.0 mmol), **1a** (6 mol %), $CoCl_2 \cdot 6H_2O$ (5 mol %), Zn dust (10 mol %), THF (4 mL). Reactions were performed at room temperature (~25 °C) after 5 min of stirring at 35−40 °C. [b] Isolated yield or yield of a mixture of regioisomers. [c] Regioisomeric ratio. [d] Meta isomer was major. [e] Ortho isomer was major.

selectively to give the corresponding **5** even with use of a nearly stoichiometric amount of **4** (entries 8, 10−12, 14). On the other hand, a 1:1 mixture of diyne **3a** and alkylacetylene **4c** provided 37% of product **5ac** with formation of dimerization product(s) derived from **3a** (total 24%, for the structures, see the Supporting Information) (entry 15). An increase of the amount of **4c** improved the yield of **5** to a synthetically useful level (entry 16). Under similar conditions, **5ad** and **5af** were obtained in good yield (entries 17 and 18).

As revealed from Table 2, summarizing other representative examples of the **1a**/$CoCl_2 \cdot 6H_2O$/Zn-catalyzed intermolecular reaction of type II, a variety of 1,6- and 1,7-diynes could couple with various alkynes **4** to provide the corresponding tetra-, penta-, and hexasubstituted benzenes in good to excellent yields, where high functional group compatibility was attained and the formation of heterocyclic compounds as well as carbocyclic ones proceeded smoothly. It was noteworthy that the reactions of unsymmetrical diynes **3c** and **3d** with terminal alkynes proceeded regioselectively and the reaction with alkyl or aryl acetylenes showed an opposite regioselectivity (entries 8−11).[16] Although simple internal alkynes such as 4-octyne did not couple with diynes **3** (data not shown), internal alkynes having an oxygen atom attached to the propargyl carbon(s) such as propargyl alcohols **4g**−**k** (entries 1−5), propargyl ether **4l** (entry 6), and α,*β*-acetylenic ester **4m** (entry 7) were good substrates.[17] This feature enables the chemoselective reaction of poly-ynes: the reaction of diynes **4n**−**p** with **3a** proceeded selectively at the propargyl alcohol moiety to yield benzyl alcohols with an alkyne substitution (entries 18−20).[17,18]

Table 3 summarizes the results of the intermolecular reaction (type III)[5,9] with a **1a**/$CoCl_2 \cdot 6H_2O$/Zn. The reagent catalyzed effectively the reaction of 1-alkynes to yield 1,2,4-trisubstituted benzenes **6** selectively or exclusively (entries

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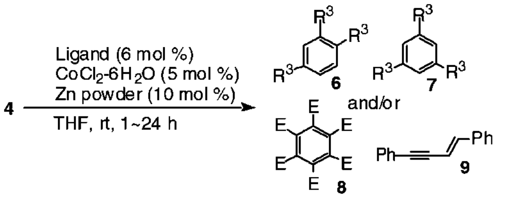
(16) Regioselectivity in catalytic cyclotrimerization reactions has been well-documented: Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143.

(17) For a directing effect with a hydroxyl group, see: Witulski, B.; Stengel, T.; Fernández-Hernández, J. M. *Chem. Commun.* **2000**, 1965 and references therein.

(18) Ni-catalyzed selective reaction of 1,4-disubstituted 1,3-diynes has been reported: Jeevanandam, A.; Korivi, R. P.; Huang, I.; Cheng, C. *Org. Lett.* **2002**, *5*, 807.

**Table 3.** Type III Reactions[a]



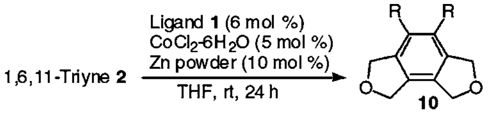
| entry | 4 | ligand | product(s) | yield, %[b] |
|---|---|---|---|---|
| 1 | **4a** | **1a** (6) | **6a** + **7a** (>99 : 1) | 91 |
| 2 | **4c** | **1a** (6) | **6c** + **7c** (63 : 37) | 72 |
| 3 | **4e** | **1a** (6) | **6e** + **7e** (60 : 40) | 88 |
| 4 | 4-octyne | **1a** (6) | no reaction | |
| 5 | $E{-}C{\equiv}C{-}E$ ( $E = CO_2Me$) | **1a** (6) | **8** | 98 |
| 6 | **4a** | dppe (6) | **9** | 64[c] |

[a] Conditions: **4** (1.0 mmol), ligand, $CoCl_2{\cdot}6H_2O$ (5 mol %), Zn dust (10 mol %), solvent(s) (4 mL). Reactions were performed at room temperature (~25 °C) after 5 min of stirring at 35−40 m °C. [b] Unless otherwise indicated, isolated (total) yield. [c] $^1H$ NMR yield.

1−3). 4-Octyne could not be trimerized at all (entry 4) but but-2-ynedioic acid dimethyl ester was quickly trimerized to **8** quantitatively (entry 5). As can be seen in entry 6, dppe/$CoCl_2{\cdot}6H_2O$/Zn catalyst could not be used for cyclotrimerization of type III, where the reaction provided enyne **9** mainly, although dppe and 2-iminomethylpyridine **1a** could equally be utilized for the reactions of type II as mentioned above. Similar results to entry 6 have been reported by Hilt et al., who have pointed out that addition of $ZnI_2$ to a $CoBr_2$/$2PR_3$, disulfide, or diimine/Zn system is important to perform the cyclotrimerization of alkynes. However, the catalyst **1a**/$CoCl_2{\cdot}6H_2O$/Zn developed here could work without any additive.

Finally, we applied the present method to an intramolecular reaction (type I)[6−8] (Table 4). As shown in entry 1, intramolecular cyclotrimerization of triyne **2a** in a 0.25 M (1.0 mmol of **2a** in 4 mL of THF) solution provided annulated benzene **10a** in 62% yield, but intermolecular-coupled compounds were coproduced. With lower concentration (0.025 M), the yield of **10a** was improved to 93% (entry 2). The reaction of triynes having no terminal alkyne moiety such as **2b** and **2c** could be converted to the corresponding **10** in good to excellent yield even under high concentration conditions (entries 4 and 5). It was observed again that use of less bulky ligand **1c** instead of **1a** was not effective (entry 3).[14]

**Table 4.** Type I Reactions[a]



| entry | R | ligand | conditions | isolated yield, % | |
|---|---|---|---|---|---|
| 1 | H | **1a** | 4 h | **10a** | 62 |
| 2[b] | H | **1a** | in 0.025M solution, 24 h | **10a** | 93 |
| 3 | H | **1c** | r.t., 24 h then 50 °C, 24 h | **10a** | trace |
| 4 | $SiMe_3$ | **1a** | 8 h | **10b** | 97 |
| 5 | Ph | **1a** | 12 h | **10c** | 82 |

[a] Conditions: **2** (1.0 mmol), **1** (6 mol %), $CoCl_2{\cdot}6H_2O$ (5 mol %), Zn dust (10 mol %), THF (4 mL)/0.25 M solution. Reactions were performed at room temperature (~25 °C) after 5 min stirring at 35−40 °C. [b] Carried out in a 0.025 M solution (40 mL of THF) for 36 h.

In conclusion, we have developed a new cobalt-based *instant* catalyst, **1a**/$CoCl_2{\cdot}6H_2O$/Zn, for alkyne cycloisomerization of types I−III.[19] The method is extremely practical since it is inexpensive, easy to handle, less sensitive to moisture, and reasonably general, where unique regio- and chemoselectivities were observed.

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**Supporting Information Available:** Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Although confirmation of the reaction mechanism must await further study, based on those proposed for the reported metal-catalyzed reactions we postulate that the reaction might proceed via a Co(I)−Co(III) catlytic cycle, involving formation of metallacyclopentadiene followed by insertion or cycloaddition of alkyne and reductive elimination reaction. Further investigation is underway in our laboratory.