Cycloaddition Catalysts

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Air-Stable {(C_5H_5)Co} Catalysts for [2+2+2] Cycloadditions[**]

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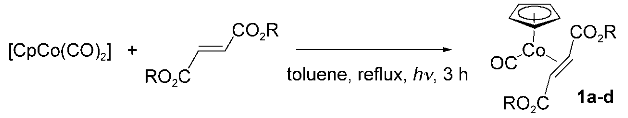
The transition metal-catalyzed [2+2+2] cycloaddition reaction is an expedient way to prepare six-membered ring systems, such as benzenes, pyridines, and cyclohexadienes, starting from alkynes, nitriles, and alkenes.[1] In this context, cobalt complexes are widely used as catalysts, which provide extensive levels of chemo-, regio-, and diastereoselectivity. Among the commercially available cyclopentadienyl catalysts,[2] [CpCo(CO)$_2$] is probably the most widely used. Its activation usually requires heat and/or visible light.[3] The use of [CpCo(cod)] (cod = 1,5-cyclooctadiene), which has been used mostly for the preparation of pyridines,[1h,4] also requires high temperatures and/or light. Conversely, [CpCo(C_2H_4)$_2$], which is also employed frequently, is active at room temperature or lower.[5] However, these very efficient catalysts are all very sensitive to air[6,7] and require the use of distilled and thoroughly degassed solvents. We describe herein the synthesis of new easy-to-handle air-stable complexes of the type [CpCo(CO)(alkene)][8] that catalyze various of [2+2+2] cycloadditions in unpurified solvents.[9,10]

The reaction of [CpCo(CO)$_2$] with one equivalent of dimethyl fumarate in refluxing toluene for 3 h under visible-light irradiation[3h] furnished complex **1a** as a deep red solid in 100% yield after flash chromatography on silica gel (Table 1).[11] The purification was carried out in air without specific precautions. The structure of this compound was unambiguously established by X-ray diffraction studies (Figure 1).[12]

Table 1: Synthesis of [CpCo(CO)(fumarate)] complexes **1a–d**.



R	Product	Yield [%]
Me	**1a**	100
*i*Bu	**1b**	100
*t*Bu	**1c**	65
1-adamantyl	**1d**	74

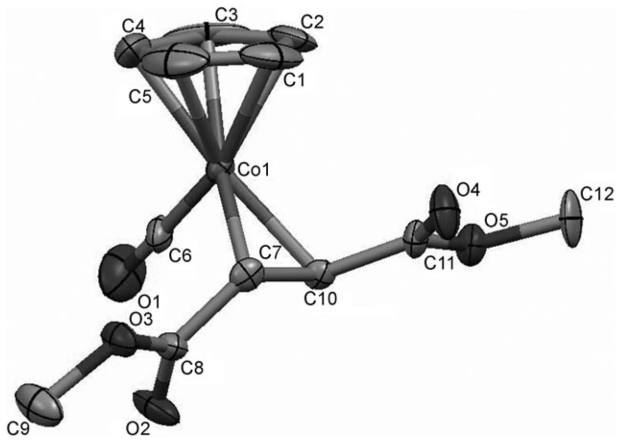
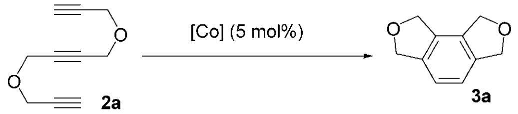


Figure 1. Molecular structure of complex **1a**. Thermal ellipsoids are set at 30% probability. Hydrogen atoms are omitted for clarity. Selected interatomic distances [Å] and angles [°]: Co1–C6 1.718, C6–O1 1.123, Co1–C7 2.005, Co1–C10 2.029, C7–C10 1.438, C8–C7 1.443, Co1–Cp-(centroid) 1.691, C6-Co1-C7 98.6, C6-Co1-C10 92.3.

The *iso*-butyl fumarate complex **1b** was also obtained in 100% yield, whereas the *tert*-butyl and 1-adamantyl derivatives **1c** and **1d** were isolated in 65% and 74% yield respectively.

These air-stable complexes were used to catalyze the intramolecular [2+2+2] cycloaddition of triyne **2a** (Table 2). Under "classical" conditions[1h] (in refluxing toluene for several hours, with visible-light irradiation), **1a** proved less efficient than [CpCo(CO)$_2$] (Table 2, entries 1 and 2).[13]

Table 2: Optimization of the reaction conditions for intramolecular [2+2+2] cycloaddition of triyne **2a**.



Entry	Conditions	[Co]	Yield [%]
1	toluene,[a] reflux, *hν*, 3 h	[CpCo(CO)$_2$]	66
2	toluene,[b] reflux, *hν*, 3 h	**1a**	51
3	toluene,[a] reflux, 3 h	[CpCo(CO)$_2$]	14
4	toluene,[b] reflux, 3 h	**1a**	85
5	MW, DMF,[b] 200 °C, 10 min	**1a**	75[c]
6	MW, DMF,[b] 200 °C, 10 min	**1b**	68
7	MW, DMF,[b] 200 °C, 10 min	**1c**	65
8	MW, DMF,[b] 200 °C, 10 min	**1d**	64
9	MW, DMF,[a] 200 °C, 10 min	[CpCo(CO)$_2$]	60
10	MW, DMF,[a] 200 °C, 10 min	[CpCo(C_2H_4)$_2$]	75

[a] Distilled and degassed under Ar. [b] Taken directly from the bottle and used without further purification. [c] 53% yield with **1a** (1 mol%).

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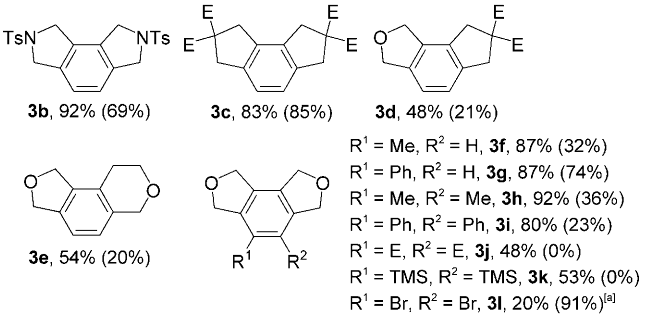
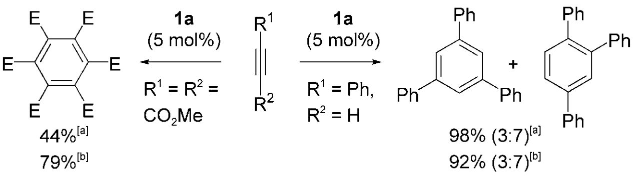
However, without irradiation (Table 2, entries 3 and 4), **1a** led to a much better yield of **3a** than $[CpCo(CO)_2]$ (85 %), the best yield of the series. Furthermore, some analytically pure catalyst could be recovered by flash chromatography,[14] which is not possible with $[CpCo(CO)_2]$ owing to fast decomposition. Catalysts **1a–d** were also effective under microwave (MW) conditions (Table 2, entries 5–8, DMF, 200 °C, 10 min).[15,16] Complex **1a** (Table 2, entry 5) gave rise to a significantly better yield[17] than **1b–d** (Table 2, entries 6–8) and $[CpCo(CO)_2]$ (Table 2, entry 9)., whereas $[CpCo(C_2H_4)_2]$ proved as efficient as **1a** (Table 2, entry 10). Decreasing the loading of **1a** from 5 mol % to 1 mol % led to a decrease in the yield (Table 2, entry 5, 53 % vs. 75 %). In addition to the fact that complexes **1a–d** are much easier to handle than $[CpCo(CO)_2]$ and $[CpCo(C_2H_4)_2]$, it is especially notable that the transformations involving these new catalysts were achieved in solvents taken "*straight from the bottle*". Neither toluene nor DMF were distilled or degassed prior to use. Even in a 1:3 mixture of H_2O and DMF, formation of **3a** using **1a** still occurred, albeit in lower yield (50 %).

To explore the scope of this intramolecular transformation, triynes displaying various tethers and alkyne termini (H, Me, Ph, CO_2Me, $SiMe_3$, Br) were heated by microwave in unpurified DMF in the presence of **1a**, giving **3b–l** in moderate to excellent yields (Scheme 1). Only the bisbrominated triyne proved poorly compatible with these experimental conditions, **3l** being isolated in only 20 % yield, accompanied by the corresponding monodebrominated product. This problem could be circumvented in refluxing toluene, **3l** being obtained in 91 % yield. All other triynes could be transformed into the corresponding tricyclic derivatives in at least 48 % (**3j**), and up to 92 % yield (**3b** and **3h**). With the exception of **3c**, refluxing in toluene for four hours instead of microwave heating in DMF for ten minutes gave rise to lower yields. Application of visible-light irradiation in addition to heating did not improve the amount of isolated product. Interestingly, **3j** and **3k** could be obtained only under microwave conditions.



Scheme 1. Tricyclic compounds prepared by intramolecular [2+2+2] cycloadditions of triynes (**1a** (5 mol %), MW, DMF, 200 °C, 10 min). E = CO_2Me; TMS = trimethylsilyl. Values in parentheses correspond to yields of reaction for 4 h in refluxing toluene, catalyzed by **1a** (5 mol %). [a] **1a** (10 mol %), toluene, reflux, 10 h.

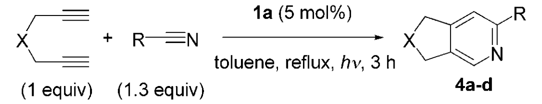
Intermolecular cyclizations could also be achieved (Scheme 2), either under microwave conditions or in refluxing toluene, without visible-light irradiation. The cyclotrimerization of dimethyl acetylenedicarboxylate (DMAD) gave rise to hexamethyl benzenehexacarboxylate in 44 % (MW/DMF) and 79 % (refluxing toluene) yields of isolated product. Phenylacetylene could be transformed into the expected regioisomeric mixture of 1,3,5- and 1,2,4-triphenylbenzene in 98 % (MW/DMF) and 92 % (refluxing toluene) total yields (ratio 3:7, in both cases).[18]



Scheme 2. Intermolecular [2+2+2] cycloaddition reactions: [a] MW, DMF, 200 °C, 10 min; [b] toluene, reflux, 3 h.

To further evaluate the potential of **1a** as a catalyst for [2+2+2] cycloaddition, we carried out bimolecular reactions between diynes and nitriles, to construct bicyclic fused pyridines (Table 3). The best yields were obtained in refluxing toluene.[19] Visible-light irradiation improved the yields significantly.[20] Microwave conditions were still effective, although the yields were markedly lower.

Table 3: Optimization of the reaction conditions for construction of fused bicyclic pyridines.

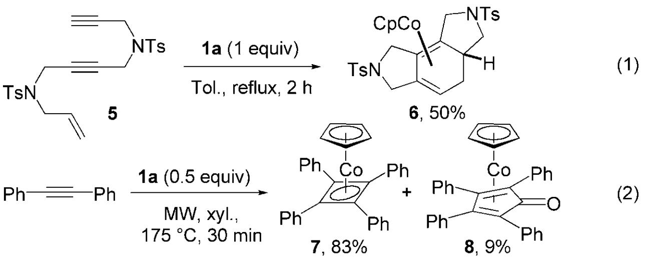


X	R	Product	Yield [%]
$(CH_2)_2$	Et	**4a**	65[a]
$(CH_2)_2$	Ph	**4b**	70[b]
NTs	Et	**4c**	63
NTs	Ph	**4d**	66

Without *hν*: [a] toluene, reflux, 7 h (44 %); xylenes, reflux, 3 h (53 %); MW, DMF, 200 °C, 10 min (45 %). [b] Toluene, reflux, 7 h (51 %).

Stoichiometric reactions were also briefly examined. The fused 1,3-cyclohexadiene **6** could be formed diastereoselectively in 50 % yield from enediyne **5** in refluxing toluene [Scheme 3, Eq. (1)]. The synthesis of the {CpCo}-complexed cyclobutadiene **7** was also accomplished under microwave irradiation, following a procedure described for diphenylacetylene and $[CpCo(CO)_2]$ [Scheme 3, Eq. (2)].[21] Interestingly, the yield (83 %) was much better than that reported with $[CpCo(CO)_2]$ (52 %), owing to a far lower contamination by the [2+2+1] adduct **8** (9 % vs. 40 % with $[CpCo(CO)_2]$).

In summary, complexes **1a–d** are versatile catalysts for various [2+2+2] cycloadditions, and related reactions, for forming benzenes, pyridines, and 1,3-cyclohexadienes. Although, in some cases, they exhibit similar activity, they present major advantages compared to common catalysts such as $[CpCo(CO)_2]$ and $[CpCo(C_2H_4)_2]$. They are air-stable and retain their activity after several months of storage in



Scheme 3. Miscellaneous Reactions mediated by **1a**.

simple vials. With the exception of pyridines, the cycloaddition products were synthesized without visible-light irradiation or under microwave conditions. The solvents could be used as found in the laboratory without further purification. Synthesis of water-soluble and solid-supported catalysts is underway in our laboratory.

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[5] For some recent examples, see: a) S. Amslinger, C. Aubert, V. Gandon, M. Malacria, E. Paredes, K. P. C. Vollhardt, *Synlett* **2008**, 2056; b) V. Gandon, C. Aubert, M. Malacria, K. P. C. Vollhardt, *Chem. Commun.* **2008**, 1599; c) C. Aubert, P. Betschmann, M. J. Eichberg, V. Gandon, T. J. Heckrodt, J. Lehmann, M. Malacria, B. Masjost, E. Paredes, K. P. C. Vollhardt, G. D. Whitener, *Chem. Eur. J.* **2007**, *13*, 7443; d) A. Geny, D. Lebœuf, G. Rouquié, K. P. C. Vollhardt, M. Malacria, V. Gandon, C. Aubert, *Chem. Eur. J.* **2007**, *13*, 5408.

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[9] For an early attempt to use [CpCo(CO)(maleic anhydride)][8a] for the cocyclization of diynes with acetone, see: D. F. Harvey, B. M. Johnson, C. S. Ung, K. P. C. Vollhardt, *Synlett* **1989**, 15.

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[11] Using dimethyl maleate instead of dimethyl fumarate resulted in a mixture of [CpCo(CO)(dimethyl fumarate)] (73% yield) and [CpCo(CO)(dimethyl maleate)] (23% yield) which could be separated by column chromatography on silica gel. The formation of the former is probably a result of photoisomerization of dimethyl maleate prior to complexation.

[12] CCDC 694920 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] Similar results were obtained in xylenes, hexane, and THF.

[14] When 30 mg of **1a** were used, 13 mg could be recovered. The collected material had undiminished catalytic activity.

[15] For selected examples of [2+2+2] cycloadditions under microwave irradiation, see: a) N. Nicolaus, S. Strauss, J.-M. Neudörfl, A. Prokop, H.-G. Schmalz, *Org Lett.* **2009**, *11*, 341; b) A. McIver, D. D. Young, A. Deiters, *Chem. Commun.* **2008**, *39*, 4750; c) D. D. Young, A. Deiters, *Angew. Chem.* **2007**, *119*, 5279; *Angew. Chem. Int. Ed.* **2007**, *46*, 5187; d) Y. Zhou, J. A. Porco, Jr., J. K. Snyder, *Org. Lett.* **2007**, *9*, 393; e) R. Hrdina, A. Kadlcikova, I. Valterova, J. Hodacova, M. Kotora, *Tetrahedron: Asymmetry* **2006**, *17*, 3185.

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radical cyclization. In our case, in 10 min without catalyst, no cyclization was detected.

[17] Similar yields were obtained at 150 °C in toluene (73 %) and THF (78 %). However these solvents are less convenient than DMF under microwave conditions as they require longer times to reach high temperatures.

[18] The ratio of regioisomers is similar to that reported using [CpCo(CO)$_2$]. For example, see: F. Montilla, T. Aviles, T. Casimiro, A. A. Ricardo, M. Nunes da Ponte, *J. Organomet. Chem.* **2001**, *632*, 113.

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[20] We suspect that the mechanism involves the thermal dissociation of the fumarate ligand to give [CpCo(CO)], which might catalyze the formation of benzenes without dissociation of CO. If this were the case, no irradiation would be required and the active species could go back to fumarate once the reaction is over (hence the recovery of some catalyst). For several reasons, [CpCo(CO)] might not be the most active species for the formation of pyridines, and the photodissociation of CO might be helpful. Since CO is lost, the catalyst can not be recovered in this case, as indicated by experimental results. Density functional calculations are underway to evaluate the potential of [CpCo(CO)] as the active species in [2+2+2] cycloadditions. For mechanistic studies relevant to this discussion, see: a) N. Agenet, V. Gandon, K. P. C. Vollhardt, M. Malacria, C. Aubert, *J. Am. Chem. Soc.* **2007**, *129*, 8860; b) V. Gandon, N. Agenet, K. P. C. Vollhardt, M. Malacria, C. Aubert, *J. Am. Chem. Soc.* **2006**, *128*, 8509; c) G. Dazinger, M. Torres-Rodriguez, K. Kirchner, M. J. Calhorda, P. J. Costa, *J. Organomet. Chem.* **2006**, *691*, 4434.

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