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Highly regio- and chemoselective [2 + 2 + 2] cycloaddition of 1,6-heptadiynes with allenes catalyzed by cobalt complexes†

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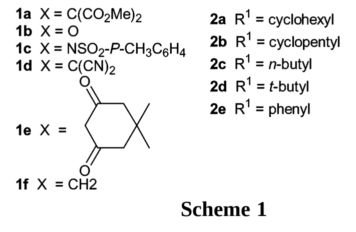
The $CoI_2(PPh_3)_2$/Zn system effectively catalyzes the [2 + 2 + 2] ene–diyne cycloaddition of 1,6-heptadiynes with allenes in a highly regio- and chemoselective fashion to yield substituted benzene derivatives in good to excellent yields.

The transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes is a powerful method for the construction of polysubstituted benzene derivatives.[1] Intermolecular cycloaddition of alkynes with alkenes provides a convenient alternative route for the synthesis of substituted benzenes, but this type of cycloaddition requires the use of electron-deficient alkynes with neutral alkenes[2] or neutral alkynes with electron-deficient alkenes.[3] The [2 + 2 + 2] cycloaddition of an electronically neutral diyne with a neutral alkene remains a great challenge to the organic chemist.[4] Recently, we reported a highly regio- and chemoselective [2 + 2 + 2] cycloaddition of electron-deficient diynes with allenes catalyzed by the Ni(dppe)Br_2/Zn system.[5] However, the diynes used were limited to those that contain at least a $-CO_2Me$ group attached to the terminal alkyne carbon. Our continued interest in metal-mediated cycloaddition chemistry[6] prompted us to search for an effective catalyst for the reaction of electronically neutral diynes with allenes. In this communication, we report the first example of highly regio- and chemoselective [2 + 2 + 2] cycloaddition of electronically neutral 1,6-heptadiynes with allenes catalyzed by cobalt complexes leading to polysubstituted benzene derivatives in good to excellent yields.

Treatment of dimethyl dipropargylmalonate **1a** with cyclohexylallene **2a** in the presence of $CoI_2(PPh_3)_2$ (5.00 mol%) and zinc powder (2.75 equiv.) in 1,2-dichloroethane at 80 °C for 8 h gave a 2,2-indene dicarboxylate derivative **4a** in 95% yield (Scheme 1). The reaction is believed to proceed *via* a [2 + 2 + 2] cycloaddition of **1a** with **2a** to form a cyclohexadiene intermediate **3a**, followed by isomerization to furnish the final substituted benzene derivative **4a**. No competitive dimerization and trimerization product of diyne **1a** was detected under these conditions as evidenced by the ^{1}H NMR spectrum of the crude reaction mixture. Control experiments indicated that in the absence of $CoI_2(PPh_3)_2$ or zinc powder, no reaction occurred.

To understand the nature of the catalytic reaction, the activities of various cobalt systems in 1,2-dichloroethane for the [2 + 2 + 2] cycloaddition of **1a** with **2a** were examined. In the presence of extra PPh_3, the catalytic reaction is strongly retarded. For example, the addition of 2 or 8 equiv. of PPh_3 relative to $CoI_2(PPh_3)_2$ to the catalytic solution reduced the yield of **4a** to 33 and 12%, respectively. The use of simple CoI_2 and Zn powder gave **4a** in 23% yield. Several bidentate phosphine complexes in the presence of Zn powder were also tested for their catalytic activities. CoI_2(dppe) gave **4a** in a moderate yield of 60%. Other bidentate phosphine complexes such as CoI_2(dppm), CoI_2(dppp), and CoI_2(dppb) were less effective, giving **4a** in less than 5% yield. A brief examination of the effect of solvent on the yield of **4a** using $CoI_2(PPh_3)_2$/Zn as the catalyst revealed that 1,2-dichloroethane was the solvent of choice. In the presence of THF, CH_3CN or DMF, the reaction was less efficient affording **4a** in 9, 23 and 30% yields respectively, whereas in toluene no cycloaddition occurred.



Scheme 1

The results for the $CoI_2(PPh_3)_2$/Zn system catalyzed [2 + 2 + 2] cycloaddition of various 1,6-heptadiynes **1a–f** with allenes **2a–e** are compiled in Table 1. The reaction of **1a** with cyclopentylallene **2b**, *n*-butylallene **2c**, *t*-butylallene **2d** and phenylallene **2e** afforded the corresponding cycloadducts **4b–e** in 71, 88, 88 and 62% yields, respectively (entries 2–5). Under similar reaction conditions, diyne **1b** having an ether linkage readily reacts with cyclohexylallene **2a** to afford isobenzofuran derivative **4f** in 84% yield (entry 6). The nitrogen containing diyne **1c** also undergoes cycloaddition with **2a** and **2d** to afford isoindole derivatives **4g** and **4h** in 79 and 75% yields, respectively (entries 7 and 8). Similarly, treatment of **1d** with **2a** afforded 2,2-indene dicarbonitrile **4i** in moderate yield (entry 9). Notably, reactions of **1e** with **2a** and **2c** under similar conditions proceeded smoothly to afford spiro compounds **4j** and **4k** in 90 and 82% yields (entries 10 and 11). Finally, the reaction of **1f** with allene **2a** furnished the corresponding indane derivative **4l** in 76% yield (entry 12). For comparison, the latter reaction carried out in the presence of Ni(dppe)Br_2 and Zn in CH_3CN at 80 °C for 8 h, gave no expected product **4l**. It is to be mentioned

Table 1 Results of cobalt-catalyzed [2 + 2 + 2] cycloaddition of 1,6-heptadiynes **1a–f** with allenes **2a–e**[a]

Entry	Diyne	Allene	Product	Yield (%)[b]
1	**1a**	**2a**	**4a**	90 (95)
2	**1a**	**2b**	**4b**	71
3	**1a**	**2c**	**4c**	88
4	**1a**	**2d**	**4d**	88
5	**1a**	**2e**	**4e**	62
6	**1b**	**2a**	**4f**	84
7	**1c**	**2a**	**4g**	79
8	**1c**	**2d**	**4h**	75
9	**1d**	**2a**	**4i**	61
10	**1e**	**2a**	**4j**	90
11	**1e**	**2c**	**4k**	82
12	**1f**	**2a**	**4l**	76

[a] The reaction of diyne (1.00 mmol) with allene (1.30 mmol) was carried out at 80 °C for 8 h in 1,2-dichloroethane (2.00 mL) using $CoI_2(PPh_3)_2$ (5.00 mol%) and Zn powder (2.75 mmol) as the catalyst. [b] Isolated yields; yield in the parentheses was measured from the crude product by the ^{1}H NMR integration method using mesitylene as an internal standard.

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† Electronic supplementary information (ESI) available: synthesis and characterization of compounds **4** and **6**. See http://www.rsc.org/suppdata/cc/b2/b212260j/

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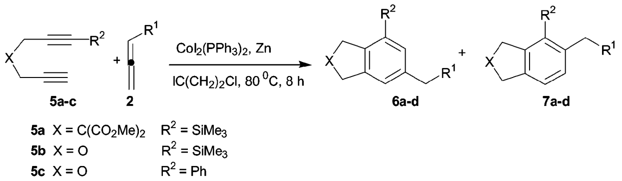
that the present cobalt-catalyzed cycloaddition of diynes with allenes produces a similar type of cycloadducts as the ruthenium-catalyzed cycloaddition of diynes with terminal acetylenes.[1d]

The current method can be successfully extended to unsymmetrical diynes **5a**–**c** (Scheme 2). The [2 + 2 + 2] cycloaddition of monosubstituted trimethylsilyl diyne **5a** with cyclohexylallene catalyzed by the $\mathrm{CoI_2(PPh_3)_2}$/Zn system is highly regio- and chemoselective furnishing *meta*-isomer **6a** exclusively in 89% yield (Table 2, entry 1). No other regioisomer was detected in the ^{1}H NMR spectrum of the crude reaction mixture. Similarly, the reaction with *n*-butylallene afforded a single *meta*-isomer **6b** in 85% yield (entry 2). Excellent regioselectivity was also observed for the cycloaddition of the oxygen containing unsymmetrical diyne **5b** with cyclohexylallene to give trimethylsilyl substituted isobenzofuran derivative **6c** (entry 3). On the other hand, the reaction of monophenyl substituted diyne **5c** with cyclohexylallene afforded a mixture of *meta*-isomer **6d** and *ortho*-isomer **7d** in a ratio of 94 : 6 (entry 4).



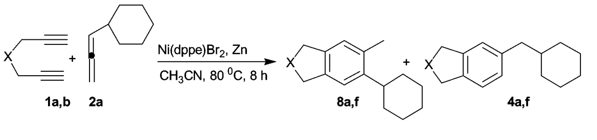
Scheme 2

Table 2 Results of cobalt-catalyzed [2 + 2 + 2] cycloaddition of unsymmetrical diynes **5a**–**c** with allenes **2**

Entry	Diyne	Allene	Product	*meta* : *ortho*	Yield (%)[a]
1	**5a**	**2a**	**6a**	> 99	89
2	**5a**	**2c**	**6b**	> 99	85
3	**5b**	**2a**	**6c**	> 99	83
4	**5c**	**2a**	**6d** + **7d**	94 : 6	71

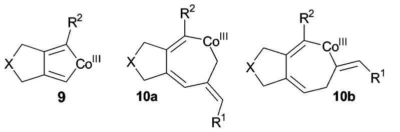
[a] Isolated yields.

There are several interesting features of the present catalytic reaction. First, the reaction is highly chemoselective with the allenes. Of the two carbon–carbon double bonds in the allenes, only the terminal double bond is involved in the cycloaddition to afford the corresponding chemoisomer **4**, and no trace of other possible chemoisomer was detected under the reaction conditions. Unlike the cobalt catalyst, the $\mathrm{Ni(dppe)Br_2}$/Zn system catalyzed the reaction of **1a** with **2a** to give a mixture of chemoisomers **8a** and **4a** in 38% yield in a 75 : 25 ratio (Scheme 3). Similarly, the reaction of dipropargyl ether **1b** with **2a** catalyzed by the same nickel system afforded a mixture of chemoisomers **8f** and **4f** in a 78 : 22 ratio in 24% total yield. The above results show clearly that the cobalt catalysts are more reactive and selective than nickel catalysts for the [2 + 2 + 2] cycloaddition of heteroatom containing 1,6-heptadiynes with allenes. Second, the allenes used in the present cycloaddition are synthetically equivalent to monosubstituted alkynes, but the regioselectivity of the present cycloaddition is much greater than the direct cycloaddition of the corresponding alkynes with diynes. For example, *n*-butylallene is equivalent to 1-heptyne. The reaction of **5a** with 1-heptyne in the presence of the $\mathrm{CoI_2(PPh_3)_2}$/Zn system afforded a mixture of *meta*-isomer **6b** and *ortho*-isomer **7b** in 84% yield in a 63 : 37 ratio. However, the same reaction with *n*-butylallene provided **6b** as the sole product in 85% yield (Table 2, entry 2). These results strongly suggest that allenes are more selective than monosubstituted alkynes in the present cycloaddition. Finally, in marked contrast to other cycloadditions that require a high ratio of alkene to diyne,[4,7] the ratio of allene to diyne is kept almost 1 : 1 for the present reaction. The competitive dimerization and trimerization of diyne is effectively suppressed and less than 5% of the dimerization product is formed in only a few reactions.



Scheme 3

The catalytic reaction is likely initiated by the reduction of Co(II) species to Co(I) species by zinc metal. Coordination of diyne to the cobalt center followed by cyclometalation produces cobaltacyclopentadiene intermediate **9**.[8] Coordination of the terminal carbon–carbon double bond of allene and selective insertion into an unsubstituted Co(III)–carbon bond gives cobaltacycloheptadiene **10a**.[1] Subsequent reductive elimination and isomerization affords the final product **6** and regenerates the Co(I) catalyst.



The highly regioselective insertion of allene into the Co(III)–carbon bond in **9** and the formation of intermediate **10a** accounts for the high *meta*-selectivity of the present cycloaddition. Other possible intermediates such as **10b** leading to *ortho*-isomer **7** are less favourable presumably due to steric effects.[1d,5]

In conclusion, we have demonstrated that the $\mathrm{CoI_2(PPh_3)_2}$/Zn system successfully catalyses the [2 + 2 + 2] cycloaddition of electronically neutral 1,6-heptadiynes with allenes. The catalytic reaction is highly regio- and chemoselective and tolerates a variety of functional groups present in the diynes. The allenes are synthetically equivalent to monosubstituted alkynes, but are superior in terms of the regioselectivity. Additionally, we have shown that the $\mathrm{CoI_2(PPh_3)_2}$/Zn system is much more active and selective than the $\mathrm{Ni(dppe)Br_2}$/Zn system. Further studies on the scope of this reaction is progress.

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