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Cobalt-catalyzed versus uncatalyzed intramolecular Diels-Alder cycloadditions

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ABSTRACT

The intramolecular [4+2] cycloadditions of dienynes was investigated using cobalt-based catalysts. Substrates without substitution on alkyne moiety were found to react under thermal activation. The use of a cobalt salt as catalyst made reactions cleaner by limiting the formation of byproducts. Cycloadditions with dienynes possessing a substituent on the alkyne pattern occurred only in presence of a cobalt catalyst which displayed a moderate to good activity depending on the substrate patterns.

Cycloisomerizations are valuable transformations to prepare straightforwardly cyclic, bicyclic or polycyclic compounds from simple and readily available acyclic materials.[1] Moreover, they belong to the class of atom-economy processes since no formal gain or loss of any atom takes place.[2] However they are generally promoted by transition metals which allow to activate polyunsaturated substrates and trigger the formation of the new C—C bonds under mild reaction conditions.[3,4] For example, the intramolecular [4+2] cycloaddition of dienynes was successfully investigated with various transition metals (Scheme 1). Wender reported first an efficient Ni(0)-based catalytic system under mild reaction conditions which unfortunately gave a rather modest *endo*/*exo* preference (1.8–2.2:1).[5] Shortly after, Livinghouse demonstrated that Rh(I)-based catalysts showed an even better efficiency since [4+2] cycloadducts were isolated with good to excellent diastereoselectivity[6] and the use of chiral phosphines allowed to perform this transformation in an enantioselective fashion.[7] Then, efforts focused on the study and improvement of Rh-catalysis,[8] and the transposition to iridium-catalysis did not led to better results.[9] Recently, Chung reported that [4+2] cycloadditions of dienynes can be achieved at room temperature with a gold(I) catalyst but only for substrates featuring terminal alkynes ($R^2 = H$).[10]

Given the costs associated with the use of noble transition metals and chiral phosphines, it will be interesting to develop a new catalytic system for this transformation based on an earth abundant transition metal. Considering that cobalt showed a good ability to catalyze various cycloadditions,[11] it seems to be a good candidate to investigate. Of note, whereas several examples of cobalt-mediated intermolecular [4+2] cycloadditions have been reported in the literature,[12] to the best of our knowledge, no intramolecular Diels-Alder cycloadditions have been described so far.[13]

Based on our previous studies on the cobalt-mediated [6+2] cycloaddition between cycloheptatriene and 2π-partners (alkynes or allenes),[14] we started to explore the cycloaddition of dienyne **1a** with CoI_2 as cobalt source, 1,2-bis(diphenylphoshino)ethane (dppe), zinc metal as reducing agent and ZnI_2 as Lewis acid (Table 1, entry 1). With this catalytic system, at 80 °C in dichloroethane, after 20 h of reaction, 34% of the expected [4+2] cycloadduct **2a** was isolated (entry 1). Pleasingly, the reaction proceeded with a high diastereoselectivity, and typically **2a** was isolated with high diastereomeric ratio >20:1.[15] Importantly, the solvent needed to be degassed to avoid the formation of substantial amounts of dimerization products[16] or oxidized product **3a**. In the absence of ZnI_2, the catalytic system performed better and 60% of **2a** was isolated (entry 2). Then, many bidentate ligands were tested, among them dppe, 1,2-bis(diphenylphoshino)methane (dppm) or 1,10-phenanthroline (entries 2–4) but only minor changes in chemical yields and diastereoselectivities were observed. As an additional evidence of the little impact of the ligand structure, when chiral ligands were used no chiral induction was detected.[17] The nature of the cobalt(II) source was also found to be a minor parameter since only little differences were obtained with CoI_2, $CoBr_2$, $CoCl_2$

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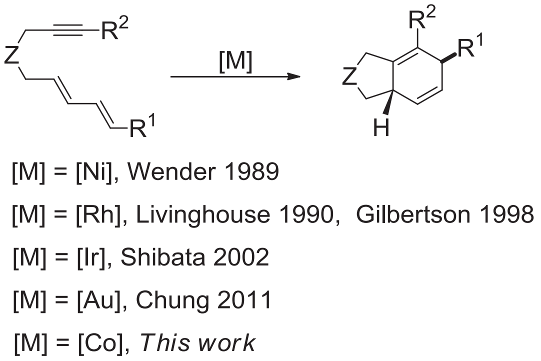


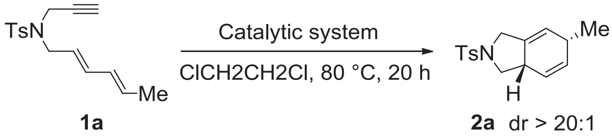
Scheme 1. Transition metal-promoted intramolecular Diels-Alder cycloadditions of dienynes.

and $Co(OAc)_2$ (entries 2, 5–7). As the ligand structure did not impact significantly the course of the reaction, we carried out experiments without ligands (entries 8 and 9). Surprisingly, the catalytic system $Co(OAc)_2$ and zinc metal performed well with the formation of 57% of **2a**. Control experiments without reducing agent were also achieved (entries 10–13). Whereas in the case of CoI_2 the yield slightly decreased, with $Co(OAc)_2$ a significant improvement was observed and 68% of **2a** was isolated. $Co(OAc)_2$·$4H_2O$ and $Co(OBz)_2$ exhibited somewhat lower activities. Importantly, we performed a control experiment without catalyst and, at 80 °C, 36% of cycloadduct **2a** with an excellent diastereoselectivity (dr > 20:1) along with 41% of **3a** (entry 14).[18] Of note, in the reactions carried out in presence of cobalt, less than 10% of **3a** was generally observed. The oxidation process affording **3a** took place only during the reaction, since the purification step did not increase its quantity and cyclohexadiene derivatives were found stable in solution few days at room temperature. Thus, it appeared that the use of $Co(OAc)_2$ allowed to reduce the oxidation process more than improve the reaction itself.

Then, we started to compare the uncatalyzed and cobalt-mediated intramolecular Diels-Alder cycloadditions of various dienynes featuring a terminal alkyne **1** (Table 2). Both reaction conditions gave [4+2] cycloadducts **2** with high diastereoselectivities. Compared to **1a**, *C*- and *O*-tethered dienynes were found less reactive. For example, **1b** gave only 11% of corresponding cycloadduct **2b** under thermal activation along with 22% of **3b**. In presence of $Co(OAc)_2$, the reaction performed better with less oxidation competing (entries 3 and 4). Similar results were obtained with dienyne **1c** to the exception that this time the use of $Co(OAc)_2$ improved yields of both cycloadduct and oxidized product (entries 5 and 6). Better outcomes were obtained for dienynes **1d** and **1e** bearing a phenyl substituent at the terminal position of the dienic moiety but no significant difference between uncatalyzed and cobalt-catalyzed reactions could be noticed (entries 7–10).

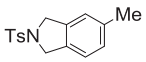
When the dienyne **4a** with a methyl substituent on the alkyne pattern was tested no reaction occurred either under thermal conditions nor in presence of $Co(OAc)_2$ or CoI_2 (Table 3, entries 1–3). Therefore, we decided to reinvestigate the catalytic system for this type of substrate. The catalytic system CoI_2, Zn, dppe and ZnI_2 was found competent to give cycloadduct **5a** (69%) along with small amount of **6a** (11% yield) (entry 4). It turned out that the use of $Co(OAc)_2$ instead of CoI_2 led to a substantial decrease of the activity with only 10% of isolated cycloadduct **5a** and 16% of **6a** (entry 5). Additional experiments proved the need of ZnI_2 that upgraded the efficiency of the cobalt-based catalyst but did not exhibit any

Table 1
Optimization of reaction conditions for the cobalt-mediated [4+2] cycloaddition.[a]



Entry	Catalytic system	Yield%
1	CoI_2, Zn, dppe, ZnI_2	34
2	CoI_2, Zn, dppe	60
3	CoI_2, Zn, dppm	65
4	CoI_2, Zn, 1,10-phenanthroline	54
5	$CoBr_2$, Zn, dppe	60
6	$CoCl_2$, Zn, dppe	53
7	$Co(OAc)_2$, Zn, dppe	53
8	CoI_2, Zn	36
9	$Co(OAc)_2$, Zn	57
10	CoI_2	21
11	$Co(OAc)_2$	68
12	$Co(OAc)_2$·$4H_2O$	57
13	$Co(OBz)_2$	59
14	none	36[b]

[a] Conditions: [Co] (5 mol%), Zn (15 mol%), Ligand (5 mol%), ZnI_2 (10 mol%), dienyne **1a** (0.5 mmol), $ClCH_2CH_2Cl$ (2 mL), 80 °C, 20 h.
[b] 41% of oxidized product **3a** was also isolated.



3a