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Air-Stable CpCo(I)-phosphite-fumarate precatalyst in cyclization reactions: comparing different methods of energy supply

Fabian Fischer[a] and Marko Hapke*[a,b]

Abstract: The robust Co(I)-precatalyst [CpCo(P{OEt}$_3$)(*trans*-$MeO_2CHC=CHCO_2Me$)] was investigated in cyclotrimerizations furnishing benzenes and pyridines from triynes, diynes and nitriles, comparing the influence of different ways of energy supply, e.g. irradiation and conventional (thermal) or microwave heating. The precatalyst was found suitable to work under all conditions, including the possibility to catalyze cyclotrimerizations at room temperature under photochemical conditions at longer reaction times. Performance of the reactions in a microwave reactor proved to be the most time-efficient way to rapidly assemble the expected reaction products, however, careful selection of reaction conditions can be required. The synthesis of pyridines and isoquinolines successfully comprised the utilization of versatile functionalized nitriles, affording structurally interesting reaction products. Exemplary comparison with the known and often applied precatalyst $CpCo(CO)_2$ demonstrated the significantly higher reactivity of the CpCo(I)-phosphite-olefin precatalyst.

Introduction

The development of isolable transition metal catalysts for organic transformations is today often outrun by the invention of *in situ* generated transition metal catalyst system. The most significant advantage of the latter approach is the flexibility in terms of the broad choice of metal sources and ligands that can be screened together, including different metal-to-ligand ratios and also the additional use of different beneficial additives. An area which is currently intensively investigated and includes both approaches, isolated precatalysts as well as *in situ* catalyst generation, lies the field of C-H activation by base metal complexes like cobalt.[1] Inherent to the application of molecularly defined transition metal precatalysts is that they usually yield only a single defined reactive species upon activation. This way usually cleaner catalytic reactions are observed as well as mechanistic studies of a certain reaction becomes possible without the interference of additional substances from an alternative *in situ* generation procedure.

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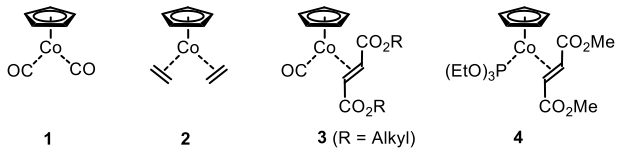
The recent developments in the area of cyclotrimerization reactions of alkynes, diynes, oligoynes and heterocumules were nursed by both approaches of catalyst employment.[2,3] Numerous studies by the groups of Okamoto, Hilt and others promoted the application of catalysts generated from simple cobalt(II) salts, appropriate ligands and reductants for the application in cyclotrimerizations.[2c,4] However, the prime catalyst source for cobalt-mediated and -catalyzed [2+2+2] cycloadditions is cyclopentadienyl cobalt(I) dicarbonyl ($CpCo(CO)_2$, **1**), introduced by Vollhardt et at. in their classical synthetic studies applying the cobalt-catalyzed cyclizations for the synthesis of annelated benzenes and finally in estrone total synthesis.[5,6] Even today this commercially available complex is still the catalyst of choice for many cobalt-catalyzed cyclotrimerizations, although it usually requires significant amounts of energy for activation. Applications comprise the synthesis of natural products, especially also those containing heterocyclic cores; examples for both include angucyclinones,[7] (dehydro)tylophorine,[8] (+)-complanadine A,[9] xylarinol A,[10] and recently cyclopropylallocolchicinoid[11] and (±)-allocolchicine.[12] Earlier reports on the photochemistry of $CpCo(CO)_2$ (**1**) discussing the possibility of the formation of clusters being regularly responsible of catalyzing the cyclotrimerizations have not been corroborated yet.[13] Recent studies only discuss mononuclear CpCo(I)-species as responsible catalytic species.

When comparing the reaction conditions in the different synthetic routes, in most cases rather high temperatures up to 150 °C (conventional heating) or 200 °C (microwave) are required, in some cases together with additional irradiation.[14] Such reaction conditions are necessitated by the tight bonding of the CO groups to the Co(I)-center in **1** (Scheme 1). Highly reactive $CpCo(olefin)_2$-complexes like **2** were introduced by Jonas et al. in the beginning of the 1980's and were utilized in a number of cases for cyclotrimerizations under very mild conditions.[15] Butenschön et al. found that phosphoryl-tethered $Cp'Co(C_2H_4)$-complexes are still active catalysts at 25 °C.[16] Aubert and Gandon et al. presented the first "upgraded" and air-stable CpCo(I)-carbonyl complex **3**, containing an electron-deficient dialkyl fumarate ligand instead of the second CO ligand, obtained by heating in toluene under reflux and irradiation.[17] While precatalysts like **3** are easy to handle, still high temperatures are required for application in cyclotrimerizations (typically refluxing toluene (110 °C) or microwave conditions (DMF, 200 °C)) due to strong bonding to the carbonyl ligand. Recently the direct thermolysis of several examples of substituted enediynes and eneynenitriles applying microwave heating (200 °C) without a catalyst was reported to yield highly substituted benzenes and pyridines.[18]



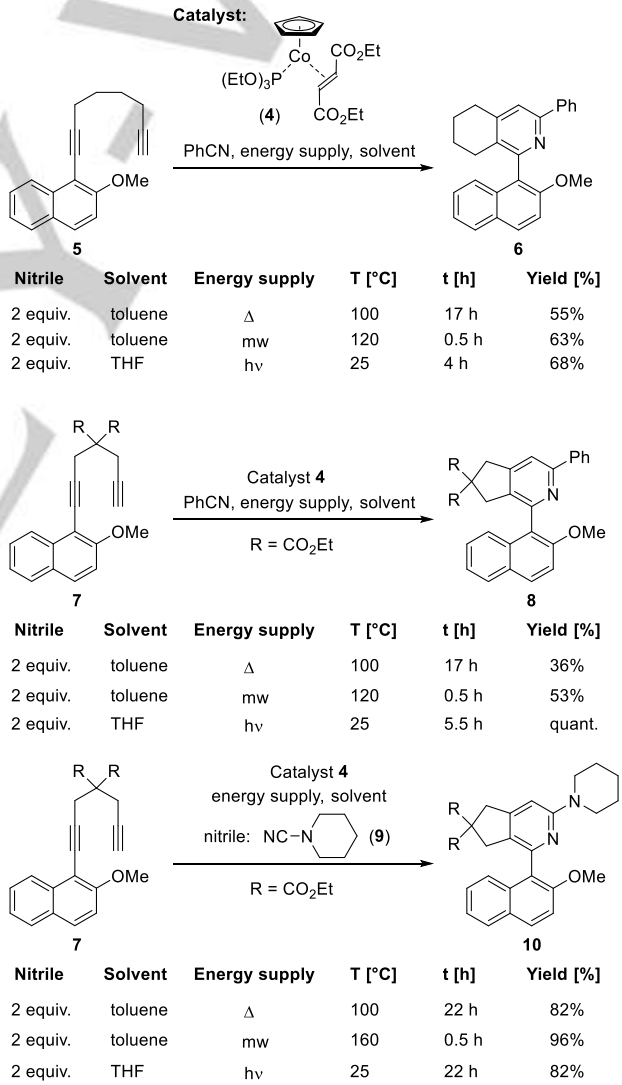
Scheme 1. CpCo(I)-catalysts: often utilized and novel precatalysts.

During our studies on novel derivatives of the Jonas complex **2**, we found that trimethylvinylsilane was a particular alkene ligand, as the Jonas complex congener with this alkene was extremely reactive in co-cyclotrimerizations with diynes and nitriles.[19] Taming the reactivity by selectively exchanging one alkene with a phosphite ligand led to CpCo(I)-complexes with mixed ligand sets, which could be used for cyclizations already at 50 °C.[20] With the obviously attractive olefin/phosphite combination we've set out for further exploration and found that a phosphite ligand together with dimethylfumarate furnished air-stable and recyclable CpCo(I)-complexes like **4**, which can easily be applied to cyclotrimerization reactions[21] and has become commercially available since.[22] This particular ligand combination also allows the efficient stabilization of functionalized Cp'Co-fragments.[23]

Showcase applications of **4** in several synthetic projects already proved to be beneficial,[24] leaving us with the idea, to explore different reaction conditions in terms of the energy supply to determine more precisely the requirements and circumstances, under which complex **4** can be successfully applied. Especially the application of irradiation versus conventional heating/microwave to activate the catalyst appears to be attractive, as there not many precatalysts, which can be efficiently activated under both activation methods. Microwave irradiation of Co-mediated cyclotrimerizations in glass reactions vessels is reported to be additionally favored by reduced induction periods and increased triplet life time of organometallic reaction intermediates.[25] Accordingly we report here the study of the cyclization of different triyne and diyne/nitrile substrates utilizing precatalyst **4** under thermal as well as photochemical conditions.

Results and Discussion

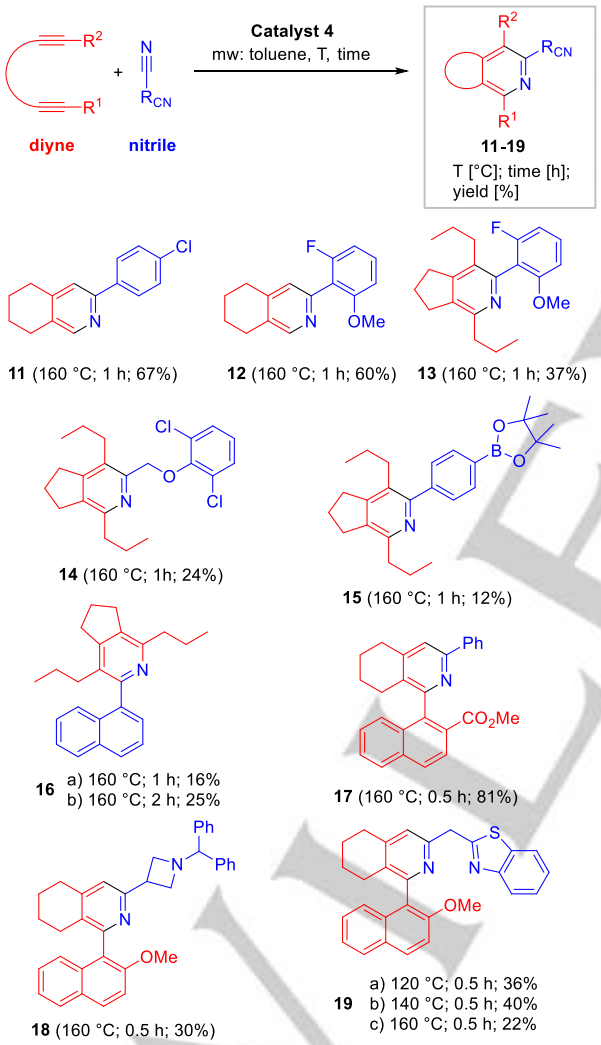
Since we have found that catalysts of the type $CpCoL_1L_2$ (L_1, L_2 = olefin, olefin/phosphite or phosphite) can be applied using conventional heating as well as microwave heating or irradiation for successful cyclization reactions, the generality of a single catalyst for such reactions for all ways of energy supply and under generally mild conditions and even "wet" solvents would be highly practical. We therefore started our investigation with selected substrates and evaluated catalyst **1** under all conditions mentioned above. In Scheme 2 the results for the diynes **5** and **7** for the reaction with benzonitrile and N-cyanopiperidine (**9**) are displayed. Biaryl **6** has been prepared stereoselectively before by the photochemical approach.[27b] The results (Scheme 2, top) show here that the photochemical approach is superior to the pure heating to 100 °C in toluene, furnishing product **6** in better yield even after only 4 h irradiation time versus the 17 h for heating and also better than the microwave-assisted reaction after 4h. Dipropargylmalonates like **7** have rarely been used for co-cyclotrimerizations under such conditions for the synthesis of pyridines. Reaction with benzonitrile (2 equiv.) furnished biaryl **8** with 36% on conventional heating to 100 °C oil-bath temperature for 17 h. Performance under microwave conditions yielded already 53% product after only 0.5 h reaction time. Irradiation for 5.5 h, however, yielded **8** with quantitative yield. In the final example, using only 2 equiv. heterocyclic nitrile **9** in the reaction with diyne **7** gave excellent yields of **10** with each way of energy supply, again with the shortest reaction time for the microwave-assisted reaction. Conducting the microwave-assisted reaction completely under air led to a lower yield of product **10**, resulting in a inseparable mixture of substrate and product.



Scheme 2. Comparison of thermal and photochemical energy supply for co-cyclotrimerization reactions of selected diynes and nitriles.

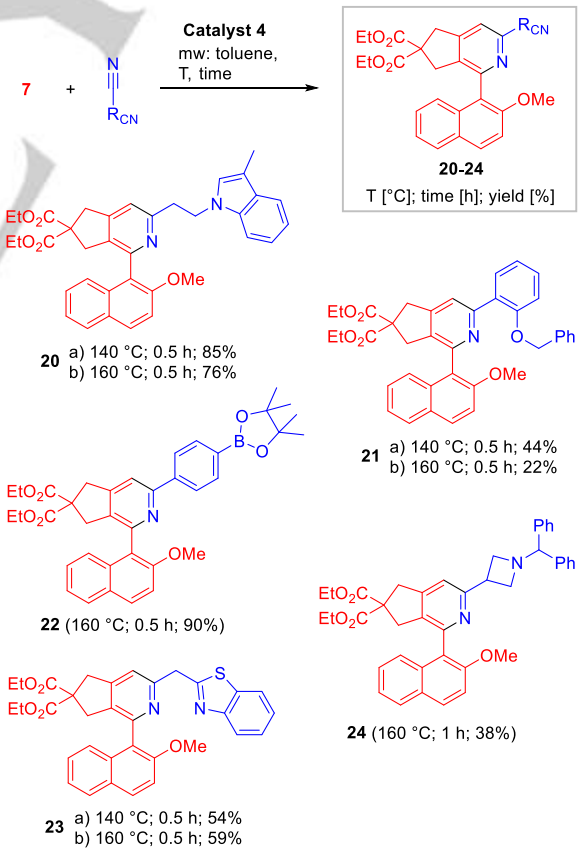
The results clearly show that photochemically assisted reactions often give excellent results at convenient temperatures, however, long reaction times are frequently required. The latter is also true for thermal reactions, taking up to 22 h for maximum conversion at 100 °C.

Microwave heating often gives superior results at higher reaction temperatures within short reaction times and therefore we applied catalyst **4** in exemplary syntheses to rapidly assemble different functionalized pyridines.[26] We were focusing on the broadness of application and screening of different nitrile substrates rather than general optimization of the reaction conditions towards yield to display instructive examples. In Scheme 3 cyclization results for internal, terminal as well as monosubstituted diynes with different nitriles are presented.



Scheme 3. Synthesis of pyridines from different diynes and nitriles (2 equiv.) using precatalyst **4** under microwave conditions.

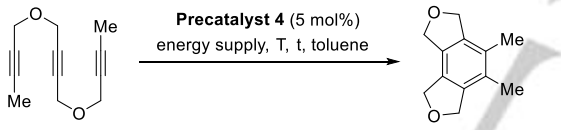
The results proof that the co-cyclotrimerization using complex **4** allows a very broad array of differently functionalized nitriles to be used. Examples **11** and **12** nicely illustrate the higher reactivity of terminal alkynes compared to internal diynes like trideca-4,9-diyne in compound **13** with significantly higher yields for **11** under identical conditions. Even *para*-chlorinated benzonitrile can be reacted with 1,7-octadiyne to give good yield of pyridine **11**. The reaction with a dichlorinated phenyl-derivative to compound **14** is possible with significantly lower yield when using trideca-4,9-diyne as coupling partner. Reactions of benzonitril-4-pinacolylboronat and 1-cyano-naphthalene with trideca-4,9-diyne yielded products **15** and **16** in yields not exceeding 25%, which again could be attributed to the lower reactivity of this internal diyne. Extended reaction time did not improve the yield significantly. The reaction of carboxynaphthly-substituted 1,7-octadiynes delivered compound **17** with very good yield. Synthesis of biaryl products **18** and **19** corroborated the ability of complex **4** to mediate reactions with unusual nitriles even containing heteroatoms, leading to products, which could act as ligands inhibiting the catalyst by coordination and preventing further catalysis.[27] Interestingly for the conversion of 2-(benzo[d]thiazol-2-yl)acetonitrile to biaryl **19** a maximum in the yield was reached at 140 °C reaction temperatures, while a higher temperature gave significantly lower yield. We extended the scope of the investigation and included the malonyl-substituted diyne **7** as substrate in our investigations (Scheme 4).



Scheme 4. Preparation of different substituted pyridines from diyne **7** and nitriles (2 equiv.) under microwave conditions.

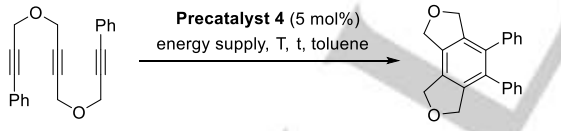
The yields obtained with diyne **7** and the different nitriles are in general acceptable to very good, even under unoptimized conditions. They were also higher than in comparable cases with compound **5** as the diyne component (compare to structurally related products **19** and **23**), which possibly could be traced back to the easier formation of the five-membered annulated pyridine ring.[28] For compounds **20** and **21** higher yields at 140 °C compared to 160 °C reaction temperature were observed. Curiously, attempts to prepare an analogue of compound **21** using diyne **5** instead **7** did not work at all. The cyclization of **7** with a borylated benzonitrile led to triaryl **22** in excellent 90% yield. Finally, using a azetidine-based nitrile could be cyclized within an hour at 160 °C furnishing pyridine **24**, albeit in mediocre yield. In summary, an interesting array of structurally more sophisticated nitriles was successfully reacted allowing access to novel bi- and triaryl motifs.

After investigating the synthesis of pyridine derivatives under the different conditions we also evaluated such conditions in the cyclization of triynes. For the study we focused on methyl- or phenyl-terminated triynes **25** and **27** and the results are shown in Scheme 5. Cyclization of **25** under conventional thermal conditions with precatalyst **4** yielded product **26** and unreacted **25** in nearly equal amounts (Scheme 5, top). Use of microwave conditions improved the yield of **26** to 52%,[29] while irradiation gave only 20% yield and most of the substrate must have reacted to different other products, which were not identified.



25 26

Solvent	Energy supply	T [°C]	t [h]	Yield [%]
toluene	Δ	100	18 h	39% (43%)*
toluene	mw	120	0.5 h	52% (36%)*
THF	hν	25	21.5 h	20% (10%)*



27 28

Solvent	Energy supply	T [°C]	t [h]	Yield [%]
toluene	Δ	100	19 h	44% (51%)*
toluene	mw	120	0.5 h	82%
THF	hν	25	19 h	35% (31%)*

** in parentheses the amount of isolated starting material is given.*

Scheme 5. Comparison of thermal and photochemical energy supply for [2+2+2] cycloaddition reactions of triynes **25** and **27**.

The results for triyne **27** were partially different compared to those achieved for **25**. Conventional heating led to rather sluggish conversion of **27**, delivering product **28** only with 44% yield after 19 h and leaving half of the starting material unchanged. Irradiation for the same time worked even less well and gave just 35% product. However, in both cases at least unreacted substrate **27** could be retained and obviously no side reaction has occurred. Applying microwave conditions, the cyclization ran smooth and gave a very good yield of **28** after just 30 minutes reaction time. This yield is superior to the experiment conducted under microwave conditions in DMF for 10 min reaction time, giving only 52% yield of **28** with catalyst **4**.[21]

The results presented above clearly provided evidence for the differences in the reaction outcome under the chosen conditions. However, which would be the conditions to choose for initial screening of reaction parameters? While photochemical conditions have the advantage to proceed under very mild conditions, the reaction times are usually relatively long and yields compared to pyridine synthesis rather low, as the examples showed. Conventional heating in toluene solution requires at least 100 °C to proceed over mostly long reaction times to drive the reaction towards completion. Therefore, microwave heating appears to be most compelling especially due to the short reaction times, although reaction temperatures of at least 120 °C for triynes are frequently required.

We investigated the cyclization of other triyne derivatives with **4** under microwave conditions and the results are given in Table 1. Entry 1 und 2 are interesting as they show that even 20 °C difference in reaction temperature for the transformation of **29** to **30** can make the difference between complete conversion and no reaction at all. The reaction time is very short (10 min) and the comparable cyclization using $CoCl(PPh_3)_3$ as catalyst gave identical yield (92%), but required 36 h at 25 °C.[30] The reaction temperature is in general lower compared to the pyridine synthesis discussed before. Also here the structure of the triyne appears to play a role for the reaction outcome, demonstrated by the lower yields for the malonyl-substituted triynes **37**, **39** and **41**, even at prolonged reaction times.

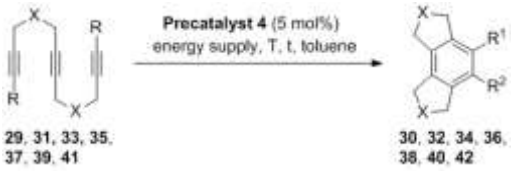
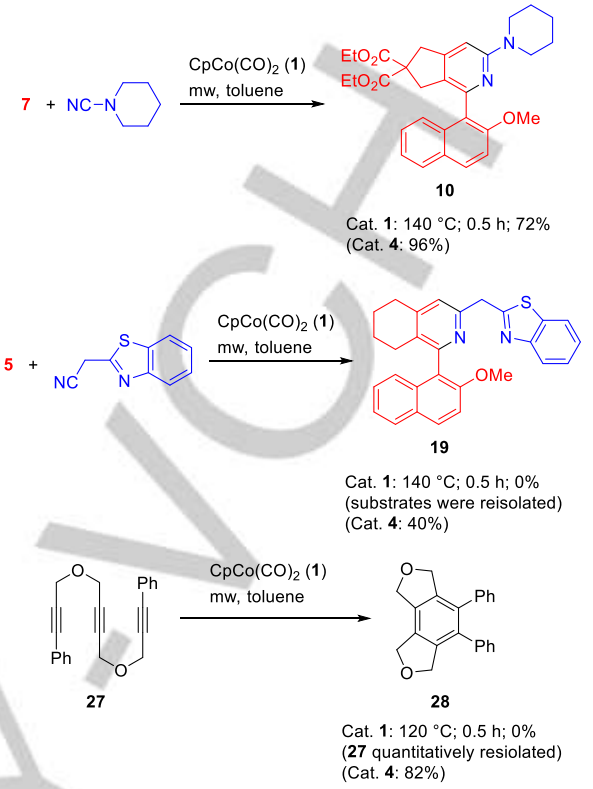


Table 1. [2+2+2] Cycloadditions of triynes under microwave conditions.

#	Triyne/ Product	X	R^1, R^2	T [°C]	t	Yield[a]
1	**29/30**	O	1-napthyl	100	10 min	0%
2	**29/30**	O	1-napthyl	120	10 min	98%
3	**29/30**	O	1-napthyl	120	10 min	78%[b]
4	**31/32**	O	2-MeO-1-naphthyl	120	10 min	34%
5	**33/34**	O	R^1=2-MeO-1-naphthyl; R^2=Ph	120	20 min	62%
6	**35/36**	O	R^1=1-naphthyl; R^2=Ph	120	20 min	83%
7	**37/38**	$(EtO_2C)_2C$	1-napthyl	120	30 min	15%
8	**39/40**	$(EtO_2C)_2C$	R^1=1-naphthyl; R^2=Ph	120	30 min	40%
9	**41/42**	$(EtO_2C)_2C$	R^1=2-MeO-1-naphthyl; R^2=Me	120	30 min	15%

[a] Isolated yield. [b] 2.5 mol% catalyst **4**.

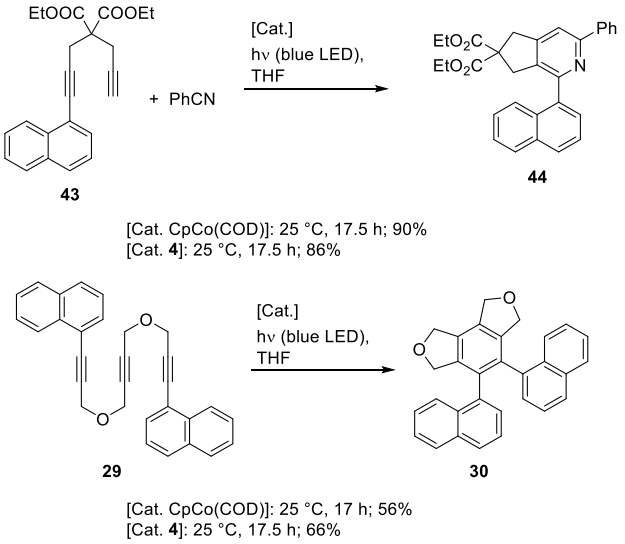
As discussed in the introduction, complex **1** has a longstanding history as catalyst for [2+2+2] cycloaddition reactions. We were keen to benchmark this precatalyst vs. complex **4** in selected reactions to see their performance compared (Scheme 6). In the first investigated reaction yielding pyridine **10** (Scheme 6, top) the yields were high in both cases under identical reaction conditions, however, complex **4** gave an even higher conversion. The outcome with the preparation of **19** as the second example (Scheme 6, middle) was even more impressive, as complex **1** failed to catalyze this transformation at all. The cyclization of triyne **27** emphasizes the versatility of complex **4** even further (Scheme 6, below), as the product **28** was obtained with 82% while complex **1** again failed to give any product at all again.



Scheme 6. Comparison of precatalysts $CpCo(CO)_2$ (**1**) and **4** in [2+2+2] cycloaddition reactions.

We showed in Scheme 2 that photochemically assisted reactions using precatalyst **4** were performing very smooth, when using a high power medium pressure mercury lamp in thermostated reaction vessels.[24] While the outcome of photochemical reactions is often quite depending on the experimental setup, we decided to exemplarily showcase reactions using a convenient setup involving LED lamps for irradiation without the requirement of extensive cooling for temperature control required for powerful mercury pressure or metal halide lamps (Scheme 7, see Supporting Informations for details).[31]

Initial experiments using diyne **5** and PhCN as substrates gave biaryl **6** with good yield (68%) after 4 h reaction time using precatalyst **4**. The reaction of diyne **40** with PhCN in the presence of **4** proceeded with excellent 86% yield after 17.5 h (Scheme 7, top), which excellently matches the results applying CpCo(COD) (COD = 1,5-cyclooctadiene) as often used precatalyst for photo-assisted [2+2+2] cycloadditions (90%). Comparable results were obtained for the cyclotrimerization of triyne **29** with a yield of 56% for triaryl **30** applying CpCo(COD) as catalyst and slightly higher 66% for precatalyst **4** (Scheme 7, below). These investigations further corroborate the usefulness of complex **4** under a variety of different reaction conditions and also different setups for cyclizations performed under photochemical conditions.



Scheme 7. Comparison of precatalysts CpCo(COD) and **4** in [2+2+2] cycloaddition reactions using LED irradiation.

Conclusions

The presented investigation concentrated on the influence different kinds of energy supply can exert on the application of CpCo(I)-precatalysts in [2+2+2] cycloaddition reactions. Investigation of the air-stable and commercially available complex CpCo[P(OEt)$_3$](dimethyl fumarate) (**4**) under conventional thermal, microwave and photochemical conditions verified the possibility to successfully perform cyclization reactions under all three types of reaction conditions. Applying microwave heating takes advantage of providing consistent high temperatures in a confined reaction chamber and allowing short reaction times, while other methods can be equally successful, however, requiring significantly longer reaction times. We applied complex **4** under microwave conditions for the synthesis of pyridines from terminal and internal alkynes and substituted alkyl and aryl nitriles, which allowed rapid access on more complex structures. This is also possible for the cyclization of triynes, even at temperatures as low as 120 °C, which can otherwise require explicitly higher temperatures. Benchmarking the reactivity of **4** against the routinely applied complex CpCo(CO)$_2$ (**1**) in pyridine and triaryl synthesis impressively demonstrated that application of **4** as catalyst can led to excellent yields even when complex **1** shows no reactivity at all. Successful utilizing of **4** in photo-catalyzed cyclizations using a convenient photo reactor with irradiation by a LED device further substantiated the broadness of application of this particular precatalyst.

Experimental Section

General information:

General Procedure 1 (GP1) for [2+2+2] Cycloaddition Reactions under Photochemically Assisted Conditions: A thermostated photochemical reactor[24a] was loaded with precatalyst **4** (5 mol%) under inert conditions and a solution of diyne (0.125 mml) and the appropriate nitrile (2-5 equiv.) THF or toluene was added. The reaction mixture was irradiated for the indicated time at 25 °C using medium-pressure metal halide lamps (2*450 W). For stopping the reaction the lamps were turned off and the reaction vessel opened to air. The reaction solution was evaporated to dryness and loaded to a small amount of silica gel, yielding a fine powder. The crude product was purified by flash chromatography, furnishing the pure product. *Exemplified synthesis for compound* **10**: For the preparation of biaryl **10** the diyne **7** (49 mg, 0.125 mmol) and piperidine-1-carbonitrile (28 mg, 0.25 mmol, 2 equiv.) as well as catalyst **4** (2.7 mg, 5 mol%) dissolved in 2 mL dry THF were irradiated according to above General Procedure for the indicated time at 25 °C. After the end of the reaction the solvent was removed in vacuum and the crude product charged to a small amount of silica gel in Et_2O and dried, to give a dark free flowing powder. Column chromatography on silica gel using cyclohexane (c-hex)-ethyl acetate (3:1, v/v) as eluent furnished one main fraction of product **10** (63 mg, quantitive yield) of a yellowish syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.12 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.58-1.65 (m, 4H), 2.98 (d, *J* = 16.3 Hz, 1H), 3.36 (d, *J* = 16.3 Hz, 1H), 3.47-3.54 (m, 4H), 3.58-3.61 (m, 2h), 3.88 (s, 3H), 4.08 (q, *J* = 7.0 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 6.61 (s, 1H), 7.29-7.35 (m, 2H), 7.35 (d, *J* = 9.2 Hz, 1H), 7.47-7.53 (m, 1H), 7.77-7.83 (m, 1H), 7.87 (d, *J* = 9.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 14.1, 24.9, 25.7, 27.0, 38.0, 40.8, 47.1 (2x), 56.9, 60.2, 61.7 (2x), 101.8, 114.0, 123.6, 125.4, 126.1, 126.3, 127.8, 129.3, 129.8, 133.2, 149.3, 151.6, 154.1, 159.7, 171.6, 171.7 ppm; HRMS (EI), $C_{30}H_{34}O_5N_2$: calc.: 502.2462; found: 502.2459.

General Procedure 2 (GP2) for [2+2+2] Cycloaddition Reactions under Standard Thermal Conditions: In a Schlenk flask precatalyst **4** was weighted under inert conditions, followed by addition of a solution of diyne (0.125 mmol) and the appropriate nitrile (2-5 equiv.) in THF or toluene. The reaction mixture was heated to 100 °C for the indicated time. After cooling the reaction solution, the solvent was removed in vacuum. The crude product was purified by flash chromatography. *Exemplified synthesis for compound* **10** from (diyne **7** (49 mg, 0.125 mmol) and piperidine-1-carbonitrile (28 mg, 0.25 mmol, 2 equiv.) as well as catalyst **4** (2.7 mg, 5 mol%) dissolved in 2 mL dry toluene were reacted according to GP2 (22 h, 100 °C oil-bath temperature). Isolation of **10** according to the aforementioned procedure gave the product with quantitive yield (63 mg) yield. The analytical data were in agreement to the data determined before.

General Procedure 3 (GP3) for [2+2+2] Cycloaddition Reactions under Microwave Conditions: In a Schlenk flask precatalyst **4** was weighted under inert conditions, followed by addition either of a solution of diyne (0.125 mmol) and the appropriate nitrile (2-5 equiv.) in toluene or the substrate triyne (0.125 mmol) in 2 mL toluene. The solution was filled under inert conditions into the microwave reaction vial equipped with a stir bar mixture. The reaction in the microwave was executed according to the specified temperature and time. After cooling the reaction solution, the solvent was removed in vacuum. The crude product was purified by automated flash chromatography. *Exemplified synthesis for compound* **10** from (diyne **7** (49 mg, 0.125 mmol) and piperidine-1-carbonitrile (28 mg, 0.25 mmol, 2 equiv.) as well as catalyst **4** (2.7 mg, 5 mol%) dissolved in 2 mL dry toluene were reacted according to above General Procedure (0.5 h, 160 °C). Isolation of **10** according to the aforementioned procedure gave the product with 96% yield (60 mg). The analytical data were in agreement to the above data.

Heterocyclic cyclization products:

3-(4-Chlorophenyl)-5,6,7,8-tetrahydroisoquinoline (11): Compound **11** was synthesized from 1,7-octadiyne (26.5 mg, 0.25 mmol) and 4-chloro benzonitrile (69 mg, 0.5 mmol, 2 equiv.) and catalyst **4** (5.4 mg, 5 mol%) in 4 mL dry toluene according to **GP3** (1 h, 160 °C). Column chromatography on silica gel using c-hex-ethyl acetate (1:1, v/v) as eluent gave pure product **11** (41 mg, 67% yield) as solid. M.p.: 96-99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.81-1.88 (m, 4H), 2.75-2.84 (m, 4H), 7.38 (s, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.89 (ddd, *J* = 8.7 Hz, 2H), 8.36 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.6, 22.8, 26.2, 29.1, 120.6, 128.1, 128.9, 132.2, 134.5, 138.3, 147.2, 150.5, 153.3 ppm; HRMS (EI), $C_{15}H_{14}ClN$: calc.: 243.0809; found: 243.0810.

3-(2-Fluoro-6-methoxyphenyl)-5,6,7,8-tetrahydroisoquinoline (12): Compound **12** was synthesized from 1,7-octadiyne (106 mg, 0.13 mL, 1.0 mmol) and 2-fluoro-6-methoxy benzonitrile (302.3 mmg, 2.0 mmol, 2 equiv.) and catalyst **4** (21.7 mg, 5 mol%) in 6 mL dry toluene according to **GP3** (1h, 160 °C). Reaction control via TLC with c-hex/ethyl acetate (1:1, v/v) showed complete conversion of the diyne starting material. The solvent was removed, and the crude product charged to a small amount of silica gel to give a dark free flowing solid. Column chromatography on silica gel using using c-hex-ethyl acetate (2:1, v/v) as eluent gave two main fractions, which were identified as pure recovered benzonitrile starting material (196 mg, according to 70% conversion) and product **12** (162 mg, 60% yield) of transparent syrupy consistency. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.80-1.87 (m, 4H), 2.76-2.82 (m, 4H), 3.78 (s, 3H), 6.74-6.81 (m, 2H), 7.09 (s, 1H), 7.28 (ddd, *J* = 8.7, 8.3, 6.6 Hz, 1H), 8.42 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.5, 22.7, 26.2, 28.9, 56.3, 106.8 (d, $J_{C,F}$ = 3.0 Hz); 108.4 (d, $J_{C,F}$ = 23.1 Hz), 126.2, 129.7 (d, $J_{C,F}$ = 11.1 Hz), 132.0, 146.3, 148.2, 150.2, 158.5 (d, $J_{C,F}$ = 7.1 Hz), 159.4, 162.4 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): 115.8 ppm; HRMS (EI), $C_{16}H_{15}ONF$: calc.: 256.1132; found: 256.1132.

3-(2-Fluoro-6-methoxyphenyl)-1,4-di-n-propyl-6,7-dihydro-5H-cyclopenta[c]pyridine (13): Pyridine **13** was synthesized from 4,9-tridecadiyne (176.3 mg, 1.0 mmol) and 2-fluoro-6-methoxy benzonitrile (302.3 mmg, 2.0 mmol, 2 equiv.) and catalyst **4** (21.7 mg, 5 mol%) in 6 mL dry toluene according to GP3 (1h, 160 °C). After completion of the reaction cycle the solvent was removed in vacuo and the crude product charged to a small amount of silica gel in Et_2O and dried, to give a dark free flowing powder. Column chromatography on silica gel using c-hex/ethyl acetate (2:1, v/v) as eluent furnished two main fractions, which were identified as pure recovered benzonitrile starting material (216 mg, according to 57% conversion) and product **13** (122 mg, 37% yield) of a transparent syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.76 (t, 3H), 0.97 (t, 3H), 1.28-1.42 (m, 2H), 1.63-1.76 (m, 2H), 2.07-2.19 (m, 2H), 2.28-2.36 (m, 2H), 2.68-2.77 (m, 2H), 2.91-2.99 (m, 4H), 3.73 (s, 3H), 6.72-6.79 (m, 2H), 7.27 (ddd, *J* = 8.7, 8.3, 6.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.2, 14.4, 22.5, 22.8, 24.5, 30.9, 31.9, 32.5, 38.3, 56.1, 106.9 (d, $J_{C,F}$ = 2.7 Hz); 108.4 (d, $J_{C,F}$ = 22.8 Hz), 129.4 (d, $J_{C,F}$ = 9.8 Hz), 131.4, 137.1, 148.0, 152.8, 155.0, 158.6 (d, $J_{C,F}$ = 7.4 Hz), 159.4, 162.7 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): δ = 114.3 ppm; HRMS (EI), $C_{21}H_{26}ONF$: calc.: 327.1986; found: 327.1993.

3-((2,6-Dichlorophenoxy)methyl)-1,4-dipropyl-6,7-dihydro-5H-cyclopenta[c]pyridine (14): For the preparation of compound **14** the 4,9-tridecadiyne (88 mg, 0.5 mmol) and 2-(2,6-dichlorophenoxy)acetonitrile (202 mg, 1 mmol, 2 equiv.) and catalyst **4** (10.8 mg, 5 mol%) in 4 mL dry toluene according to **GP3** (1 h, 160 °C). After performing the microwave-assisted reaction the reaction solvent was removed in vacuo and the crude product charged to a small amount of silica gel in ethyl acetate and dried. Column chromatography on silica gel using c-hex/ethyl acetate (3:1, v/v) as eluent furnished two main fractions, which were identified as pure recovered nitrile starting material (70 mg, according to 62% conversion) and product **14** (45 mg, 24% yield) as orange syrup. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, *J* = 7.4 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 1.58-1.71 (m, 4H), 2.06-2.15 (m, 2H), 2.62-2.67 (m, 2H), 2.82-2.87 (m, 2H), 2.91 (ddd, *J* = 8.0, 7.6, 2.7 Hz, 4H), 5.21 (s, 2H), 6.90 (dd, *J* = 8.3, 7.8 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.3, 14.7, 22.3, 23.9, 24.7, 30.9, 31.6, 31.7, 37.8, 75.6, 125.0, 129.0 (2C), 130.1 (2C), 131.9, 138.1, 150.5, 151.8, 153.3, 154.5 ppm; HRMS (EI), $C_{21}H_{25}Cl_2NO$: calc.: 377.1308; found: 377.1301.

1,4-Dipropyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6,7-dihydro-5H-cyclopenta[c]pyridine (15): For the preparation of triaryl **15** the 4,9-tridecadiyne (44 mg, 0.25 mmol) and 4-(cyanophenyl)boronic acid pinacol ester (114.5 mg, 0.5 mmol, 2 equiv.) and catalyst **4** (5.4 mg, 5 mol%) in 4 mL dry toluene according to **GP3** (1 h, 160 °C). After performing the microwave-assisted reaction the reaction solvent was removed in vacuum and the crude product charged to a small amount of silica gel in ethyl acetate and dried. Column chromatography on silica gel using c-hex/ethyl acetate (3:1, v/v) as eluent furnished and product **15** (23 mg, 24% yield) of yellowish syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.80 (t, *J* = 7.3 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), 1.36 (s, 12H), 1.38-1.46 (m, 2H), 1.67-1.78 (m, 2H), 2.08-2.18 (m, 2H), 2.45-2.52 (m, 2H), 2.68-2.75 (m, 2H), 2.90-2.98 (m, 4H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.36, 14.44, 22.6, 23.4, 24.8, 25.0 (4x), 30.9, 32.0, 32.2, 38.2, 83.9 (2C), 128.5 (2C), 129.4, 134.6 (2C), 144.7, 153.2, 154.6, 156.3 (1 C could not be detected due to C-B coupling) ppm; ^{11}B NMR ($CDCl_3$, 96 MHz): δ = 30.9 ppm; HRMS (EI), $C_{26}H_{36}BO_2N$: calc.: 405.2834; found: 405.2830.

3-(Naphthalen-1-yl)-1,4-dipropyl-6,7-dihydro-5H-cyclopenta[c]-pyridine (16): Pyridine **16** was synthesized from 4,9-tridecadiyne (176.3 mg, 1.0 mmol) and 1-naphthonitrile (308 mg, 2.0 mmol, 2 equiv.) and catalyst **4** (21.7 mg, 5 mol%) in 6 mL toluene according to **GP3** (2 h, 160 °C). After completion of the reaction cycle the solvent was removed in vacuo and the crude product charged to a small amount of silica gel in ethylacetat and dried. Column chromatography on silica gel using c-hex/ethyl acetate (3:1, v/v) as eluent furnished two main fractions, which were identified as pure recovered 1-naphthonitrile starting material (238 mg, according to 78% recovery) and product **16** (80 mg, 25% yield) as orange syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.64 (t, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H), 1.27 (q, *J* = 7.4 Hz, 2H), 1.72 (q, *J* = 7.4 Hz, 2H), 2.11-2.25 (m, 3H), 2.32-2.45 (m, 1H), 2.71-2.79 (m, 2H), 2.95-3.05 (m, 4H), 7.30-7.47 (m, 4H), 7.51 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.86 (dd, *J* = 8.2, 3.4 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.3, 14.4, 22.9, 23.3, 24.8, 31.0, 32.0, 32.4, 38.2, 125.3, 125.7, 125.9, 126.2, 126.8, 127.7, 128.2, 130.9, 132.6, 133.9, 136.7, 139.1, 153.1, 154.7, 155.4 ppm; HRMS (EI), $C_{24}H_{27}N$: calc.: 329.2138; found: 329.2126.

Methyl 1-(3-phenyl-5,6,7,8-tetrahydroisoquinolin-1-yl)-2-naphthoate (17): Pyridine **17** was synthesized from methyl 1-(octa-1,7-diyn-1-yl)-2-naphthoate (37 mg, 0.125 mol) and benzonitrile (26 mg, 0.25 mmol, 2 equiv.) and catalyst **4** (2.7 mg, 5 mol%) in 2 mL dry toluene according to **GP3** (0.5 h, 160 °C). After completion of the reaction cycle the solvent was removed in vacuum and the crude product charged to a small amount of silica gel in ethylacetat and dried. Column chromatography on silica gel using c-hex/ethyl acetate (3:1, v/v) as eluent furnished one main fraction, which were product **17** (40 mg, 81% yield) of a yellowish solid. The identification was accomplished by comparison with published NMR data.[27b]

3-(1-Benzhydrylazetidin-3-yl)-1-(2-methoxynaphthalen-1-yl)-5,6,7,8-tetrahydroisoquino-line (18): Compound **18** was synthesized from diyne **5** (33 mg, 0.125 mmol) and 1-benzhydrylazetidine-3-carbonitrile (62 mg, 0.25 mmol, 2 equiv.) and catalyst **4** (2.7 mg, 5 mol%) in 2 mL toluene according to **GP3** (0.5 h, 160 °C). After completion of the reaction

cycle the solvent was removed in vacuo and the crude product charged to a small amount of silica gel in ethylacetat and dried. Column chromatography on silica gel using c-hex/ethyl acetate (3:1, v/v) as eluent furnished two main fractions, which were identified as pure recovered 1-benzhydrylazetidine-3-carbonitrile starting material (40 mg, according to 65% recovery) and product **18** (19 mg, 30% yield) as syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.56-1.82 (m, 4H), 2.05-2.17 (m, 1H), 2.33-2.46 (m, 1H), 2.89 (dd, *J* = 7.1, 6.2 Hz, 2H), 3.34 (ddd, *J* = 7.2, 7.1, 2.4 Hz, 2H), 3.60-3.69 (m, 2H), 3.81-3.91 (m, 1H), 3.83 (s, 3H), 4.46 (s, 1H), 7.09-7.21 (m, 4H), 7.23-7.33 (m, 6H), 7.35 (d, *J* = 9.1 Hz, 1H), 7.41-7.46 (m, 1H), 7.79-7.84 (m, 1H), 7.89 (d, *J* = 9.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.5, 23.1, 25.5, 29.8, 36.7, 56.9, 59.6, 59.7, 78.1, 114.0, 120.5, 123.6, 123.8, 124.7, 126.6, 127.1 (2C), 127.71 (4x), 127.74 (4x), 128.0, 128.5 (2C), 129.4, 129.7, 131.0, 133.3, 142.5, 146.8, 154.0, 158.6 ppm; HRMS (EI), $C_{36}H_{34}ON_2$: calc.: 510.2666; found: 510.2669.

2-((1-(2-Methoxynaphthalen-1-yl)-5,6,7,8-tetrahydroisoquinolin-3-yl)methyl)benzo[d]-thiazole (19): Biaryl **19** was synthesized from diyne **5** (33 mg, 0.125 mmol) and 2-(benzo[d]thiazol-2-yl) acetonitrile (44 mg, 0.25 mmol, 2 equiv.) and catalyst **4** (2.7 mg, 5 mol%) in 2 mL toluene according to **GP3** (0.5 h, 140 °C). After completion of the reaction cycle the solvent was removed in vacuo and the crude product charged to a small amount of silica gel in ethylacetat and dried. Column chromatography on silica gel using c-hex/ethyl acetate (1:1, v/v) as eluent furnished two main fractions, which were identified as pure recovered 2-(benzo[d]thiazol-2-yl)acetonitrile starting material (27 mg, according to 61% recovery) and product **19** (22 mg, 40% yield) as yellow-orange solid. M.p.: 129-131 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.55-1.81 (m, 4H), 2.09-2.21 (m, 1H), 2.36-2.48 (m, 1H), 2.81 (t, *J* = 6.2 Hz, 2H), 3.88 (s, 3H), 4.67 (s, 2H), 7.13 (s, 1H), 7.17-7.21 (m, 1H), 7.30-7.37 (m, 3H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.46 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.79-7.86 (m, 2H), 7.92 (d, *J* = 9.0 Hz, 1H), 8.04-8.0 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.3, 22.9, 25.5, 27.0, 29.6, 43.2, 56.8, 113.8, 121.6, 122.8, 123.1, 123.7, 124.7, 124.8, 125.9, 126.7, 128.1, 129.4, 130.0, 136.2, 153.2 (2C), 154.2, 170.3 ppm (two carbon resonances are missing presumably due to signal overlay); HRMS (EI), $C_{28}H_{23}ON_2S$: calc.: 435.1526; found: 435.1525.

Diethyl 1-(2-methoxynaphthalen-1-yl)-3-(2-(3-methyl-1H-indol-1-yl)ethyl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (20): Compound **20** was synthesized from diyne **7** (49 mg, 0.125 mmol) and 3-(3-methyl-1H-indol-1-yl)propanenitrile (46 mg, 0.25 mmol, 2 equiv.) and catalyst **4** (2.7 mg, 5 mol%) in 2 mL dry toluene according to **GP3** (0.5 h, 140 °C). After completion of the reaction cycle the solvent was removed in vacuo and the crude product charged to a small amount of silica gel in ethylacetat and dried. Column chromatography on silica gel using c-hex/ethyl acetate (3:1, v/v) as eluent furnished one main fraction, which were identified as product **20** (61 mg, 85% yield) of off-white syrupy consistency. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 2.29 (d, *J* = 0.8 Hz, 3H), 3.08 (d, *J* = 16.8 Hz, 1H), 3.30 (t, *J* = 6.8 Hz, 2H), 3.34 (d, *J* = 16.8 Hz, 1H), 3.48-3.60 (m, 2H), 3.91 (s, 3H), 4.04-4.15 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.50 (t, *J* = 6.8 Hz, 2H), 6.80 (d, *J* = 9.1 Hz, 2H), 7.06-7.11 (m, 1H), 7.14-7.19 (m, 1H), 7.23-7.29 (m, 2H), 7.34-7.37 (m, 2H), 7.40 (d, *J* = 9.1 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.82-7.87 (m, 1H), 7.95 (d, *J* = 9.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.7, 14.0, 14.1, 38.5, 39.2, 40.6, 46.4, 56.7, 59.8, 61.9 (2C), 109.4, 110.2, 113.6, 118.5, 118.8, 119.0, 121.3, 123.8, 124.6, 125.8, 126.9, 128.1, 128.8, 129.3, 130.4, 133.0, 135.4, 136.4, 150.7, 151.9, 154.3, 157.3, 171.2, 171.3 ppm; HRMS (EI), $C_{36}H_{36}O_5N_2$: calc.: 576.2619; found: 576.2619.

Diethyl 3-(2-(benzyloxy)phenyl)-1-(2-methoxynaphthalen-1-yl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (21): Triaryl **21** was synthesized from diyne **7** (49 mg, 0.125 mmol) and 2-(benzyloxy)benzonitrile (52 mg, 0.25 mmol, 2 equiv.) and catalyst **4** (2.7 mg, 5 mol%) in 2 mL dry toluene according to **GP3** (0.5 h, 140 °C). After completion of the reaction cycle the solvent was removed in vacuo and the crude product charged to a small amount of silica gel in ethylacetat and dried. Column chromatography on silica gel using c-hex/ethyl acetate (3:1, v/v) as eluent furnished one main fraction, which were identified as product **21** (33 mg, 44% yield) of a transparent syrup. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.14 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.18 (d, *J* = 17 Hz, 1H), 3.54 (t, *J* = 17 Hz, 1H), 3.71 (bs, 2H), 3.88 (s, 3H), 4.06-4.18 (m, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 5.18 (t, *J* = 1.6 Hz, 2H), 6.97-7.05 (m, 2H), 7.27-7.49 (m, 10H), 7.79-7.85 (m, 3H), 7.92 (d, *J* = 9.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 14.1, 38.8, 40.8, 56.7, 59.9, 61.9, 70.8, 113.4, 113.6, 120.1, 121.2, 121.6, 123.7, 125.0, 126.7, 127.1, 127.2 (2C), 127.8, 128.0, 128.3, 128.6 (2C), 128.8, 129.3, 129.6, 130.3, 131.9, 133.2, 135.7, 137.4, 151.6, 154.4, 154.7, 156.3, 171.4, 171.5 ppm; HRMS (EI), $C_{38}H_{35}NO_6$: calc.: 601.2459; found: 601.2448.

Diethyl 1-(2-methoxynaphthalen-1-yl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (22): For the preparation of triaryl **22**, diyne **7** (49 mg, 0.125 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (57 mmg, 0,25 mmol, 2 equiv.) and catalyst **4** (2.7 mg, 5 mol%) dissolved in 2 mL dry toluene according to **GP3** (0.5 h, 160 °C). After performing the microwave-assisted reaction the reaction solvent was removed in vacuo and the crude product charged to a small amount of silica gel in ethyl acetate and dried. Column chromatography on silica gel using c-hex/ethyl acetate (5:1, v/v) as eluent furnished one main fraction, which were identified as pure product **22** (70 mg, 90% yield) of yellowish syrupy consistency. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.14 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 12H), 3.15 (d, *J* = 17.1 Hz, 1H), 3.54 (d, *J* = 17.1 Hz, 1H), 3.76 (bs, 2H), 3.89 (s, 3H), 4.07-4.16 (m, 2H), 4.22 (qd, *J* = 7.1, 0.8 Hz, 2H), 7.32-7.37 (m, 2H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.42-7.46 (m, 1H), 7.70 (s, 1H), 7.82-7.87 (m, 3H), 7.94 (d, *J* = 9.0 Hz, 1H), 8.00-8.04 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 14.2, 25.0 (2C), 38.8, 40.8, 56.7, 59.9, 62.0, 83.9, 113.7, 115.8, 122.5, 123.8, 125.0, 126.5, 126.8, 128.0, 129.4, 130.4, 133.2, 135.2, 136.4, 142.4, 150.9, 152.1, 154.3, 156.3, 171.3, 171.4 ppm; HRMS (EI), $C_{37}H_{40}BNO_7$: calc.: 621.2892; found: 621.2892.

Diethyl 3-(benzo[d]thiazol-2-ylmethyl)-1-(2-methoxynaphthalen-1-yl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (23): Pyridine **23** was synthesized from diyne **7** (49 mg, 0.125 mmol) and 2-(benzo[d]thiazol-2-yl)acetonitrile (44 mg, 0.25 mmol, 2 equiv.) and catalyst **4** (2.7 mg, 5 mol%) dissolved in 2 mL dry toluene according to **GP3** (0.5 h, 160 °C). After completion of the reaction cycle the solvent was removed in vacuo and the crude product charged to a small amount of silica gel in ethyl acetate and dried. Column chromatography on silica gel using c-hex/ethyl acetate (1:1, v/v) as eluent furnished product **23** (42 mg, 59% yield, orange-brown solid). M.p.: 155-158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.20 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 3.12 (d, *J* = 17 Hz, 1H), 3.46 (d, *J* = 17 Hz, 1H), 3.67 (bs, 2H), 3.88 (s, 3H), 4.03-4.14 (m, 2H), 4.18 (qd, *J* = 7.2, 0.7 Hz, 2H), 4.72 (d, *J* = 1.5 Hz, 2H), 7.29 (bs, 1H), 7.30-7.34 (m, 3H), 7.34-7.39 (m, 2H), 7.46 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.80-7.85 (m, 2H), 7.93 (d, *J* = 9.1 Hz, 1H), 8.01-8.05 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 14.1, 38.6, 40.7, 43.3, 56.6, 59.8, 61.9, 113.5, 118.5, 121.6, 122.9, 123.8, 124.9 (2x), 126.0, 126.8, 128.0, 129.3, 130.5, 132.9, 136.1, 136.2, 151.4, 152.1, 153.2, 154.3, 155.5, 171.2 (2x), ppm (two carbon resonances are missing presumably due to signal overlay); HRMS (EI), $C_{33}H_{30}N_2O_5S$: calc.: 566.1870; found: 566.1861.

Diethyl 3-(1-benzhydrylazetidin-3-yl)-1-(2-methoxynaphthalen-1-yl)-5,7-dihydro-6H-cyclopenta[c]pyridine-6,6-dicarboxylate (24): The

cyclization of diyne **7** (98 mg, 0.25 mmol) and 1-benzhydrylazetidine-3-carbonitrile (124 mg, 0.5 mmol, 2 equiv.) and catalyst **4** (5.4 mg, 5 mol%) dissolved in 4 mL dry toluene was conducted according to **GP3** (1 h, 160 °C). For workup the solvent was removed and the crude product charged to a small amount of silica gel in ethyl acetate and dried. Purification by column chromatography on silica gel eluting with c-hex/ethyl acetate (3:1, v/v) furnished product **24** (61 mg, 38% yield, yellowish syrup). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.15 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 3.10 (d, *J* = 16.9 Hz, 1H), 3.39 (q, *J* = 7.4 Hz, 2H), 3.48 (d, *J* = 16.9 Hz, 1H), 3.61-3.69 (m, 2H), 3.71-3.75 (m, 2H), 3.86 (s, 3H), 3.87-3.96 (m, 1H), 4.06-4.17 (m, 2H), 4.21 (qd, *J* = 7.2, 0.5 Hz, 2H), 4.47 (bs, 1H), 7.15-7.22 (m, 2H), 7.24-7.38 (m, 8H), 7.38 (s, 1H), 7.42-7.47 (m, 4H), 7.79-7.85 (m, 1H), 7.92 (d, *J* = 9.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0, 14.1, 37.0, 38.7, 40.8, 56.7, 59.6, 59.7, 59.8, 61.9, 78.0, 113.7, 116.0, 123.8, 124.9, 126.7, 127.1, 127.67 (2x), 127.72 (2x), 128.0, 128.5 (4C), 129.3, 130.3, 133.1, 135.1, 142.4, 150.6, 151.3, 154.2, 161.2, 171.4, 171.5 ppm.

Supporting Information (see footnote on the first page of this article): Synthesis of substrates (compounds **7** and **43**), experimental procedures for cyclizations and data (products **6**, **8**, **26**-**44**), benchmark experiments with $CpCo(CO)_2$ (**1**) and the photochemical cyclizations; copies of NMR spectra.

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Keywords: Cobalt • [2+2+2] Cycloaddition • Catalyst activation • Microwave • Pyridines

[1] Recent overview on moleculary defined precatalysts and *in situ* generated catalysts in C-H activation: M. Moselage, J. Li, L. Ackermann, *ACS Catal.* **2016**, *6*, 498-525.

[2] Recent overviews: (a) A. Thakur, J. Louie, *Acc. Chem. Res.* **2015**, *48*, 2354-2365; (b) M. Amatore, C. Aubert, *Eur. J. Org. Chem.* **2015**, 265-286; (c) S. Okamoto, Y. Sugiyama, *Synlett* **2013**, *24*, 1044-1060; (d) C. Wang, B. Wan, *Chin. Sci. Bull.* **2012**, *57*, 2338-2351; (e) Y. Shibata, K. Tanaka, *Synthesis* **2012**, *44*, 323-350; (f) S. Okamoto, *Heterocycles* **2012**, *85*, 1579-1602; (g) D. L. J. Broere, E. Ruijter, *Synthesis* **2012**, *44*, 2639-2672.

[3] Overview on transition metal catalysts applied for the cyclotrimerization of alkynes: M. Hapke, N. Weding, K. Kral, in *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1 (Eds.: B. Cornils, W. A. Herrmann, M. Beller, R. Paciello), Wiley-VCH, Weinheim, **2017**, pp. 375-409.

[4] (a) G. Hilt, W. Hess, T. Vogler, C. Hengst, *J. Organomet. Chem.* **2005**, *690*, 5170-5181; (b) L. Fiebig, J. Kuttner, G. Hilt, M. C. Schwarzer, G. Frenking, H.-G. Schmalz, M. Schäfer, *J. Org. Chem.* **2013**, *78*, 10485-10493; (c) A. Goswami, T. Ito, S. Okamoto, *Adv. Synth. Catal.* **2007**, *349*, 2368-2374.

[5] (a) R. L. Funk, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1980**, *102*, 5253-5261; (b) R. L. Hillard III, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1977**, *99*, 4058-4069; (c) R. L. Hillard III, K. P. C. Vollhardt, *Angew. Chem.* **1975**, *87*, 744-745.

[6] K. P. C. Vollhardt, *Acc. Chem. Res.* **1977**, *10*, 1-8.

[7] C. Kesenheimer, A. Kalogerakis, A. Meißner, U. Groth, *Chem. Eur. J.* **2010**, *16*, 8805-8821.

[8] A. McIver, D. D. Young, A. Deiters, *Chem. Commun.* **2008**, 4750-4752.

[9] (a) C. Yuan, C.-T. Chang, D. Siegel, *J. Org. Chem.* **2013**, *78*, 5647-5668; (b) C. Yuan, C.-T. Chang, A. Axelrod, D. Siegel, *J. Am. Chem. Soc.* **2010**, *132*, 5924-5925.

[10] A. A. More, C. V. Ramana, *Chem. Asian J.* **2014**, *9*, 1557-1562.

[11] A. A. More, C. V. Ramana, *J. Org. Chem.* **2016**, *81*, 3400-3406.

[12] D. J. Paymode, C. V. Ramana, *ACS Omega* **2017**, *2*, 5591-5600.

[13] K. P. C. Vollhardt, J. E. Bercaw, R. G. Bergman, *J. Organomet. Chem.* **1975**, *97*, 283-297.

[14] N. Agenet, O. Buisine, F. Slowinski, V. Gandon, C. Aubert, M. Malacria, *Org. React.* **2007**, *68*, 1-302.

[15] K. Jonas, *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 295–311.

[16] L. Yong, H. Butenschön, *Chem. Commun.* **2002**, 2852-2853.

[17] A. Geny, N. Agenet, L. Iannazzo, M. Malacria, C. Aubert, V. Gandon, *Angew. Chem.* **2009**, *121*, 1842-1845.

[18] P. J. Parsons, D. R. Jones, A. C. Padgham, L. A. T. Allen, C. S. Penkett, R. A. Green, A. J. P. White, *Chem. Eur. J.* **2016**, *22*, 3981-3984.

[19] M. Hapke, N. Weding, A. Spannenberg, *Organometallics* **2010**, *29*, 4298-4304.

[20] I. Thiel, H. Jiao, A. Spannenberg, M. Hapke, *Chem. Eur. J.* **2013**, *19*, 2548-2554.

[21] I. Thiel, A. Spannenberg, M. Hapke, *ChemCatChem* **2013**, *5*, 2865-2868.

[22] Commercially available from TCI, order no. C3165, CAS no. 1487195-87-8 (http://www.tcichemicals.com/).

[23] I. Thiel, M. Hapke, *J. Mol. Catal. A: Chem.* **2014**, *383–384*, 153-158.

[24] (a) F. Fischer, A. F. Siegle, M. Checinski, C. Fischer, K. Kral, R. Thede, O. Trapp, M. Hapke, *J. Org. Chem.* **2016**, *81*, 3087-3102; (b) V. Trommer, F. Fischer, M. Hapke, *Monatsh. Chem.*, **2018**, DOI: 10.1007/s00706-017-2083-9.

[25] (a) A. M. Rodriguez, C. Cebrián, P. Prieto, J. I. García, A. de la Hoz, Á. Díaz-Ortiz, *Chem. Eur. J.* **2012**, *18*, 6217-6224; (b) B. Gutmann, D. Obermayer, B. Reichart, B. Prekodravac, M. Irfan, J. M. Kremsner, C. O. Kappe, *Chem. Eur. J.* **2010**, *16*, 12182-12194.

[26] Examples for the application of micrawve irradiation in pyridine synthesis by cocyclotrimerization: (a) R. Hrdina, A. Kadlčíková, I. Valterová, J. Hodačová, M. Kotora, *Tetrahedron: Asymmetry* **2006**, *17*, 3185-3191; (b) J. A. Teske, A. Deiters, *J. Org. Chem.* **2007**, *73*, 342-345; (c) Y. Zhou, J. A. Porco, J. K. Snyder, *Org. Lett.* **2007**, *9*, 393-396; (d) D. D. Young, A. Deiters, *Angew. Chem.* **2007**, *119*, 5279-5282; (e) R. Hrdina, M. Draínský, I. Valterová, J. Hodaová, I. Císaová, M. Kotora, *Adv. Synth. Catal.* **2008**, *350*, 1449-1456; (f) L. Garcia, A. Pla-Quintana, A. Roglans, T. Parella, *Eur. J. Org. Chem.* **2010**, *2010*, 3407-3415.

[27] The application of, e.g. 2-cyanopyridines as coupling partners in cyclotrimerizations with CpCo(I)-catalysts requires rather drastical reaction conditions to proceed, due to the potential of the forming 2,2'-bipyridine fragment to act as inhibitor during further reaction, compare (a) G. Chelucci, Tetrahedron: Asymmetry **1995**, 6, 811-826 and (b) M. Hapke, K. Kral, C. Fischer, A. Spannenberg, A. Gutnov, D. Redkin, B. Heller, J. Org. Chem. **2010**, 75, 3993-4003. However, an in situ cobalt-bisphosphine catalyst is able to perform cyclizations with 2-cyanopyridines: (c) A. Goswami, K. Ohtaki, K. Kase, T. Ito, S. Okamoto, Adv. Synth. Catal. **2008**, 350, 143-152.

[28] See for example: (a) R. Grigg, R. Scott, P. Stevenson, *Tetrahedron Lett.* **1982**, *23*, 2691-2692; (b) R. Grigg, R. Scott, P. Stevenson, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357-1364; (c) P. Novák, R. Pohl, M. Kotora, M. Hocek, *Org. Lett.* **2006**, *8*, 2051-2054.

[29] Triyne **25** was also cyclized by catalyst **3** under microwave conditions (10 min, 200°C) in DMF, which gave better yields (92%), see ref. [17].

However, the result obtained under thermal conditions (4h, refluxing toluene) was basically identical to ours.

[30] P. Jungk, F. Fischer, I. Thiel, M. Hapke, *J. Org. Chem.* **2015**, *80*, 9781-9793.

[31] We used a commercially available photoreactor system of HepatoChem (EvoluChem™ PhotoRedOx Box) for these experiments.

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Fire, light and microwave: An air-stable CpCo(I)-precatalyst was able to catalyze the synthesis of highly substituted benzenes and pyridines exploiting all kinds of energy supply, proving to be more reactive than, e.g. $CpCo(CO)_2$ as standard catalyst.

[2+2+2] Cycloadditions

*Fabian Fischer, Marko Hapke**

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Air-stable CpCo(I)-phosphite-fumarate precatalyst in cyclization reactions: comparing different methods of energy supply