DOI: 10.1002/adsc.200900240

Conventional Tetrakis(triphenylphosphine)palladium-Copper(I) Iodide-Catalyzed Sonogashira Coupling of Free and BOC-Protected Propargylic Amines “On Water”

Bartomeu Soberats,[a] Luis Martínez,[a] Manuel Vega,[a] Carmen Rotger,[a] and Antoni Costa[a,]*

[a] Department de Química, Universitat de les Illes Balears, 07122 Palma de Mallorca, Spain
Fax: (+34)-971-173266; e-mail: antoni.costa@uib.es

Received: April 8, 2009; Revised: June 3, 2009; Published online: July 16, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900240.

Abstract: Alkynylation of aryl iodides with propargylic amines has been achieved by means of a Sonogashira coupling using “on water” methods. The use of less than 0.2 mol% of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] and 1.5 mol% copper(I) iodide [CuI] in the presence of diisopropylethylamine (DIPEA) allows the coupling to proceed at 95 °C yielding moderate to good yields of mono-, bis-, and tris-aminoalkynylbenzene derivatives.

Keywords: “on water” reactions; palladium-catalyzed reactions; propargylic amines; Sonogashira reaction

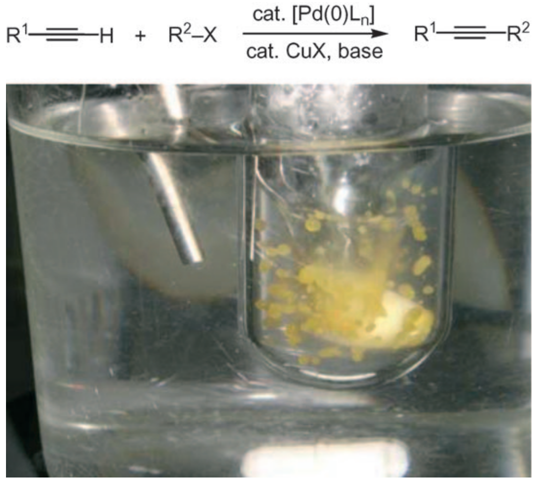


Figure 1. Sonogashira coupling performed under “on water” conditions.

The Sonogashira coupling of terminal alkynes with aryl or vinyl halides provides a powerful and widely used tool for carbon-carbon bond formation in organic synthesis.[1] The reaction has a broad scope, although it works better using electron-poor aryl iodides in combination with electron-rich alkynes, tolerating the presence of a variety of functional groups. In the classical and, probably, the more common formulation, this coupling is performed in the presence of a base, copper(I) iodide as co-catalyst and a palladium catalyst such as [$PdCl_2(PPh_3)_2$] or $Pd(PPh_3)_4$ in organic solutions under an inert atmosphere (Figure 1).[2] Recent alternatives include copper- and ligand-free reactions,[3] new palladium catalyst systems,[4] as well as significant changes in the reaction conditions and solvents. Among these, the use of water as a solvent or co-solvent has attracted increasing attention,[5] not just for the sake of environmental sustainability, but for selectivity and activation reasons as well. A number of the palladium-catalyzed alkynylations carried out under more or less aqueous conditions which have been described so far are mediated by solubilizing additives or a co-solvent,[6] and/or they are performed under forced conditions such us microwave heating,[7] and/or superheated water.[8] In addition, the coupling also works well in heterogeneous aqueous media with supported Pd catalysts.[9] In pure water, the Sonogashira coupling is effective in the presence of hydrophilic Pd catalysts,[10] a modification which is the key for the synthesis of water-soluble biomolecules.[11] In all the above experiments the different components are mixed “in water” and much emphasis is put on increasing the overall solubility of the reactants.

In spite of the problems associated with the lack of solubility of organic substrates in water, recent work by Bhattacharya and Sengupta[12] has demonstrated the feasibility of conducting Sonogashira couplings in pure water without the need for soluble catalysts. In this context, we postulated that Sonogashira couplings in pure water could experience beneficial effects with regard to rate and selectivity parameters when carried out under "on water" conditions according to the definition coined by Sharpless.[13]

In order to assess the utility of this protocol for Pd-catalyzed alkynylations and, in connection with our studies on the preparation of squaramide-based receptors,[14] we report here the direct alkynylation of aryl iodides using relatively unreactive propargylic amines[4] in order to prepare di- and tripodal free and Boc-protected arylpropargylic amines. We expected that the resulting bis- or tris-derivatives, due to their primary amino groups being separated, could serve as versatile non-collapsible spacer units for molecular recognition studies.

A brief survey of different substrates identified the hydrophobic alkynes **a** and **b** (Table 1) as effective components for the coupling "on water". To take advantage of the "on water" conditions the hydrophobic tetrakis(triphenylphosphine)palladium was selected. Copper(I) iodide was used as co-catalyst because it is insoluble in water and readily emulsified within the organic droplets. Using DIPEA as base,[15] the reactions proceeded typically at 90–95 °C in an Schlenk tube with mechanical stirring as shown in Figure 1. Remarkably, these couplings are performed with as little as 0.1–0.2 mol% Pd and (1–1.5)×N mol% CuI/substrate ratio in a 0.6–1 mmol scale. Under these conditions water-insoluble reactants and catalysts form droplets that move quickly "on water", Figure 1. The use of larger amounts of CuI, i.e., >3 mol% led to the formation of a semisolid sticky paste and a marked decrease in the product yield.

Initial experiments were carried out under ultrasonic irradiation (130 W, 20 kHz); however, we soon learned this was not avantageous but sometimes harmful to the reaction. In addition, although we never observed the competitive formation of homocoupling products[16] we used simple inert gas balloon protection as a routine.

To test the validity of the method "on water" we examined the reaction of 1,4-diiodobenzene **3** with 1-ethynylcyclohexylamine **a** dissolved either in DMF, in dioxane or in toluene for homogeneous coupling. These reactions, performed under the same experimental conditions with regard to temperature, base and catalysts as were used with water, all afforded significantly low yields ($<8\%$) of the coupling products **11** and **16**. On the other hand, aryl bromides do not react with propargyllic amines under identical experimental conditions.

The progress of the coupling "on water" was monitored by ^{1}H NMR. Figure 2 shows the changes observed over time in the aromatic protons of the initial 1,4-diiodobenzene **3** as well as in those corresponding to the mono- and bis-propargylamine derivatives, **16** and **11**, respectively. Within one hour of the addition of the reactants the intermediate monocoupled iodophenyl propargylamine **16** was produced in 55% yield along with the bis-propargylamine **11** in 25% yield. After this initial fast reaction, which consumed nearly 80% of the initial diiodobenzene, the reaction slowed and longer reaction times, 24–48 h, were required for complete evolution. No other significant products were detected during this reaction period, thus allowing the bis-propargylamine **11** to be isolated in good yield, Table 1.

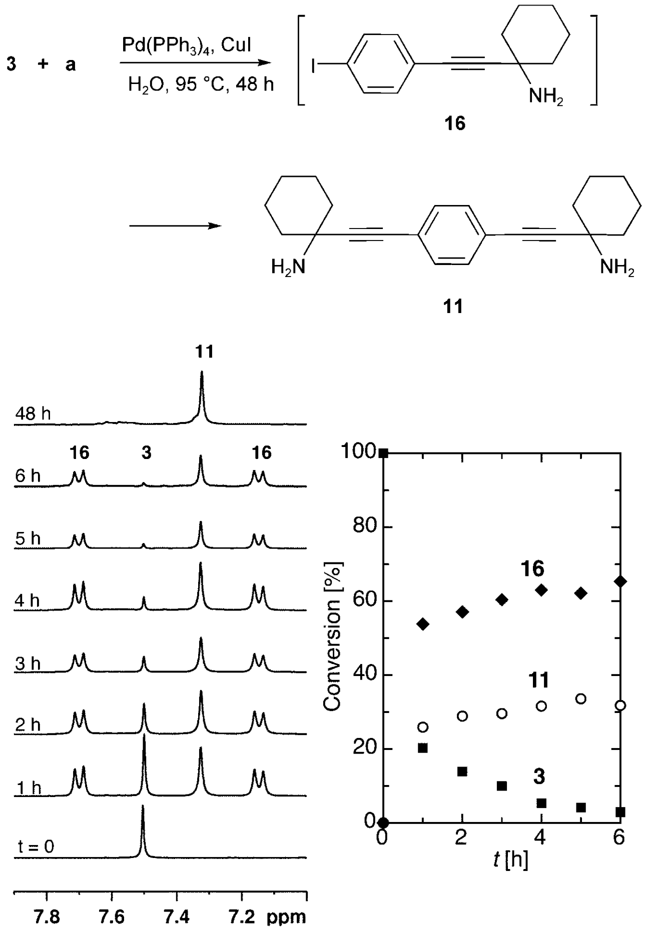
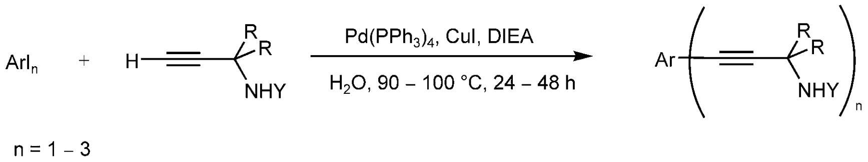
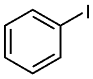
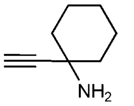
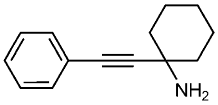
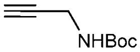
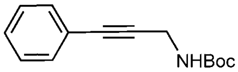
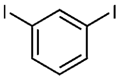
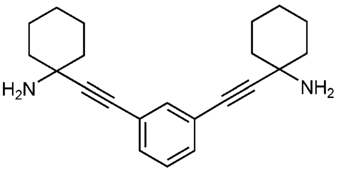
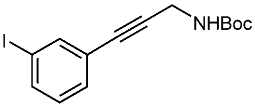
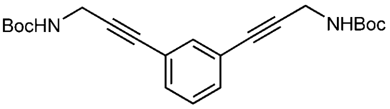
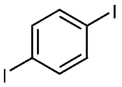
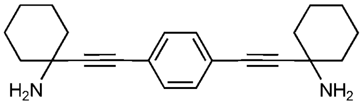
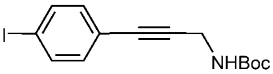
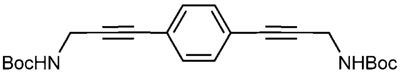
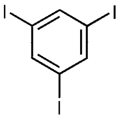
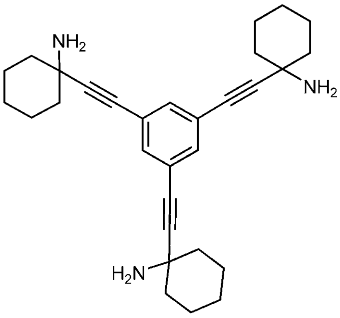
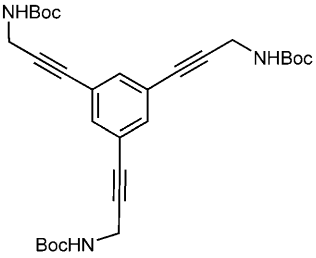


Figure 2. Evaluation of the "on water" protocol for the Sonogashira coupling of diiodide **3** with alkyne **a**. (*Left*) Relative changes in the aromatic portion of the ^{1}H NMR (DMSO-d_6) spectra over time. (*Right*) Percentage of **3** converted and formed by coupling, **16** and **11**. The relative amounts of **3**, **16** and **11** were determined by integration.

Coupling of iodobenzene derivatives **2**–**4** with propargylic amines **a** and **b** under the same experimental conditions afforded moderate to good yields of mono-, bis-, and tris-aminoalkynylbenzene derivatives. A somewhat incomplete reaction was observed for the Boc-protected series, but it still produced satisfactory

Table 1. "On water" alkynylation of mono-, di- and triiodobenzenes.



Iodide		Alkyne		Product		Yield [%][a,b]
	**1**	**a**			**6**	65
	1	**b**			**7**	40
	**2**	**a**			**8**	80
	2	**b**			**9**	25
					**10**	40
	**3**	**a**			**11**	85
	3	**b**			**12**	25
					**13**	50
	**4**	**a**			**14**	75
	4	**b**			**15**	60[c]

---

[a] See Experimental Section.

[b] Isolated yields from aryl iodides at 0.6–1 mmol scale.

[c] Estimated by ^1H NMR.

results. In fact, in this case the procedure can be optimized, by shortening the time of reaction, towards the obtention of monocoupled products.

In general, it was observed that the reaction proceeds better with unprotected alkyne **a** with TONs around 1000. This result was somewhat unexpected as free unsubstituted propargylic amines are known to be quite unreactive substrates for Sonogashira coupling.[4]

In the present case, the success of the alkynylation of aryl iodides with 1-ethynylcyclohexylamine and NBoc-protected propargylamine is mainly attributed to the increase in the effective local concentration of water-insoluble substrates and catalysts within the organic droplets compared to the concentration found in organic solution. Although other factors, such as favourable desolvation energies and hydrogen bond interactions of polar amino or amido groups with the surrounding aqueous environment, cannot be ruled out on this basis alone. Hence, we attributed the unsatisfactory results observed with propargylamine itself (3-aminopropyne), not to the already known low reactivity of this amine,[17] but to its miscibility with water which decreases the local concentration of the alkyne substrate within the organic droplets with a concomitant reduction in the rate of coupling.

In conclusion, we succeeded in applying "on water" conditions to the synthesis of arylpropargylic amines from the corresponding aryl iodides and propargylic amines *via* Sonogashira coupling. In the examples presented here, the use of "on water" conditions has a number of advantages over traditional methods, including enhanced reactivity of otherwise unreactive propargylic amines, a minimum use of Pd catalyst and the use of neat water as reaction medium. Overall, these are attractive features when considering multiple reactions for library generation or for large-scale applications.

Experimental Section

Representative Procedure for the Reaction "On Water"

A 25-mL Schlenk flask fitted with a reflux condenser was charged with an aryl iodide ($n=1$), diodide ($n=2$) or triiodide ($n=3$), (**1–4**, 1 mmol), a propargylic amine (**a**, **b**, $1.1\times n$ mmol) and 3 mL of deionized water. Then, DIPEA ($1.1\times n$ mmol) was added and the mixture stirred at 700 rpm and 95 °C. After 5 min, $Pd(PPh_3)_4$ (2–4 mg, 0.1–0.2 mol%), CuI [1.9–2.8 mg, $(1–1.5)\times 2$ mol%] and 4 mL of water were added. After heating at 95 °C under argon for 48 h, the mixture was cooled at room temperature. Then the aqueous mixture was extracted three times using ether from which the propargylic amines were isolated by conversion into hydrochlorides by slow addition of HCl in cold ether. More detailed experimental procedures are provided as Supporting Information.

Acknowledgements

This work is supported by a MEC grant ref. CTQ2008-00841/BQU and a CAIB grant ref. PCTIB-2005GC3-08 contract. B. S. thanks the DGR+D+I (Govern Balear) for a predoctoral fellowship.

References

[1] For selected recent reviews, see: a) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874–922; b) A. Nagy, Z. Novák, A. Kotschy, *J. Organomet. Chem.* **2005**, *690*, 4453–4461; c) C. J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; d) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516–4563; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; e) E. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2018; f) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46–49.

[2] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; b) H. A. Dieck, F. R. Heck, *J. Organomet. Chem.* **1975**, *93*, 259–263; c) L. Cassar, *J. Organomet. Chem.* **1975**, *93*, 253–257.

[3] S. Urgaonkar, J. G. Verkade, *J. Org. Chem.* **2004**, *69*, 5752–5755.

[4] For a comprehensive recent review on palladium-based catalysts, see: H. Doucet, J. C. Hierso, *Angew. Chem.* **2007**, *119*, 850–888; *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871, and refererences cited therein.

[5] For some recent reviews, see: a) J. Pierre Genet, M. Savignac, *J. Organomet. Chem.* **1999**, *576*, 305–317; b) ref.[1c]; c) L. Chen, C. J. Li, *Adv. Synth. Catal.* **2006**, *348*, 1459–1484; d) K. H. Shaughnessy, R. B. De Vasher, *Curr. Org. Chem.* **2005**, *9*, 585–604.

[6] a) M. S. M. Ahmed, A. Sekiguchi, K. Masui, A. Mori, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 160–168; b) A. Mori, M. S. M. Ahmed, A. Sekiguchi, K. Masui, T. Koike, *Chem. Lett.* **2002**, *31*, 756–757; c) M. Pal, V. Subramanian, K. Parasuraman, K. R. Yeleswarapu, *Tetrahedron* **2003**, *59*, 9563–9570; 60–168; d) C. Najera, J. Gil-Molto, S. Karlstrom, L. R. Falvello, *Org. Lett.* **2003**, *5*, 1451–1454; e) J. Gil-Molto, C. Najera, *Eur. J. Org. Chem.* **2005**, *19*, 4073–4081; f) C. Wolf, R. Lerebours, *Org. Biomol. Chem.* **2004**, *2*, 2161–2164; g) B. H. Lipshutz, D. W. Chung, B. Rich, *Org. Lett.* **2008**, *10*, 3793–3796; h) J. Z. Jiang, C. Cai, *J. Colloid Interface Sci.* **2007**, *307*, 300–303; i) V. R. Batchu, V. Subramanian, K. Parasuraman, N. K. Swamy, S. Kumar, M. Pal, *Tetrahedron* **2005**, *61*, 9869–9877; j) B. Liang, M. Dai, J. Chen, Z. Yang, *J. Org. Chem.* **2005**, *70*, 391–393;.

[7] a) G. Chen, X. Zhu, J. Cai, Y. Wan, *Synth. Commun.* **2007**, *37*, 1355–1361; b) H. Kawanami, K. Matsushima, M. Sato, Y. Ikushima, *Angew. Chem.* **2007**, *119*, 5221; *Angew. Chem. Int. Ed.* **2007**, *46*, 5129.

[8] a) J. T. Guan, T. Q. Weng, G. A. Yu, S. H. Liu, *Tetrahedron Lett.* **2007**, *48*, 7129–7133; b) P. Appukkuttan, W.

Dehaen, E. Van der Eycken, *Eur. J. Org. Chem.* **2003**, 4713–4716.

[9] a) R. J. Brea, M. P. López-Deber, L. Castedo, J. R. Granja, *J. Org. Chem.* **2006**, *71*, 7870–7873; b) P. Rollet, W. Kleist, V. Dufaud, L. Djakovitch, *J. Mol. Catal. A: Chem.* **2005**, *241*, 39–51; c) K. W. Anderson, S. L. Buchwald, *Angew. Chem.* **2005**, *117*, 6329; *Angew. Chem. Int. Ed.* **2005**, *44*, 6173; d) J. Gil-Moltó, S. Karlström, C. Nájera, *Tetrahedron* **2005**, *61*, 12168–12176; e) P. H. Li, L. Wang, *Adv. Synth. Catal.* **2006**, *348*, 681–685; f) C. Sotiriou-Leventis, *Synth. Commun.* **2008**, *38*, 2285–2298; g) Z. Novák, A. Szabó, J. Répási, A. Kotschy, *J. Org. Chem.* **2003**, *68*, 3327–3329; h) Z. W. Ye, W. B. Yi, *J. Fluorine Chem.* **2008**, *129*, 1124–1128; i) C. Xue, K. Palaniappan, G. Arumugam, S. A. Hackney, J. Liu, H. Liu, *Catal. Lett.* **2007**, *116*, 94–100; j) S. Raju, P. R. Kumar, K. Mukkanti, P. Annamalai, M. Pal, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6185–6189; k) Y. Uozumi, Y. Kobayashi, *Heterocycles* **2003**, *59*, 71–74; l) B. Inés, R. SanMartin, F. Churruca, E. Domínguez, M. K. Urtiaga, M. I. Arriortua, *Organometallics* **2008**, *27*, 2833–2839.

[10] a) K. H. Shaughnessy, *Eur. J. Org. Chem.* **2006**, *8*, 1827–1835; b) E. Genin, R. Amengual, V. Michelet, M. Savignac, A. Jutand, L. Neuville, J. P. Genet, *Adv. Synth. Catal.* **2004**, *346*, 1733–1741.

[11] a) H. Dibowski, F. P. Schmidtchen, *Tetrahedron Lett.* **1998**, *39*, 525–528; b) D. T. Bong, M. R. Ghadiri, *Org. Lett.* **2001**, *3*, 2509–2512.

[12] S. Bhattacharya, S. Sengupta, *Tetrahedron Lett.* **2004**, *45*, 8733–8736.

[13] a) S. Narayan, J. Muldoon, M. G. Finn, H. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339–3343; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279; for some recent examples of "on water" reactions see: b) A. Podgorvsek, S. Stavber, M. Zupan, J. Iskra, *Tetrahedron Lett.* **2006**, *47*, 1097–1099; c) S. Tiwari, A. Kumar, *Chem. Commun.* **2008**, 4445–4447; d) P. G. Cozzi, L. Zoli, *Angew. Chem.* **2008**, *120*, 4230–4234; *Angew. Chem. Int. Ed.* **2008**, *47*, 4162–4166; e) D. Bürtscher, K. Grela, *Angew. Chem.* **2008**, *120*, 2–2; *Angew. Chem. Int. Ed.* **2008**, *47*, 2–15.

[14] a) S. Tomas, R. Prohens, G. Deslongchamps, P. Ballester, A. Costa, *Angew. Chem.* **1999**, *111*, 2346–2349; *Angew. Chem. Int. Ed.* **1999**, *38*, 2208–2211; b) C. Rotger, M. N. Pina, M. Vega, P. Ballester, P. M. Deyà, A. Costa, *Angew. Chem.* **2006**, *118*, 6998–7002; *Angew. Chem. Int. Ed.* **2006**, *45*, 6844–6848.

[15] Pyrrolidine produced similar yields in this coupling. However, triethylamine led to incomplete reactions and reduced yields in the same experimental conditions.

[16] In this respect, it must be emphasized that oxygen solubility in water is at least one order of magnitude lower than in common organic solvents, see: R. Battino, T. R. Rettich, T. Tominaga, *J. Phys. Chem. Ref. Data* **1983**, *12*, 163–178.

[17] A. S. K. Hashmi, P. Haufe, A. R. Nass, J. W. Bats, *Adv. Synth. Catal.* **2004**, *346*, 421–424.