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A Straightforward Procedure for the [2+2+2] Cycloaddition of Enediynes

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Abstract: Enediynes undergo intramolecular [2+2+2] cycloaddition in the presence of cobalt(II) iodide (CoI_2), manganese and an N-heterocyclic carbene (IPr) generated *in situ* from the corresponding imidazolium salt and butyllithium (BuLi). Polycyclic cyclohexadienes are obtained selectively. This new method represents an interesting alternative to those employing air-sensitive cyclopentadienylcobalt [$CpCoL_2$ ($L=CO$, C_2H_4)] catalysts. Moreover, the N-heterocyclic carbene can be used catalytically, which is a significant improvement compared to the corresponding phosphine-based system which requires an excess of ligand.

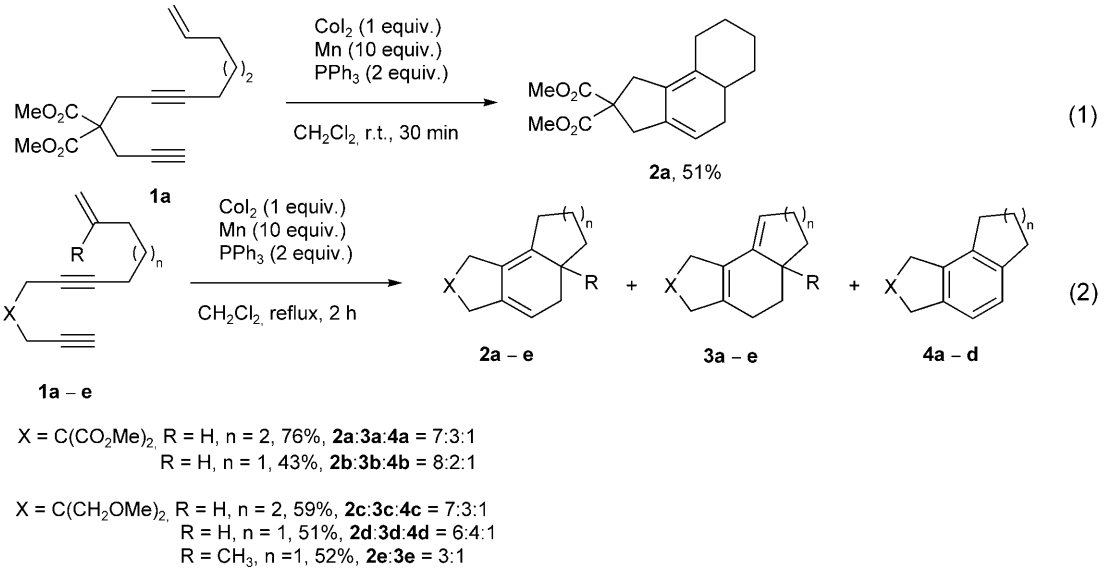
Keywords: cobalt; cycloaddition; dienes; manganese; N-heterocyclic carbenes; polycycles

Introduction

Cobalt complexes are powerful catalysts for the chemo-, regio,- and diastereoselective formation of 1,3-cyclohexadienes by [2+2+2] cycloaddition of two alkynes to one alkene.[1] In an intramolecular fashion, α,δ,ω-enediynes can be transformed into complex structures,[2] allowing access to natural products such as steroids,[3] or illudol derivatives.[4] Numerous examples involving complexes of type $CpCoL_2$ ($L=C_2H_4$, CO) have been reported. However, both groups of catalysts are air-sensitive and difficult to handle. Although $CpCo(C_2H_4)_2$ is very active and can be used over at room or lower temperature,[5] it is quite difficult to prepare.[6] On the other hand, $CpCo(CO)_2$ (commercially available) requires heat and/or visible light to be active,[7] and these harsh conditions may isomerize the desired product.[8] Most of the time, a stoichiometric amount of cobalt is required, for the final product may trap the catalyst as a very stable η^4-(1,3-cyclohexadiene) complex that will be unable to turn over.[9] However, the use of one equivalent of a cobalt complex, especially simple salts such CoX_2 ($X=Cl$, Br, I), is still competitive compared to rhodium-, iridium-, or ruthenium-containing catalysts that may require up to 20 mol% loads.[10] CoX_2 and $Co(acac)_3$, usually associated with phosphines or amines, zinc, manganese, or Et_2AlCl, and possibly other additives, have been used with success to catalyze [2+2+2] cyclotrimerizations of alkynes,[11] including by us,[11a] and [2+2+2] cocyclizations of alkynes and nitriles.[12,13] Diels–Alder,[14] homo-Diels–Alder reactions,[15] and Alder-ene reactions,[16] [6+2],[17] reductive [3+2],[18] and [4+2+2] cycloadditions,[19] cyclizations of *o*-iodobenzoates with aldehydes,[20] aryl-sulfur bond formations,[21] Reformatsky reactions,[22] cross-couplings and conjugate additions[23] were also performed under these conditions. Therefore, common catalysts of type $CpCoL_2$ could be replaced by catalytic systems much easier to handle (and sometimes more efficient[11a]) to generate benzenes or pyridines by [2+2+2] approaches. Yet the case of enediynes remained rather unexplored, with only one example to the best of our knowledge.[11a] In this update, we report a new cobalt-containing system that can easily transform enediynes into polycyclic fused 1,3-cyclohexadienes.

Results and Discussion

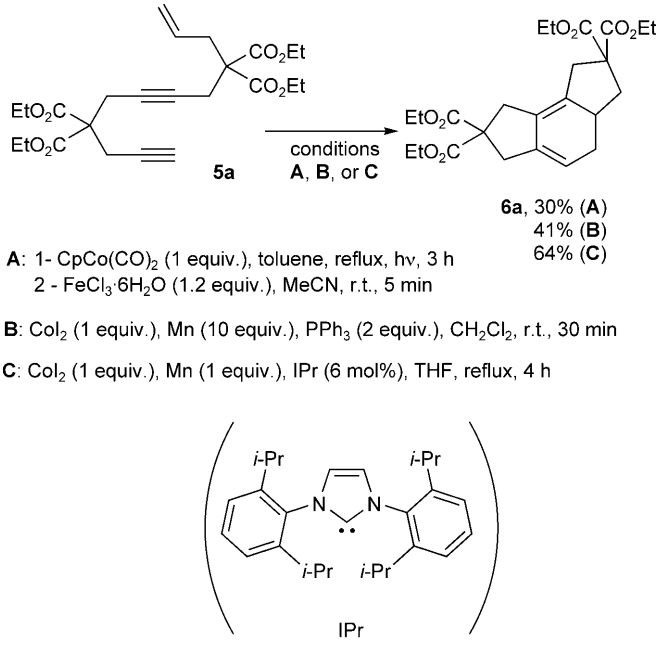
We disclosed that the transformation of enediyne **1a** into cyclohexadiene **2a** could be achieved in 30 min at room temperature using $CoI_2/PPh_3/Mn$ (1/2/10) in dichloromethane [Scheme 1, Eq. (1)].[11a] Using other cobalt halides ($CoCl_2$, $CoBr_2$), phosphines (e.g.,



Scheme 1. Cyclization of enediynes using CoI_2/Mn/PPh_3.

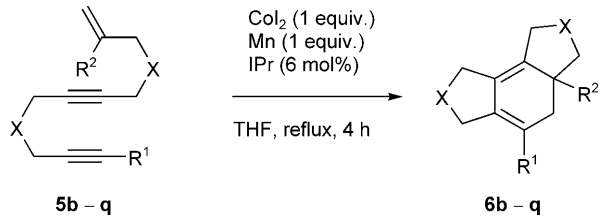
dppe), and reducing agents (e.g., Zn), gave rise to lower yields. Use of one equivalent of CoI_2 was necessary to achieve complete conversion of the substrate.[24] Lowering the amount of PPh_3 to one equivalent resulted in a lower yield of 17%. A large excess of manganese was also necessary for the reaction to start rapidly. Under refluxing conditions the yield could be increased to 76% [Eq. (2)], however the homoannular 1,3-cyclohexadiene **2a** was accompanied by the corresponding heteroannular 1,3-diene **3a** and also a small amount of aromatization product **4a**. The isomerization of **2a** into **3a** was complete after a few days in the NMR tube ($CDCl_3$).[25] The same problems were encountered with other substitution patterns and tether lengths (enediynes **1b–e**).

Various cobalt catalysts were screened for effectiveness in the above transformations, however $Co(acac)_3$, $Co_2(CO)_8$ in the presence of dppe, or $ClCo(PPh_3)_3$ in different solvents were not active, the starting material remaining unchanged. It is now well established that the replacement of phosphines, amines or cyclopentadienyl ligands by N-heterocyclic carbenes (NHC) can have a dramatic influence on both reactivity and selectivity.[26] Although NHC-Co complexes are known,[27] the association of NHCs with cobalt for synthetic purposes remains very scarce. Intramolecular cycloadditions of triynes catalyzed by NHC-$CoCl_2$/Zn have been reported,[28] as well as NHC-$CoCl_2$-catalyzed sequential cyclization/cross-coupling reactions of 6-halo-1-hexene derivatives with Grignard reagents,[29] and also dehydrohalogenation reactions.[30] In this context, an important breakthrough was made while studying the cyclization of enediyne **5a** under various experimental conditions (Scheme 2). Whereas the "classical" two-step conditions **A** involving $CpCo(CO)_2$ and subsequent oxidative demetallation[31] furnished the expected product **6a** in 30% yield, and the CoI_2/Mn/PPh_3 system in 41% yield (**B**), it was possible to reach 64% yield by replacing the phosphine by an NHC (**C**). The standard carbene (IPr) was generated *in situ* from the corresponding imidazolium chloride (commercially available) and BuLi in THF at 0 °C.[32] This solution was then transferred to CoI_2 at 0 °C and then to **5a** and Mn at room temperature before refluxing for 4 h.[33]



Scheme 2. Cyclization of **5a** under various conditions.

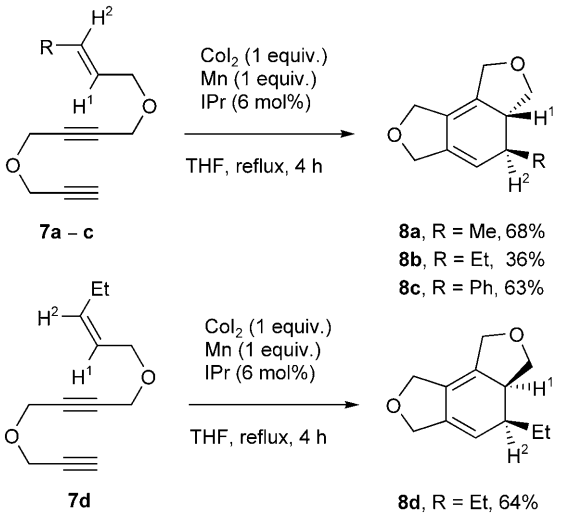
Table 1. Cyclization of enediynes using CoI_2/Mn/IPr.



Entry	Enediyne	X	R^1	R^2	Product	Yield [%][a]
1	**5b**	NTs	H	H	**6b**	66
2	**5c**	O	H	H	**6c**	84
3	**5d**	O	Me	H	**6d**	76
4	**5e**	O	Ph	H	**6e**	72
5	**5f**	O	*n*-Bu	H	**6f**	83
6	**5g**	O	CO_2Me	H	**6g**	81
7	**5h**	O	$SiMe_3$	H	–	–[b]
8	**5i**	O	Br	H	–	–[b]
9	**5j**	O	H	Me	**6j**	79
10	**5k**	O	H	Ph	**6k**	73
11	**5l**	O	CO_2Me	Me	**6l**	42
12	**5m**	$C(CO_2Et)_2$	H	Me	**6m**	54
13	**5n**	$C(CO_2Et)_2$	H	Ph	**6n**	30
14	**5o**	$C(CO_2Et)_2$	CO_2Me	H	**6o**	68
15	**5p**	$C(CH_2OMe)_2$	H	H	**6p**	64
16	**5q**	$C(CH_2OMe)_2$	H	Me	**6q**	65

[a] Isolated yields.
[b] No reaction.

It is worthy of note that CoI_2 remains the reagent of choice, even with IPr instead of PPh_3. Indeed, $CoCl_2$, $CoBr_2$, $Co(acac)_x$ (x = 2 or 3) or $FeCl_3$ failed to mediate the cyclization. The association of Zn instead of Mn with any of these salts and IPr did not work either. In addition to the fact that the yield was actually the best with the carbene-based system, several other major advantages compared to the phosphine-containing mixture could be found. (*i*) Whereas PPh_3 had to be used in excess, only a catalytic amount of carbene was required to promote the cyclization. The optimized amount of carbene was found to be 6 mol%. Lower loads of IPr resulted in longer reaction times (e.g., 24 h with 4 mol%, 4 days with 1 mol%), and extensive levels of aromatization. (*ii*) Of particular interest, when IPr was used instead of PPh_3, *it was no longer required to use an excess of manganese*, only one equivalent proved enough to ensure complete conversion of the substrate.[34] (*iii*) Last but not least, neither isomerization of the diene fragment nor aromatization were observed when 6 mol% IPr were used instead of PPh_3. The scope and limitations associated with these new reaction conditions were investigated next. We found that the reaction tolerated the presence of heteroatoms in the tethers (Table 1, entries 1–11). With the exception of $SiMe_3$ (entry 7) and Br (entry 8), which, presumably for steric reasons, impede the cyclization, substitution at the terminal alkyne terminus was possible, as shown by the transformation of methyl-, phenyl- and butyl-substituted enediynes (entries 3–5). Interestingly, the reaction proved to be also compatible with an ester group at the alkyne (entries 6, 11 and 14). Substitution at the internal alkene carbon was also possible, as shown in entries 9–13, and 16. In particular, we could achieve the cyclization of a disubstituted enediyne (entry 11), albeit in a modest 42% yield. Overall, the yields range from 30 to 84%, most of them being particularly good.



Scheme 3. Diastereoselective cyclizations of enediynes **7a–d.**

Substitution at the external alkene carbon was also studied (Scheme 3). Methyl, ethyl, and phenyl groups gave the expected products **8a–d** in moderate to good yields. The cyclization proved to be diastereospecific: (*E*)-enediynes **7a–c** led to products **8a–c** in which H^1 and H^2 were found to be *trans* to each other (e.g., 11% nOe between H^1 and Me in **8a**, no effect between H^1 and H^2), whereas the (*Z*)-enediyne **7d** gave **8d** exclusively, displaying a *cis* relationship between H^1 and H^2 (11% nOe).

Conclusions

The association of NHCs with cobalt salts for mediating organic transformations is still in its infancy. In this update, we describe a new cobalt-containing system capable of mediating the [2+2+2]cycloaddition of enediynes (CoI_2/Mn/IPr). It is easier to implement than $CpCo(CO)_2$ and seemingly more efficient. The NHC can be used catalytically, and the chemoselectivity of the reaction was improved compared to the corresponding PPh_3-based system. Efforts are underway to achieve chirality transfers from enantiopure NHCs to the reaction products.

Experimental Section

General Procedure for the Cyclization of Enediynes

A solution of 1,3-bis(2,6-diisopropylphenyl)-3*H*-imidazolium carbene (0.06 mmol) in THF (3 mL) (prepared at 0 °C from 1,3-bis(2,6-diisopropylphenyl)-3*H*-imidazolium chloride (25 mg, 0.06 mmol) and BuLi (0.3 mL, 0.2 M in hexanes, 0.06 mmol) in THF (3 mL) was added in the dark, at 0 °C to a mixture of anhydrous CoI_2 (313 mg, 1 mmol) in THF (4 mL). After 15 min, this solution was added to a suspension of enediyne (1 mmol) and Mn (55 mg, 1 mmol) in THF (3 mL) at room tmperature. The resulting mixture was stirred at reflux in the dark for 4 h. After being cooled down, the mixture was filtered through a pad of celite with EtOAc and strd NH_4Cl was added. The mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$. The solvent was removed under vacuum. The crude product was purified *via* flash column chromatography using gradient mixtures of pentane and EtOAc to give the corresponding cyclohexadiene.

Supporting Information

Preparation of the starting enediynes and characterization data of all new compounds is available in a Supporting Information.

Acknowledgements

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[31] See inter alia ref.[4c].

[32] The carbene is now also commercially available and can be used directly.

[33] We checked that CoI_2/Mn/imidazolium chloride, CoI_2/Mn/BuLi, CoI_2/NHC, or even the NHC alone did actually not catalyze the cyclization.

[34] This is of course critically dependent on the quality of Mn.

