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Pd-EnCat™ TPP30 as a Catalyst for the Generation of Highly Functionalized Aryl- and Alkenyl-Substituted Acetylenes via Microwave-Assisted Sonogashira Type Reactions

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Keywords: Cross-coupling / Heterogeneous catalysis / Reusable catalyst / Palladium / Microwave chemistry / Enynes

We report a rapid microwave-assisted Sonogashira cross-coupling of aryl iodides and bromides with terminal alkynes using Pd-EnCat™ TPP30. Both electron-rich and electron-deficient aryl halides reacted smoothly with a broad variety of terminal alkynes in MeCN at 100–120 °C. The coupling products were obtained in good to excellent yields and in high purity. This reaction can be performed under copper- and DMF-free conditions and does not require an inert atmosphere. Furthermore, the encapsulated catalyst can be recovered and recycled by a simple filtration of the reaction mixture. It can be reused in further reactions with only minor decrease in activity. Additionally, we were able to produce a variety of enyne derivatives under modified conditions employing the same Pd-EnCat™ source.

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Introduction

The Sonogashira cross-coupling reaction is a powerful method for C–C bond formation.[1] This reaction has found a variety of applications ranging from the preparation of fine chemicals to the synthesis of biologically active substances.[2] Traditionally, this transformation is carried out in polar, high-boiling solvents such as DMF, NMP and DMSO, with a complex palladium catalyst in conjunction with a copper co-catalyst.[3] The difficult removal of the solvent and the oxidative homo-coupling of acetylenes (Glaser coupling)[4] in the presence of copper(I) salts renders these protocols less than straightforward to employ. In addition, the palladium complexes are often costly, not necessarily readily available and their use in large-scale reactions can be problematic. As a result of these problems, several modifications to the Sonogashira coupling procedure have been published, among them reactions in ionic liquids,[5] reactions in water,[6] polymer- and zeolite-supported catalytic reaction systems,[7] various copper-free conditions[8] and the use of microwave irradiation.[9]

More recently, commercially available Pd-EnCat™ catalysts have been described as an advanced palladium source for cross-coupling reactions reducing palladium leaching and being easier to handle, recover and reuse.[10] The possibility to recover and to reuse this catalyst system is highly desirable as this leads to more sustainable chemical practices. This type of heterogeneous catalyst was successfully applied in hydrogenation reactions as well as in various C–C bond-forming reactions like Suzuki, Heck, and Stille cross-couplings.[10a,10b,11] Very recently, the use of Pd-EnCat™ was applied to Sonogashira coupling reactions mainly with phenylacetylene reacting with aryl iodides.[12] We were interested in extending these studies to include a larger range of acetylenes and effect coupling with more readily available aryl bromides to define a robust and easy to operate process that would tolerate wide functionality.

As a consequence we report herein various copper-free Sonogashira reactions between a broad variety of mainly aryl bromides and some aryl iodides and various terminal alkynes as well as some reactions of olefinic halides with terminal alkynes catalyzed by Pd-EnCat™ TPP30 using microwave activation.

Results and Discussion

For the optimization of the reaction, different catalyst forms and ratios, solvents, bases, and conditions for the microwave heating were examined. Because heterogeneous catalysis often suffers from unfavourable kinetics compared to the homogeneous processes, and because the encapsulated catalyst itself often needs prior activation, we decided to use microwave irradiation as a method of heating. In order to avoid thermal decomposition using high power microwave irradiation, the microwave vial was simultaneously cooled by flowing a compressed air stream around the microwave cavity. This procedure repeatedly resulted in products with significantly higher purity.[10a,10b,13]

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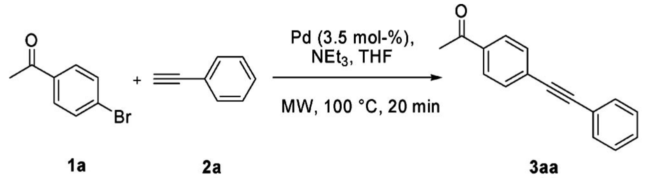
Optimization Studies

We began by investigating the effect of different Pd-EnCat™ species on the model reaction between 4-bromoacetophenone (**1a**) and phenylacetylene (**2a**) catalyzed by 3.5 mol-% of encapsulated palladium in the presence of triethylamine as base and THF as a solvent (Table 1). In this initial coupling reaction the PPh_3-containing Pd-EnCat™ TPP30 proved to be superior to Pd-EnCat™ TOT30, Pd-EnCat™ BINAP30, Pd-EnCat™ 30 and Pd-EnCat™ 40.[14] In the absence of any catalyst no coupling was observed (Table 1, Entry 6).

Table 1. Influence of the palladium source on the Sonogashira coupling reaction.[a]



Entry	Catalyst	Conversion [%][b]
1	Pd-EnCat 30	12
2	Pd-EnCat 40	55
3	Pd-EnCat TPP30	62
4	Pd-EnCat TOT30	49
5	Pd-EnCat BINAP30	31
6	no catalyst	0

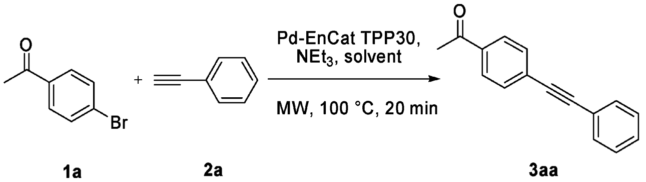
[a] Reactions were carried out using 0.5 mmol of 4-bromoacetophenone (**1a**), 1.0 mmol of phenylacetylene (**2a**), 1.0 mmol of NEt_3 and 3.5 mol-% of Pd under cooled microwave irradiation in THF (0.8 mL) using a sealed tube at 100 °C for 20 min. [b] Conversions were determined by ^1H NMR spectroscopy.

We then examined the influence of the solvent on the coupling reaction. Protic solvents such as *i*PrOH and EtOH led to only moderate formation of the desired coupling product **3aa** (Table 2, Entries 6 and 7). However, higher yields were obtained in aprotic solvents, such as MeCN and DMF (Table 2, Entries 3 and 4). MeCN was easier to remove and as it was preferred due to environmental reasons this was used as the solvent of choice in all further experiments.

Finally we tested different bases, as the presence of a base is a fundamental requirement for the reaction (Table 3, Entry 1). The most effective base was DBU (Table 3, Entry 7). Secondary amine bases like $(iPr)_2NH$, pyrrolidine and morpholine, which are commonly applied in Sonogashira couplings,[1] were less effective when using encapsulated Pd-species.

Further screening experiments with regard to the stoichiometry of the Sonogashira reaction revealed that a ratio of aryl halide/acetylene as low as 1:1.2:1.2 could be utilized. This constitutes a substantial decrease in the acetylene component and is an improvement when compared to other protocols reported for the Sonogashira coupling.

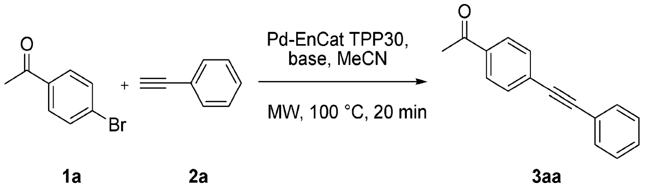
Table 2. Influence of the solvent on the Sonogashira coupling reaction.[a]



Entry	Solvent	Conversion [%][b]
1	THF	62
2	1,4-dioxane	58
3	MeCN	70
4	DMF	73
5	toluene	22
6	*i*PrOH	44
7	EtOH	35

[a] Reactions were carried out using 0.5 mmol of aryl halide (**1a**), 1.0 mmol of phenylacetylene (**2a**), 1.0 mmol of NEt_3 and 3.5 mol-% of Pd under cooled microwave irradiation, in 0.8 mL of solvent in a sealed tube at 100 °C for 20 min. [b] Conversions were determined by ^1H NMR spectroscopy.

Table 3. Influence of the base on the Sonogashira coupling reaction.[a]



Entry	Base	Conversion [%][b]
1	no base	0
2	NEt_3	70
3	iPr_2NEt	27
4	iPr_2NH	72
5	pyrrolidine	86
6	morpholine	41
7	DBU	99

[a] Reactions were carried out using 0.5 mmol of 4-bromoacetophenone (**1a**), 1.0 mmol of phenylacetylene (**2a**), 1.0 mmol of base and 3.5 mol-% of Pd under cooled microwave irradiation in MeCN (0.8 mL) using a sealed tube at 100 °C for 20 min. [b] Conversions were determined by ^1H NMR spectroscopy.

In addition, we investigated the influence of catalyst loading on the Sonogashira reaction (Table 4). For the favaourable substrate combination of **1j** and **2b** (formation of **3jb**) the amount of palladium could be reduced to 0.5 mol-% without significantly effecting the conversion. However, in the case of the more challenging pairing of **1j** and **2e** using only 0.5 mol-% of palladium gave a poor conversion of only 9%. In order to create a generic protocol we decided to apply 3.5 mol-% of palladium for all Sonogashira couplings to ensure maximum conversions and fast reactions. The reusable nature of the catalyst also renders this higher loading of palladium of reduced significance.

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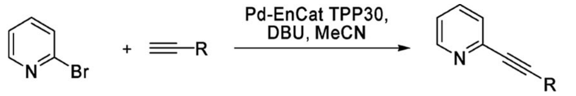
Table 4. Influence of the catalyst loading on the Sonogashira coupling reaction.[a]



1j **2b** (R = 3-MeOC$_6$H$_4$) **2e** (R = *n*Bu) **3jb** (R = 3-MeOC$_6$H$_4$) **3je** (R = *n*Bu)

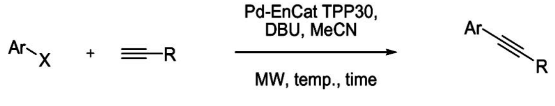
Entry	Product	Catalyst loading [mol-%]	Conversion [%][b]
1	**3jb**	3.5	69
2	**3jb**	2	63
3	**3jb**	1	62
4	**3jb**	0.5	59
5	**3je**	3.5	53
6	**3je**	2	42
7	**3je**	1	11
8	**3je**	0.5	9

[a] Reactions were carried out under the corresponding reaction conditions indicated in Table 5, Entries 31 and 32. [b] Conversions were determined by ^{1}H NMR spectroscopy.

Scope and Limitations

Under these optimized reaction conditions a variety of mainly aryl bromides and some aryl iodides reacted well with a broad range of terminal acetylenes affording the corresponding coupling products in good to excellent yields (Table 5). This cross-coupling procedure tolerated *ortho*-substitution in the aryl halides (Table 5, Entries 7–9, 16–17, and 20–23). A high functional group compatibility (acetyl, alcohol, ester, chloride, amide, nitrile and nitro) as well as good yields and high-purity products were observed. Both electron-deficient and electron-rich aryl halides were effective coupling partners for the Sonogashira coupling under these new conditions. Regardless of their electronic properties, aryl-, heteroaryl- and alkyl-substituted terminal alkynes reacted smoothly with a variety of aryl halides to produce the desired products. In addition, heterocyclic compounds such as 2-bromopyridine and 3-bromochinoline could be used as the halogen component to react with terminal acetylenes yielding the corresponding disubstituted

Table 5. Sonogashira coupling reactions of aryl halides with terminal acetylenes.[a]



1 **2** **3**

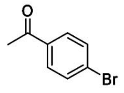
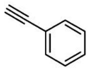
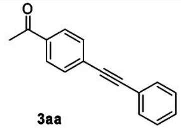
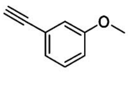
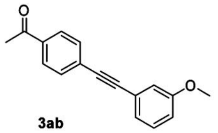
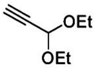
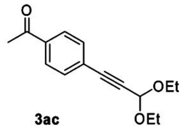
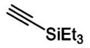
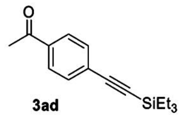
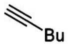
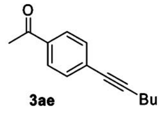
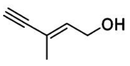
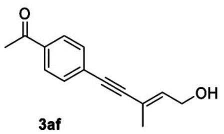
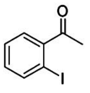
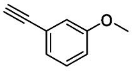
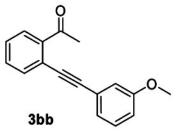
Entry	Aryl halide	Acetylene	Temp. [°C]	Time [min]	Product	Isolated yield [%]
1	 **1a**	 **2a**	120	10	 **3aa**	98
2		 **2b**	120	10	 **3ab**	99
3		 **2c**	120	30	 **3ac**	89
4		 **2d**	120	20	 **3ad**	67
5		 **2e**	120	30	 **3ae**	84
6		 **2f**	100	20	 **3af**	73
7	 **1b**	 **2b**	120	10	 **3bb**	97

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Table 5. *(continued)*

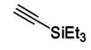
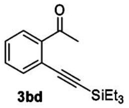
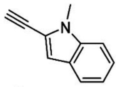
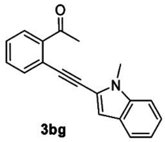
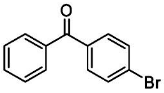
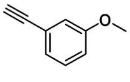
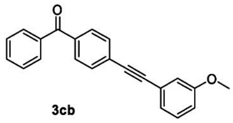
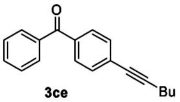
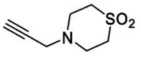
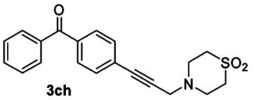
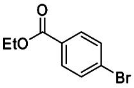
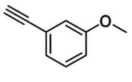
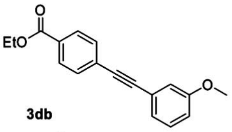
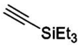
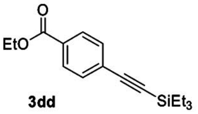
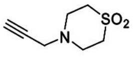
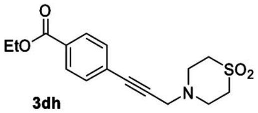
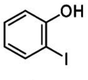
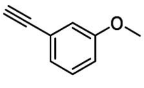
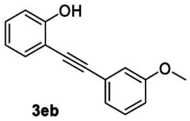
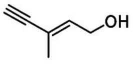
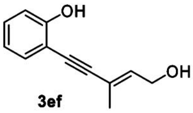
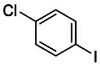
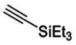
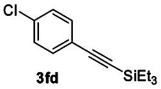
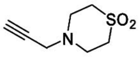
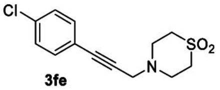
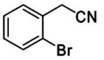
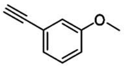
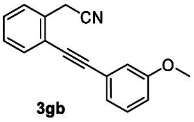
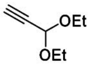
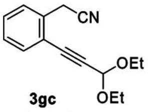
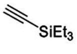
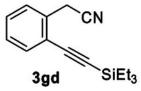
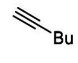
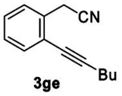
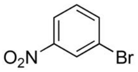
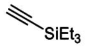
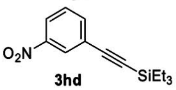
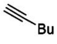
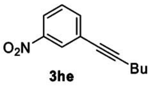
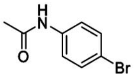
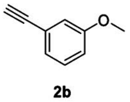
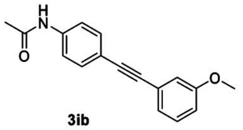
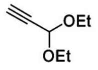
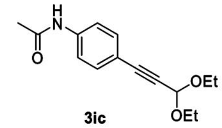
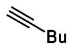
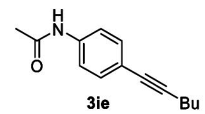
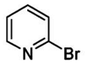
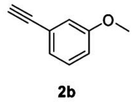
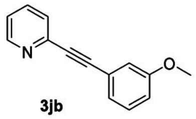
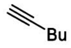
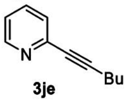
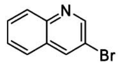
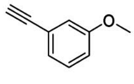
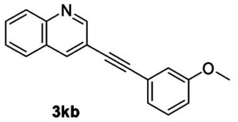
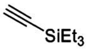
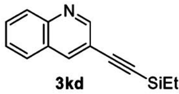
Entry	Aryl halide	Acetylene	Temp. [°C]	Time [min]	Product	Isolated yield [%]
8		 **2d**	120	20	 **3bd**	73
9		 **2g**	100	20	 **3bg**	86
10	 **1c**	 **2b**	120	10	 **3cb**	88
11		 **2e**	120	15	 **3ce**	78
12		 **2h**	120	20	 **3ch**	80
13	 **1d**	 **2b**	100	10	 **3db**	99
14		 **2d**	120	20	 **3dd**	80
15		 **2h**	100	20	 **3dh**	76
16	 **1e**	 **2b**	100	25	 **3eb**	77
17		 **2f**	120	10	 **3ef**	89
18	 **1f**	 **2d**	120	20	 **3fd**	94
19		 **2h**	120	20	 **3fe**	76
20	 **1g**	 **2b**	100	30	 **3gb**	75
21		 **2c**	120	20	 **3gc**	68
22		 **2d**	120	30	 **3gd**	80

Table 5. *(continued)*

Entry	Aryl halide	Acetylene	Temp. [°C]	Time [min]	Product	Isolated yield [%]
23		 **2e**	120	30	 **3ge**	65
26	 **1h**	 **2d**	120	50	 **3hd**	55
27		 **2e**	120	50	 **3he**	63
28	 **1i**	 **2b**	100	60	 **3ib**	67
29		 **2c**	120	40	 **3ic**	53
30		 **2e**	120	60	 **3ie**	traces
31	 **1j**	 **2b**	100	10	 **3jb**	69
32		 **2e**	120	10	 **3je**	53
33	 **1k**	 **2b**	100	40	 **3kb**	79
34		 **2d**	120	40	 **3kd**	58

[a] Reactions were carried out using 0.3 mmol of aryl halide, 0.36 mmol of acetylene, 0.36 mmol of DBU and 3.5 mol-% of Pd under cooled microwave irradiation in MeCN (0.8 mL) in a sealed tube. Compound purity determined by NMR and LCMS.

acetylenes in moderate to good yields (Table 5, Entries 31–34). As expected, less activated aryl halides in combination with less reactive terminal alkynes gave slightly lower yields under the optimized standard conditions (Table 5, Entries 23, 29–30, and 32, 34). *N*-(4-Bromophenyl)acetamide proved to be a difficult coupling partner (Table 5, Entries 33 and 34). Unprotected 4-bromoaniline and aryl chlorides in general could not be coupled under the optimized reaction conditions.

Formation of Enynes

Enynes represent important building blocks in organic synthesis,[15] we were also interested in their preparation employing the new procedure.

Indeed we were able to generate a number of functionalized enynes which can be further transformed to useful products. Using a *cis*/*trans*-mixture of β-bromostyrene (**1l**) as a vinyl bromide type substrate, the corresponding enynes **3ld** and **3lf** were isolated as mixtures of their geometric isomers in good yields (Scheme 1). Additionally we showed that the Sonogashira type coupling of both *cis*- and *trans*-1,2-dichloroethylene (Table 6, **1m**, **1n**, respectively) as halogen partners were effective in Sonogashira couplings. Unfortunately, only traces of the desired enynes were observed when employing the standard conditions; we recovered mainly unreacted starting materials. Employing the corresponding 1,2-dibromoethylene also did not lead to a successful reaction.[16] Finally it was determined that working under an inert atmosphere in dry toluene as solvent, using

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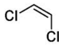
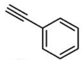
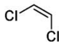
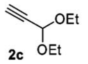
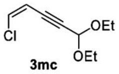
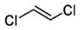
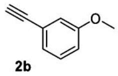
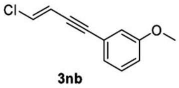
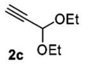
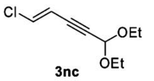
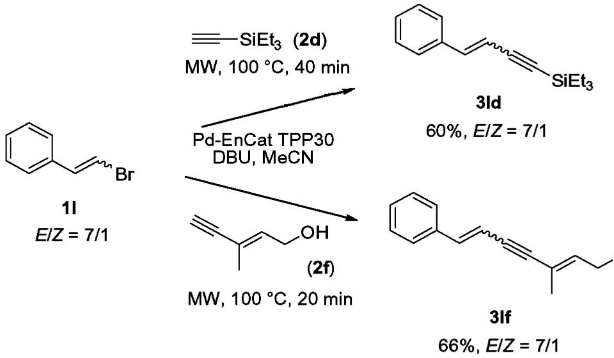
Table 6. Sonogashira-type coupling reactions of *cis*- and *trans*-1,2-dichloroethylene (**1m**, **1n**).

Entry	Dihalogen-ethylene (equiv.)	Acetylene (equiv.)	Base (equiv.)	CuI/ mol-%	Pd/ mol-%	Solvent (c [M])[a]	Temp. [°C]	Time [min]	Product	Isolated yield [%]
1	 **1m** (1.0)	 **2a** (3.0)	DBU (3.0)	–	10	MeCN (0.2)	75	180	incomplete reaction, complex mixture	–
2	 **1m** (1.0)	 **2c** (0.5)	DBU (0.5)	6	4	PhMe (0.33)	100	10	 **3mc**	89
3	 **1n** (1.0)	 **2b** (0.5)	DBU (0.5)	6	4	PhMe (0.33)	100	10	 **3nb**	67
4	(1.0)	 **2c** (0.5)	DBU (0.5)	6	4	PhMe (0.33)	100	10	 **3nc**	67

[a] Concentration is given for the halogen component.

the Pd-EnCat™ TPP30 together with a catalytic amount of copper(I) iodide the desired enynes could be generated in reasonable yields (Table 5, Entries 2–4).[17] Under these conditions the *cis*-1,2-dichloroethylene was more reactive than the *trans*-isomer.[18]



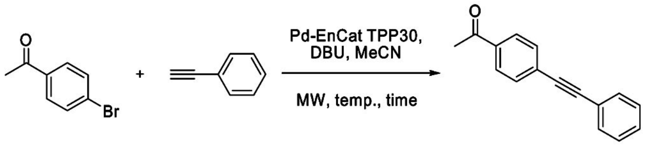
Scheme 1. Sonogashira reactions of β-bromostyrene. Reactions were carried out using 0.3 mmol of aryl halide, 0.36 mmol of acetylene, 0.36 mmol of DBU and 3.5 mol-% of Pd under cooled microwave irradiation in MeCN (0.8 mL) in a sealed tube.

Recycling of the Catalyst

Reusability of the catalyst is an important consideration pertaining to cost reduction and lowering the environmental impact, the recycle of the Pd-EnCat™ was investigated (Table 7). The coupling reaction between 4-bromoacetophenone (**1a**) and phenylacetylene (**2a**) was chosen to examine the reusability of the encapsulated palladium species. After carrying out the transformation, the reaction mixture was filtered, and the residue was washed with diethyl ether and dichloromethane. The polymeric species was dried under vacuum and subsequently reused without additional treatment. No significant loss in the catalytic activity of the Pd-EnCat™ TPP30 was observed up to the fifth use. However, for the sixth run a slightly longer reaction time was necessary to achieve the same result. These findings correspond to the fact, that the encapsulated Pd-species used in the reactions are known to release metals only very slowly,[9] which eventually lead to depletion of the metal reservoir of the Pd-EnCat™.

We also wished to establish the mode of action of the Pd-EnCat™ system by evaluating the level of active metal leached into solution. In order to test the residual palladium following a transformation substrates **1a** and **2a** were coupled under the previously optimized reaction conditions giving quantitative conversion to **3aa**. The reaction mixture was then immediately filtered to remove the heterogeneous catalyst and a second substrate combination (**1a** and **2e**) was added to the solution. The homogeneous reaction mixture was heated and the resulting solution analyzed. No formation of the desired product **3ae** was detected. It was however apparent from visual inspection of the dark coloured reaction that small quantities of palladium are leached under the standard reaction conditions albeit this species is catalytically inactive and is presumably palladium

Table 7. Reusability of the Pd-EnCat™ TPP30.[a]



1a **2a** **3aa**

Entry	Run	Temp. [°C]	Time [min]	Conversion [%][b]
1	1	120	10	98
2	2	120	10	98
3	3	120	10	92
4	4	120	10	94
5	5	120	10	90
6	6	120	15	92

[a] Reactions were carried out using 0.3 mmol of a 4-bromoacetophenone (**1a**), 0.36 mmol of phenylacetylene (**2a**), 0.36 mmol of DBU and 3.5 mol-% of Pd-EnCat™ TPP30 under cooled microwave irradiation in 0.8 mL of MeCN in a sealed tube. [b] Conversions were determined by ^{1}H NMR spectroscopy.

black. In an extension of this investigation we added an excess of a strong palladium scavenger resin, Quadrapure-TU, to a new reaction mixture prior to heating (**1a** and **2a**). This reaction proceeded to completion in an analogous way to the original reaction to furnish **3aa**. In addition the reaction mixture showed none of the previously observed dark contamination (Figure 1). We believe that these results indicate that catalysis predominantly occurs within the EnCat™ matrix (in association with the phosphane backbone) and that a combination of the heterogeneous catalyst and a scavenger resin is an ideal combination to preform these reactions cleanly.

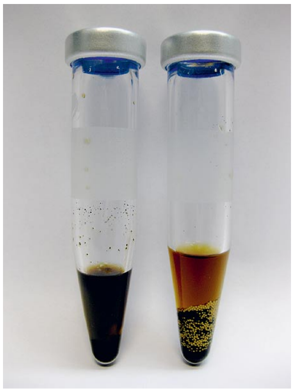


Figure 1. Comparision of the Pd-EnCat™ TPP30 (left vial) and Pd-EnCat™ TPP30 with Quadrapure-TU scavenger resin (right vial).

Conclusions

We have developed an efficient, rapid, easy to operate catalytic procedure for the microwave-assisted Sonogashira cross-coupling reaction by using an encapsulated palladium species Pd-EnCat™ TPP30 as catalyst in MeCN under copper-free reaction conditions. Various aryl iodides and bromides as well as heteroaryl species underwent the coupling reaction with differently substituted terminal alkynes to afford the corresponding coupling products in moderate to excellent yields. In addition, we were able to produce enynes using the polymeric catalyst. Finally, we demonstrated that the Pd-EnCat™ TPP30 can easily be recovered and reused for at least five cycles without a significant loss in catalytic activity.

Experimental Section

General Remarks: Acetonitrile was used as purchased without further purification. Toluene was dried, freshly distilled, and degassed before use. All reactions in toluene were performed under an atmosphere of argon and carried out using oven-dried glassware. All reactants and reagents were used as purchased without further purification. Copper(I) iodide was stored under an inert atmosphere. All microwave heating was performed on an Emrys synthesizer (Biotage AG, 1725 Discovery Drive, Charlottesville, Virginia 22911, USA) Reaction temperatures were measured using the internal IR-detector and are specified without reference to internal calibration and may differ from the true value. Air cooling of the microwave reactions is via a regulated 2 bar nitrogen pressure delivered at atmospheric temperature (20 °C). A constant microwave power input of 70–85 W was required to maintain the specified temperature of 100 or 120 °C. Infrared spectra were recorded as neat samples on a Perkin–Elmer Spectrum One FT-IR spectrometer fitted with an ATR sampling accessory. ^{1}H NMR spectra were recorded at 27 °C on Bruker DPX-400. Residual protic solvent was used as the internal reference ($CHCl_3$ δ_H = 7.27 ppm). ^{13}C NMR spectra were recorded at 100 MHz, 125 MHz and 150 MHz on Bruker DPX-400. The resonance $CDCl_3$ (δ_C = 77.0 ppm, t) was used as the internal reference. Mass spectra were recorded on Waters LCT Premier, Bruker Daltronics Bioapex II or Kratos Concept spectrometers. Accurate mass data were obtained on Micromass Q-TOF by electrospray ionisation (ESI). Melting points were performed on a Reichert hot-stage apparatus and are uncorrected. Flash column chromatography was carried out using silica gel [Merck or Breckland (230–400 mesh)] under pressure with DE/PE mixtures (DE = diethyl ether, PE = petroleum ether, boiling range 40–60 °C).

Representative Procedure for the Preparation of the Aryl Acetylenes and the Enynes 3ld and 3lf by Sonogashira Type Cross-Coupling Reactions Using Pd-EnCat™ TPP30: Preparation of 1-[4-(Phenylethynyl)phenyl]ethanone (3aa): Under aerobic conditions, a microwave vial was charged with Pd-EnCat™ TPP30 (40 mg, containing 0.01 mmol of Pd), DBU (45 µL, 0.3 mmol), 4-bromoacetophenone (**1a**) (49.8 mg, 0.25 mmol), phenylacetylene (**2a**) (30.6 mg, 0.3 mmol) and MeCN (0.8 mL). The vial was sealed and the reaction mixture was then irradiated under simultaneous cooling with streaming air for 10 min at 100 °C. After the reaction was cooled to ambient temperature, the crude reaction mixture was diluted with diethyl ether and then filtered through a short plug of silica gel. The organic layer was concentrated to yield the coupling product **3aa** in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.3 Hz, 2 H, Ph/Ar), 7.62 (d, J = 8.3 Hz, 2 H, Ph/Ar), 7.60–7.54 (m, 2 H, Ph/Ar), 7.39–7.37 (m, 3 H, Ph/Ar), 2.62 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3 (C=O), 136.1 (Ph/Ar), 131.7 (Ph/Ar), 131.6 (Ph/Ar), 128.8 (Ph/Ar), 128.4 (Ph/Ar), 128.2 (Ph/Ar), 122.6 (Ph/Ar), 92.6 (C≡C), 88.5 (C≡C), 26.6 (CH_3) ppm. The spectroscopic data correspond to the literature.[9b]

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Representative Procedure for the Preparation of the Enynes 3mc, 2nb, and 3nc by Sonogashira Type Cross-Coupling Reactions Using Pd-EnCat^{TM} TPP30: Preparation of (*Z*)-1-Chloro-5,5-diethoxypent-1-en-3-yne (3mc): Under inert conditions, a microwave vial was charged with Pd-EnCat^{TM} TPP30 (80 mg, containing 0.02 mmol of Pd), CuI (9 mg, 0.06 mmol) and with dry and degassed toluene (3 mL). Then *cis*-dichloroethylene (**1m**) (75 µL, 1.0 mmol), 3,3-diethoxyprop-1-yne (**2c**) (72 µL, 0.5 mmol) and DBU (76 µL, 0.5 mmol) were added. The vial was sealed and the reaction mixture was then irradiated for 10 min at 100 °C. After the reaction was cooled to ambient temperature, the crude reaction mixture was diluted with diethyl ether and then filtered through a short plug of silica gel. The crude mixture was purified by column chromatography to yield coupling product **3mc** in 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (d, J = 7.6 Hz, 1 H, ClHC=CH), 5.91 (dd, J = 7.6, 1.2 Hz, 1 H, ClHC=CH), 5.43 [br. d, J = 1.2 Hz, 1 H, C$H(OCH_2CH_3)_2$], 3.84–3.68 (m, 2 H, $OCH_{A2}CH_3$), 3.67–3.52 (m, 2 H, $OCH_{B2}CH_3$), 1.25 (t, J = 7.0 Hz, 6 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.0 (ClHC=C), 111.3 (ClHC=C), 92.4 (C≡C), 91.2 (C≡C), 75.1 [$CH(OCH_2CH_3)_2$], 61.3 (OCH_2CH_3), 15.0 (OCH_2CH_3) ppm. The spectroscopic data correspond to the literature.[18]

Supporting Information (see also the footnote on the first page of this article): Full experimental data and complete spectroscopic data for every newly synthesized compound.

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[1] a) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; b) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; c) E.-I. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2018; d) K. Sonogashira, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds: E.-I. Negishi, A. Meijere), Wiley-VCH, New York, **2002**, pp. 493–529; e) K. Sonogashira, in: *Metal-Catalyzed Cross-Coupling Reactions* (Eds: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 203–229; f) S. Takahashi, Y. Kuroyama, K. Sonogashira, N. Hagihara, *Synthesis* **1980**, 627–630; g) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; h) H. A. Dieck, F. R. Heck, *J. Organomet. Chem.* **1975**, *93*, 259–263.

[2] a) Z. Novnk, A. Kotschy, *Org. Lett.* **2003**, *5*, 3495–3497; b) *Chemistry and Biology of Naturally Occurring Acetylenes and Related Compounds* (Eds: J. Lam, H. Breteler, T. Arnason, L. Hansen), Elsevier, Amsterdam, **1988**.

[3] a) H. Doucet, J. C. Hierso, *Angew. Chem.* **2007**, *119*, 850–888; *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871; b) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922.

[4] P. Siemens, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740–2767; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657.

[5] a) H. Cao, L. McNamee, H. Alper, *Org. Lett.* **2008**, *10*, 5281–5284; b) P. G. De Lima, O. A. C. Antunes, *Tetrahedron Lett.* **2008**, *49*, 2506–2509; c) J.-C. Hierso, J. Boudon, M. Picquet, P. Meunier, *Eur. J. Org. Chem.* **2007**, *4*, 583–587.

[6] J. T. Guan, T. Q. Wenig, G.-A. Yu, S. H. Liu, *Tetrahedron Lett.* **2007**, *48*, 7129–7133.

[7] a) S. Mori, T. Yanase, S. Aoyagi, Y. Monguchi, T. Maegawa, H. Sajiki, *Chem. Eur. J.* **2008**, *14*, 6994–6999; b) P.-H. Li, L. Wang, *Adv. Synth. Catal.* **2006**, *348*, 681–685; c) M. B. Thathagar, G. Rothenberg, *Org. Biomol. Chem.* **2006**, *4*, 111–115; d) L. Djakovitch, P. Rollet, *Adv. Synth. Catal.* **2004**, *346*, 1782–1792; e) E. Gonthier, R. Breinbauer, *Synlett* **2003**, 1049–1051; f) Y. Uozumi, Y. Nakai, *Org. Lett.* **2002**, *4*, 2997–3000.

[8] Selected citations: a) A. Komáromi, Z. Novák, *Chem. Commun.* **2008**, 4968–4970; b) B. Liang, M. Dai, J. Chen, Z. Jang, *J. Org. Chem.* **2005**, *70*, 391–393; c) K. Heuzé, D. Méry, D. Gauss, J.-C. Blais, D. Astruc, *Chem. Eur. J.* **2004**, *10*, 3936–3944; d) N. E. Leadbeater, B. J. Tominack, *Tetrahedron Lett.* **2003**, *44*, 8653–8656.

[9] a) R. O. M. A. de Souza, M. S. Bittar, L. V. P. Mendes, C. M. F. da Silva, V. T. da Silva, O. A. C. Antunes, *Synlett* **2008**, 1777–1780; b) H. Huang, H. Liu, H. Jiang, K. Chen, *J. Org. Chem.* **2008**, *73*, 6037–6040; c) B. K. Singh, N. Kaval, S. Tomar, E. Van der Eycken, V. S. Parmar, *OPRD* **2008**, *12*, 468–474; d) K. M. Dawood, W. Solodenko, A. Kirschning, *ARKIVOC* **2007**, 104–124; e) O. G. Schramm, T. J. J. Müller, *Adv. Synth. Catal.* **2006**, *348*, 2565–2571.

[10] a) I. R. Baxendale, C. M. Griffiths-Jones, S. V. Ley, G. K. Tranmer, *Chem. Eur. J.* **2006**, *12*, 4407–4416; b) C. K. Y. Lee, A. B. Holmes, S. V. Ley, I. F. McConvey, B. Al-Duri, G. A. Leeke, R. C. D. Santos, J. P. K. Seville, *Chem. Commun.* **2005**, 2175–2177; c) D. A. Pears, S. C. Smith, *Aldrichimica Acta* **2005**, *38*, 23–33; d) http://www.reaxa.com/products/download-centre-2.html.

[11] a) J. Toubiana, M. Chidambaram, A. Santo, Y. Sasson, *Adv. Synth. Catal.* **2008**, *350*, 1230–1234; b) S. V. Ley, A. J. P. Stewart-Liddon, D. Pears, R. H. Perni, K. Treacher, *Beilstein J. Org. Chem.* **2006**, *2*, 15–19; c) S. J. Broadwater, D. T. McQuade, *J. Org. Chem.* **2006**, *71*, 2131–2134; d) C. Ramarao, D. J. Tapolczay, I. M. Shirley, S. C. Smith, S. V. Ley, US Patent Application 20040254066, **2004**.

[12] A. Carpita, A. Ribecai, *Tetrahedron Lett.* **2009**, *50*, 204–207.

[13] a) E. Comer, M. G. Organ, *J. Am. Chem. Soc.* **2005**, *127*, 8161–8167; b) W. Solodenko, H. L. Wen, S. Leue, F. Stuhlmann, G. Sourkouni-Argirusi, G. Jas, H. Schonfeld, U. Kunz, A. Kirschning, *Eur. J. Org. Chem.* **2004**, 3601–3610; c) C. O. Kappe, *Angew. Chem.* **2004**, *116*, 6408–6443; *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284; d) F. Mathew, K. N. Jayaprakash, B. Fraser-Reid, J. Mathew, J. Scicinski, *Tetrahedron Lett.* **2003**, *44*, 9051–9054; e) J. J. Chen, S. V. Deshpande, *Tetrahedron Lett.* **2003**, *44*, 8873–8876; f) B. L. Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews NC, **2002**; g) J. P. Tierney, P. Lidström (Ed.) *Microwave Assisted Organic Synthesis*, Blackwell Publishing Ltd., **2005**, ISBN 1-4051-1560-2; h) I. R. Baxendale, J. J. Hayward, S. V. Ley, *Comb. Chem. High Throughput Screening* **2007**, *10*, 802–836; i) I. R. Baxendale, M. R. Pitts, *Chim. Oggi* **2006**, *24*, 41–45.

[14] Pd-EnCat^{TM} BINAP30 was prepared in our group. For a convenient procedure for preparing encapsulated Pd-catalysts, see, for instance: a) C. Ramarao, S. V. Ley, S. C. Smith, I. M. Shirley, N. DeAlmeida, *Chem. Commun.* **2002**, 1132–1133; b) S. V. Ley, C. Ramarao, R. S. Gordon, A. B. Holmes, A. J. Morrison, I. F. McConvey, I. M. Shirley, S. C. Smith, M. D. Smith, *Chem. Commun.* **2002**, 1134–1135.

[15] a) J. W. Grissom, G. U. Gunawardena, D. Klingberg, D. Huang, *Tetrahedron* **1996**, *52*, 6453–6518.

[16] We also employed 1-iodo-2-bromoethylene as halogen component, different bases and different commonly used solvents such as DMF, THF and mixtures of solvents.

[17] a) During the investigations it emerged that the solvent has to be dry and especially well degassed. As soon as there are traces of oxygen present, the Glaser coupling reaction of the terminal acetylenes competes significantly. In those cases in which no copper(I) source was present, we assume a base-induced halogen scrambling resulting in a halogenated acetylene which then undergoes an Cadiot–Chodkiewicz type reaction with a metallated acetylene; see: W. Shi, Y. Luo, X. Luo, L. Chao, H. Zhang, J. Wang, A. Lei, *J. Am. Chem. Soc.* **2008**, *130*, 14713–14720;

see as well: b) M. Alami, F. Ferri, *Tetrahedron Lett.* **1996**, *37*, 2763–2766; c) J. Wityak, J. B. Chan, *Synth. Commun.* **1991**, *21*, 977–979; d) S. A. Nye, K. T. Potts, *Synthesis* **1988**, 375–377.

[18] A. S. Kende, C. A. Smith, *J. Org. Chem.* **1988**, *53*, 2655–2657.

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