Copper- and Phosphine-Free *Sonogashira* Coupling Reaction Catalyzed by Polyurea-Encapsulated Palladium(II)

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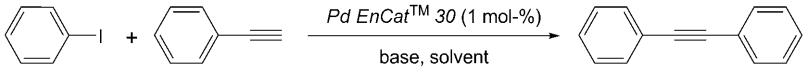
A polyurea-encapsulated palladium catalyst (*Pd EnCat*™ *30*) was first applied to *Sonogashira* cross-coupling reactions in the absence of a copper salt co-catalyst and under phosphine-free conditions. This polymer-anchored homogeneous palladium catalyst efficiently catalyzed the *Sonogashira* reaction of various iodoarenes with terminal alkynes in H_2O/MeCN, and good yields were obtained at 40° after 3–7 h in the presence of piperidine. Moreover, this catalyst maintains its efficiency through three recycle runs.

Introduction. – The *Sonogashira* cross-coupling reaction between aryl halides and terminal alkynes, which provides a powerful tool for the formation of arylalkynes, has been widely applied in natural-product synthesis and material science [1a–e] for a recent review of the *Sonogashira* coupling, see [1f]. The most commonly used catalytic systems for this transformation are $[Pd(PPh_3)_4]$, $[PdCl_2(PPh_3)_2]$, or $PdCl_2/PPh_3$ and a copper salt as co-catalyst [2]. However, the phosphines in palladium complexes are often air-sensitive, and the presence of a copper salt can result in the *in situ* formation of some copper(I) acetylides that can induce *Glaser*-type homocoupling reactions of alkynes readily [3]. To avoid this, copper- and phosphine-free *Sonogashira* reactions have been developed in recent years resulting in excellent chemoselectivity [4]. Although these examples contributed to the improvement of the *Sonogashira* coupling reaction, the use of homogeneous palladium-complex catalysts makes the separation and the recovery of the catalysts tedious and might result in unacceptable palladium contamination of the products. A way to overcome these drawbacks would be the use of a heterogeneous palladium catalyst. Recently, our attention was attracted by a series of commercially available encapsulated Pd^{II} catalysts which have been widely utilized in catalyzing C–C bond-forming processes such as carbonylations and *Suzuki*-, *Heck*-, and *Stille*-type coupling reactions in both conventional and supercritical CO_2 solvent systems in the absence of phosphine ligands [5]. Investigations on the Pd^{II}/polyurea microcapsules (*Pd EnCat*™) revealed that they are air-stable, highly active, and recoverable catalysts withstanding high temperatures and vigorous stirring. Taking these facts into consideration, we were convinced that *Pd EnCat*™ would promote the *Sonogashira* coupling in the absence of copper salts and phosphine ligands. To the best of our knowledge, there has been no full report on the *Sonogashira* reaction catalyzed by *Pd EnCat*™. In this paper, we describe a mild protocol for the copper- and phosphine-free *Sonogashira* coupling of iodoarenes with terminal alkynes in H_2O/MeCN in the presence of polyurea-encapsulated $[Pd(OAc)_2]$ catalyst (*Pd EnCat*™ *30*).

Results and Discussion. – In recent years, the development of Pd-catalyzed *Sonogashira* reactions in H_2O has aroused much interest due to economical and environmental reasons [6]. In connection with the results of microcapsule swelling behavior and palladium-leaching experiments for *Pd EnCat*™ *30* in different organic solvents [7], we initially chose the coupling of iodobenzene and ethynylbenzene in aqueous solution as the model reaction to determine the optimum reaction conditions. The coupling was carried out with 1 mol-% of *Pd EnCat*™ *30* as catalyst in the presence of a base in different solvent mixtures. As seen in *Table 1*, the best yield of the target product was obtained in the solvent H_2O/MeCN 1:1 (*Entry 5*). Having selected H_2O/MeCN 1:1 as the optimal solvent, we investigated the effect of various bases on the coupling reaction (*Entries 7–14*). The reaction proceeded well when organic bases were used, and the best result was obtained in the case of piperidine (*Entry 14*). Moreover, the *Sonogashira* reaction was faster when the temperature was increased (*Entries 15–18*); however, the GC/MS analysis demonstrated that the polyurea matrix tended to be degraded at high temperature, which might lead to many coupling by-products formed by the leaching of catalyst [$Pd(OAc)_2$] (*Entry 18*). Thus, it is appropriate that the reaction is conducted at 40°.

Table 1. *Effect of Solvent, Base, and Temperature on the* Sonogashira *Reaction*[a])



Entry	Solvent (*v/v*, 1:1)	Base	Temp. [°]	Time [h]	Yield [%][b])
1	H_2O/Me_2CO	piperidine	60	3	72
2	H_2O/EtOH	piperidine	60	3	39
3	H_2O/i-PrOH	piperidine	60	3	53
4	H_2O/dioxane	piperidine	60	3	52
5	H_2O/MeCN	piperidine	60	3	89
6	H_2O/toluene	piperidine	60	3	46
7	H_2O/MeCN	NaOH	60	7	5
8	H_2O/MeCN	KOH	60	7	0
9	H_2O/MeCN	Na_2CO_3	60	3	15
10	H_2O/MeCN	K_2CO_3	60	3	10
11	H_2O/MeCN	Et_3N	60	3	63
12	H_2O/MeCN	Bu_3N	60	3	27
13	H_2O/MeCN	i-Pr_2NH	60	3	48
14	H_2O/MeCN	piperidine	60	3	90
15	H_2O/MeCN	piperidine	20	20	51
16	H_2O/MeCN	piperidine	40	4	89
17	H_2O/MeCN	piperidine	60	3	85
18	H_2O/MeCN	piperidine	80	1.5	40

[a]) Reaction conditions: iodobenzene (1 mmol), ethynylbenzene (1.2 mmol), base (2 mmol). [b]) GC/MS Yield based on the amount of iodobenzene used.

We next investigated the copper- and phosphine-free reactions of a variety of iodoarenes with three alkynes catalyzed by polyurea-encapsulated [$Pd(OAc)_2$] in aqueous media. As summarized in *Table 2*, the optimized catalyst system (see *Table 1*)

is quite general and tolerant of a range of functionalities. For the electron-deficient iodobenzenes (*Table 2*, *Entries 7–12*), the coupling reactions were completed within 4 h, and the other iodoarenes with electron-donating groups such as a 4-MeO group required longer reaction times. The coupling reaction of iodoheteroarenes, *e.g.*, 2-iodothiophene, with terminal alkynes also proceeded smoothly under the same condition affording the corresponding coupling products in good yields (*Entries 13–15*). However, when the less reactive bromobenzene was used in the catalytic system, the desired product was obtained in poor yield after 24 h (*Entry 16*). This is consistent with the reported results on the *Sonogashira* coupling reaction of bromoarenes with terminal alkynes which was usually only well performed by Pd-catalyst in the presence of phosphine ligands or copper salts as co-catalysts [8]. The recycling studies with the polyurea-encapsulated catalyst showed that the *Pd EnCat*™ *30*, recovered by a simple filtration, kept its catalytic activity in the coupling reaction of iodobenzene and ethynylbenzene for three recycle runs under the optimal reaction condition (*Table 3*).

Conclusions. – In summary, we explored the copper- and phosphine-free *Sonogashira* coupling of iodoarenes with terminal alkynes in H_2O/MeCN in the presence of a polyurea-encapsulated [$Pd(OAc)_2$] catalyst (*Pd EnCat*™ *30*) for the first time. It is a practical, economical, and environmentally benign system for the formation of alkynylarenes.

Experimental Part

General. Reagents and chemicals were purchased from commercial suppliers and used without further purification. TLC: silica gel GF_{254} plates. M.p.: *WRB-1B* digital melting-point apparatus. ^{1}H-NMR Spectra: *Bruker-Avance-400* spectrometer; $CDCl_3$ soln.; chemical shifts δ in ppm and coupling constants J in Hz. MS: *Agilent-6890N* network GC system/*Agilent-5975* mass selective detector.

Sonogashira *Reaction of Iodoarenes: General Procedure. Pd EnCat*™ *30* (25 mg, 1 mol-% of Pd, 0.4 mmol of Pd/g) was suspended in a mixture of piperidine (0.17 g, 2 mmol) and distilled H_2O/MeCN 1:1 (4 ml). Then the iodoarene (1.0 mmol) and the alkyne (1.2 mmol) were added. The mixture was stirred at 40° for a certain period of time at 1 atm. The resulting mixture was filtered and washed with distilled H_2O (6 × 4 ml) and AcOEt (6 × 4 ml). The org. phase was dried (Na_2SO_4) and concentrated and the final product isolated by CC (SiO_2, petroleum ether/AcOEt) and identified by MS and ^{1}H-NMR.

1,1′-(Ethyne-1,2-diyl)bis[benzene]. White solid. M.p. 61–61.7° ([4b]: 60°). ^{1}H-NMR: 7.53 (*dd*, J = 4.0, 8.0, 4 H_o); 7.34 (*dd*, J = 4.0, 8.0, 4 H_m); 7.33 (*d*, J = 4.0, 2 H_p). EI-MS: 178 (100, M^+).

1-(2-Phenylethynyl)cyclohexanol. Colorless needles. M.p. 58–59° ([9a]: 59–60°). ^{1}H-NMR: 7.44–7.41 (*m*, 2 H_o); 7.30 (*dd*, J = 4.0, 8.0, 2 H_m); 7.29 (*d*, J = 4.0, H_p); 2.07–1.99 (*m*, 2 H); 1.76–1.31 (*m*, 8 H). EI-MS: 200 (40, M^+), 157 (100), 144 (25), 129 (50), 115 (30).

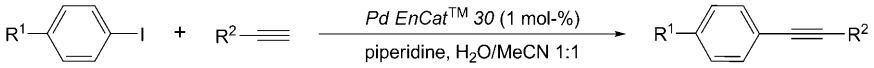
Hex-1-yn-1-ylbenzene. Pale-yellow oil. ^{1}H-NMR: 7.41–7.38 (*m*, 2 H_o); 7.29 (*dd*, J = 4.0, 8.0, 2 H_m); 7.27 (*d*, J = 4.0, H_p); 2.43 (*t*, J = 8.0, $CH_2C{\equiv}C$); 1.64–1.58 (*m*, CH_2); 1.54–1.48 (*m*, CH_2); 0.98 (*t*, J = 8.0, Me). EI-MS: 158 (40, M^+), 143 (75), 129 (80), 115 (100).

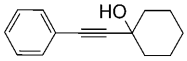
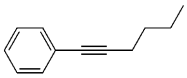
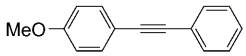
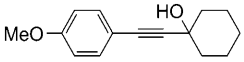
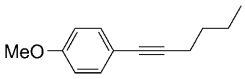
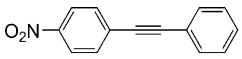
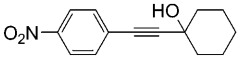
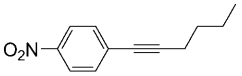
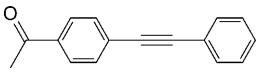
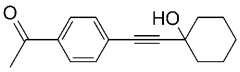
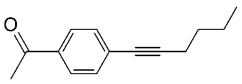
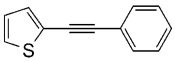
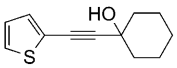
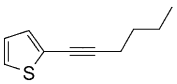
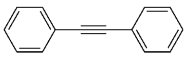
1-Methoxy-4-(2-phenylethynyl)benzene. White power. M.p. 57.3–58.1° ([9b]: 57–58°). ^{1}H-NMR: 7.48 (*d*, J = 6.0, 2 arom. H); 7.46 (*d*, J = 2.0, 2 arom. H); 7.34–7.32 (*m*, 3 arom. H); 6.87 (*d*, J = 6.0, 2 arom. H); 3.83 (*s*, MeO). EI-MS: 208 (100, M^+), 193 (40), 165 (30).

1-[2-(4-Methoxyphenyl)ethynyl]cyclohexanol. Pale-yellow oil. ^{1}H-NMR: 7.40 (*d*, J = 8.0, 2 arom. H); 6.82 (*d*, J = 8.0, 2 arom. H); 3.80 (*s*, MeO); 2.00–1.92 (*m*, 2 H); 1.70–1.30 (*m*, 8 H). EI-MS: 230 (50, M^+), 201 (25), 187 (100), 159 (30), 55 (25).

1-(Hex-1-yn-1-yl)-4-methoxybenzene. Colorless oil. ^{1}H-NMR: 7.32 (*d*, J = 8.0, 2 arom. H); 6.80 (*d*, J = 8.0, 2 arom. H); 3.80 (*s*, MeO); 2.38 (*t*, J = 8.0, CH_2); 1.61–1.54 (*m*, CH_2); 1.52–1.44 (*m*, CH_2); 0.94 (*t*, J = 8.0, Me). EI-MS: 188 (80, M^+), 145 (100).

Table 2. Sonogashira *Reaction of Iodoarenes with Terminal Alkynes*[a])



Entry	Ar–I	Alkyne	Product	Time [h]	Yield [%][b])
1	PhI	ethynylbenzene		4	90
2	PhI	1-ethynylcyclohexanol		5	85
3	PhI	hex-1-yne		5	88
4	4-MeO–C_6H_4–I	ethynylbenzene		6	85
5	4-MeO–C_6H_4–I	1-ethynylcyclohexanol		7	80
6	4-MeO–C_6H_4–I	hex-1-yne		7	81
7	4-NO_2–C_6H_4–I	ethynylbenzene		3	99
8	4-NO_2–C_6H_4–I	1-ethynylcyclohexanol		4	95
9	4-NO_2–C_6H_4–I	hex-1-yne		4	92
10	4-Ac–C_6H_4–I	ethynylbenzene		4	91
11	4-Ac–C_6H_4–I	1-ethynylcyclohexanol		4	90
12	4-Ac–C_6H_4–I	hex-1-yne		4	85
13	2-iodothiophene	ethynylbenzene		5	88
14	2-iodothiophene	1-ethynylcyclohexanol		6	80
15	2-iodothiophene	hex-1-yne		6	82
16	PhBr	ethynylbenzene		24	39[c])

[a]) Reaction conditions: iodoarene (1 mmol), terminal alkyne (1.2 mmol), 1 mol-% of *Pd EnCat*™ *30*, piperidine (2 mmol), H_2O/MeCN 1 : 1 (4 ml), 40°. [b]) Yields of isolated material. [c]) GC/MS Yield based on the amount of bromobenzene used.

Table 3. *Recycling Experiment*[a])

	Time [h]	Yield [%][b])
Cycle 1	8	88
Cycle 2	24	85
Cycle 3	40	80

[a]) Reaction conditions: iodoarene (1 mmol), terminal alkyne (1.2 mmol), 1 mol-% of *Pd EnCat*™ *30*, piperidine (2 mmol), H_2O/MeCN 1 : 1 (4 ml), 40°. [b]) GC/MS yield based on the amount of iodobenzene used.

1-Nitro-4-(2-phenylethynyl)benzene. Pale-yellow power. M.p. 117.5–118.5° ([9b]: 119–120°). ^{1}H-NMR: 8.22 (*d*, *J* = 8.8, 2 arom. H); 7.66 (*d*, *J* = 8.8, 2 arom. H); 7.57 (*d*, *J* = 9.2, 2 arom. H); 7.40–7.37 (*m*, 3 arom. H). EI-MS: 223 (100, M^+), 193 (20), 176 (60), 151 (25).

1-[2-(4-Nitrophenyl)ethynyl]cyclohexanol. Pale-yellow powder. M.p. 101.2–101.4°. ^{1}H-NMR: 8.18 (*d*, *J* = 8.0, 2 arom. H); 7.57 (*d*, *J* = 8.0, 2 arom. H); 2.03–1.98 (*m*, 2 H); 1.79–1.56 (*m*, 8 H). EI-MS: 245 (8, M^+), 228 (35), 202 (100).

1-(Hex-1-yn-1-yl)-4-nitrobenzene. Pale-yellow oil. ^{1}H-NMR: 8.12 (*d*, *J* = 8.0, 2 arom. H); 7.48 (*d*, *J* = 8.0, 2 arom. H); 2.43 (*t*, *J* = 8.0, CH_2); 1.61–1.55 (*m*, CH_2); 1.49–1.43 (*m*, CH_2); 0.94 (*t*, *J* = 8.0, Me). EI-MS: 203 (66, M^+), 188 (100), 142 (92), 128 (90), 115 (56).

1-[4-(2-Phenylethynyl)phenyl]ethanone. Colorless needles. M.p. 100.0–100.4° ([4b]: 95–96°). ^{1}H-NMR: 7.92 (*d*, *J* = 8.0, 2 arom. H); 7.56 (*d*, *J* = 8.0, 2 arom. H); 7.55–7.52 (*m*, 2 arom. H); 7.33–7.38 (*m*, 3 arom. H); 2.60 (*s*, Me). EI-MS: 220 (70, M^+), 205 (100), 176 (40), 151 (15).

1-{4-[2-(1-Hydroxycyclohexyl)ethynyl]phenyl}ethanone. Colorless crystals. M.p. 82–83° ([4b]: 82–83°). ^{1}H-NMR: 7.90 (*d*, *J* = 8.0, 2 arom. H); 7.51 (*d*, *J* = 8.0, 2 arom. H); 2.60 (*s*, Me); 2.07–2.00 (*m*, 3 H); 1.77–1.57 (*m*, 7 H). EI-MS: 242 (55, M^+), 199 (100), 171 (41).

1-[4-(Hex-1-yn-1-yl)phenyl]ethanone. Colorless oil. ^{1}H-NMR: 7.86 (*d*, *J* = 8.0, 1 arom. H); 7.82 (*d*, *J* = 8.0, 1 arom. H); 7.65 (*d*, *J* = 8.0, 1 arom. H); 7.45 (*d*, *J* = 8.0, 1 arom. H); 2.58 (*s*, Me); 2.31 (*t*, *J* = 8.0, CH_2); 1.64–1.57 (*m*, CH_2); 1.53–1.40 (*m*, CH_2); 0.95 (*t*, *J* = 8.0, CH_2). EI-MS: 200 (27, M^+), 185 (100), 157 (19), 129 (27), 115 (17).

2-(2-Phenylethynyl)thiophene. Colorless oil. ^{1}H-NMR: 7.56–7.53 (*m*, 2 arom. H); 7.38–7.36 (*m*, 3 arom. H); 7.31–7.30 (*m*, 2 arom. H); 7.03 (*dd*, *J* = 4.0, 8.0, 1 arom. H). EI-MS: 184 (100, M^+), 152 (10), 139 (15).

1-[2-(2-Thienyl)ethynyl]cyclohexanol. Colorless needles. M.p. 95.5–96.6° ([9c]: 97–99°). ^{1}H-NMR: 7.23 (*d*, *J* = 4.0, 1 arom. H); 7.19 (*d*, *J* = 4.0, 1 arom. H); 6.96 (*dd*, *J* = 4.0, 8.0, 1 arom. H); 2.04–1.98 (*m*, 3 H); 1.77–1.58 (*m*, 7 H). EI-MS: 206 (42, M^+), 163 (100), 150 (30), 135 (41), 110 (20).

2-(Hex-1-yn-1-yl)thiophene. Colorless oil. ^{1}H-NMR: 7.15 (*d*, *J* = 4.0, 1 arom. H); 7.10 (*d*, *J* = 4.0, 1 arom. H); 6.92 (*dd*, *J* = 4.0, 8.0, 1 arom. H); 2.42 (*t*, *J* = 8.0, CH_2); 1.61–1.52 (*m*, CH_2); 1.50–1.41 (*m*, CH_2); 0.88 (*t*, *J* = 8.0, Me). EI-MS: 164 (64, M^+), 149 (49), 135 (50), 121 (100).

REFERENCES

[1] a) M. Erdélyi, A. Gogoll, *J. Org. Chem*. **2001**, *66*, 4165; b) M. V. Skorobogatyi, A. A. Pchelintseva, A. L. Petrunina, I. A. Stepanova, V. L. Andronova, G. A. Galagov, A. D. Malakhov, V. A. Korshun, *Tetrahedron* **2006**, *62*, 1279; c) D. Rai, M. Johar, T. Manning, B. Agrawal, D. Y. Kunimoto, R. Kumar, *J. Med. Chem*. **2005**, *48*, 7012; d) M. Kozaki, K. Okada, *Org. Lett*. **2004**, *6*, 485; e) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem., Int. Ed*. **2000**, *39*, 2632; f) R. Chinchilla, C. Nájera, *Chem. Rev*. **2007**, *107*, 874.

[2] N. A. Bumagin, L. I. Sukhomlinova, E. V. Luzikova, T. P. Tolstaya, I. P. Beletskaya, *Tetrahedron Lett.* **1996**, *37*, 897; D. Ma, F. Liu, *Chem. Commun.* **2004**, 1934; A. Elangovan, Y.-H. Wang, T.-I. Ho, *Org. Lett.* **2003**, *5*, 1841; D. Yue, T. Yao, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 10292.

[3] C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; Q. Liu, D. J. Burton, *Tetrahedron Lett.* **1997**, *38*, 4371; J.-H. Li, Y. Liang, X.-D. Zhang, *Tetrahedron* **2005**, *61*, 1903.

[4] a) M. Pal, K. Parasuraman, S. Gupta, K. R. Yeleswarapu, *Synlett* **2002**, 1976; b) A. R. Gholap, K. Venkatesan, R. Pasricha, T. Daniel, R. J. Lahoti, K. V. Srinivasan, *J. Org. Chem.* **2005**, *70*, 4869; c) J.-H. Kim, D.-H. Lee, B.-H. Jun, Y.-S. Lee, *Tetrahedron Lett.* **2007**, *48*, 7079; d) B. Liang, M. Dai, J. Chen, Z. Yang, *J. Org. Chem.* **2005**, *70*, 391.

[5] 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; 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; S. J. Broadwater, D. T. McQuade, *J. Org. Chem.* **2006**, *71*, 2131, and ref. cit. therein.

[6] B. Liang, M. Dai, J. Chen, Z. Yang, *J. Org. Chem.* **2005**, *70*, 391; M. Cai, Q. Xu, J. Sha, *J. Mol. Catal. A: Chem.* **2007**, *272*, 293; J. T. Guan, T. Q. Weng, G.-A. Yu, S. H. Liu, *Tetrahedron Lett.* **2007**, *48*, 7129; K. W. Anderson, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.

[7] D. A. Pears, S. C. Smith, *Aldrichimica Acta* **2005**, *38*, 23.

[8] T. Mino, Y. Shirae, T. Saito, M. Sakamoto, T. Fujita, *J. Org. Chem.* **2006**, *71*, 9499; Y. Liang, Y.-X. Xie, J.-H. Li, *J. Org. Chem.* **2006**, *71*, 379; S. Y. Shi, Y. H. Zhang, *Synlett* **2007**, 1843.

[9] a) A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron* **1985**, *41*, 5121; b) N. S. Nandurkar, B. M. Bhanage, *Tetrahedron* **2008**, *64*, 3655; c) M. Csékei, Z. Novák, A. Kotschy, *Tetrahedron* **2007**, *64*, 975.

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