DOI: 10.1002/ejoc.201100367

Thermoregulated Copper-Free Sonogashira Coupling in Water

Ning Liu,[a] Chun Liu,*[a] Qiang Xu,[a] and Zilin Jin[a]

Keywords: Cross-coupling / Palladium / Green chemistry / Biphasic catalysis / Ligand effects

The Sonogashira cross-coupling reaction between aryl halides and terminal alkynes was carried out smoothly in water over a thermoregulated ligand–palladium catalyst under copper-free conditions, resulting in good to excellent yields. The Sonogashira reaction was sensitive to the electronic nature of the substituents on the aryl halides. Aryl halides with an electron-withdrawing group showed higher reactivity than those with an electron-donating group. Particularly, this protocol could be applied to the synthesis of liquid crystals involving *trans*-cyclohexyltolans. The products could be separated from the reaction system easily by decanting, and the catalyst was recovered in water and used directly for the next run.

Introduction

The palladium-catalyzed Sonogashira cross-coupling reaction is the most powerful method for sp^2–sp carbon–carbon bond formation between aryl or vinyl halides and terminal alkynes.[1] Both aryl alkynes and conjugated enynes find applications as pharmaceuticals, natural products, and molecular organic materials.[2]

Typical Sonogashira reactions are performed in the presence of a palladium/copper co-catalyst. The limitation of this method is that copper acetylides generated in situ tend to promote homocoupling of the terminal alkyne.[1d] Therefore, a series of palladium/silver,[3] palladium/gold,[4] and palladium-only[5] catalytic systems have been developed in recent years. Another important area of the Sonogashira reaction is the use of green solvents. In most cases, the Sonogashira reaction proceeds in organic solvents, however, developments in the use of environmentally benign solvents for such a transformations have been reported in literature, including the use of aqueous solvent,[6] solvent-free conditions,[7] ionic liquid,[8] as well as supercritical carbon dioxide.[9] Among them, the use of water as a solvent has attracted increasing attention due to cost, safety, and environmental concerns. A number of palladium-catalyzed Sonogashira reactions are performed in aqueous media with the help of solubilizing additives[10] or organic co-solvents.[11] In some cases, the aqueous protocols required more forcing reaction conditions, such as microwave heating,[12] sub-supercritical water,[13] or photo-activation.[14] However, the cross-coupling of aryl bromides with terminal alkynes using water as sole medium is rarely reported.[10b,15] In this paper, we report efforts to carry out the Sonogashira cross-coupling reaction successfully in the absence of both copper and organic solvent.

Thermomorphic systems offer an alternative approach that facilitates catalyst recycling and thus has attracted considerable attention.[16] Thermomorphic systems for the palladium-catalyzed Sonogashira reaction were reported by the groups of Bergbreiter,[17] Chiba[18] and Lu.[19] However, these methods require either copper co-catalyst or organic co-solvent, and some suffer from limited substrate scope. To the best of our knowledge, a thermoregulated ligand–palladium catalyzed copper-free Sonogashira coupling of aryl bromides in water has not been reported. Herein, we report a thermoregulated Sonogashira coupling of aryl bromides with terminal alkynes in the absence of both copper and organic solvent.

The key to the success of this approach is the use of a polyethylene glycol modified phosphane ligand, which possesses a phase-transfer property due to the cloud point (*C*p), like a non-ionic surfactant. As shown in Figure 1, the

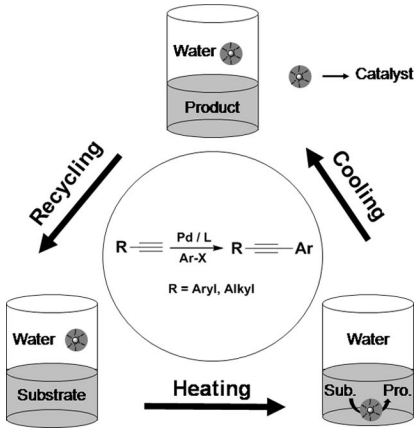


Figure 1. Thermoregulated ligand–palladium-catalyzed Sonogashira reaction in water.

[a] State Key Laboratory of Fine Chemicals, Dalian University of Technology,
Linggong Road 2, Dalian 116024, P. R. of China
Fax: +86-411-8899-3854
E-mail: chunliu70@yahoo.com

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100367.

thermoregulated catalyst is able to transfer into the substrate phase (organic phase) to catalyze the reaction at temperatures above its *C*p, thus allowing the reaction to take place in the substrate phase. As soon as the system is cooled to a temperature below the *C*p, the catalyst returns to the water phase and can be reused for the next run.

Results and Discussion

A thermoregulated ligand, $Ph_2P(CH_2CH_2O)_nCH_3$ (n = 22) (**L**; *C*p: 93 °C), was prepared according to a reported method.[20] A water-soluble palladium complex, generated in situ from **L** and $PdCl_2$ in water at room temperature, was applied to the copper-free Sonogashira reaction between aryl halides and terminal alkynes.

It is known that control of the reaction temperature is important for the efficiency of a reaction. To evaluate the influence of reaction temperature on the Sonogashira reaction, the cross-coupling of 4-bromo-1-nitrobenzene (0.5 mmol) with phenylacetylene (0.75 mmol) using $PdCl_2$ (0.3 mol-%) and **L** (0.6 mol-%) in water (1 mL), was chosen as a model reaction. As shown in Figure 2, the reaction temperature was found to play a crucial role in the Sonogashira reaction. The cross-coupling was slow at temperatures below 72 °C, and only 28% isolated yield was obtained. The coupling reaction sharply accelerated when it was performed 74 °C, affording the product in 68% yield. Upon further increasing the reaction temperature to 78 °C, the isolated yield increased to 82%. These results indicate that the cloud point of the palladium catalyst is around 74 °C. The catalyst stays in the water phase at lower temperatures (below 74 °C) and transfers into the substrate phase at higher temperatures (above 74 °C).

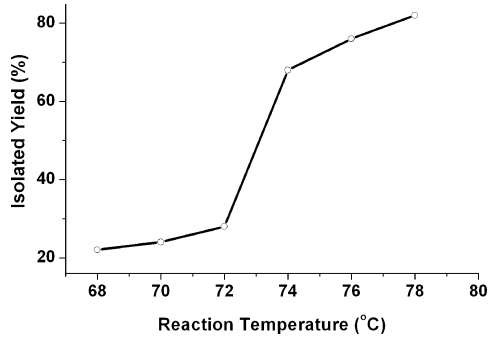
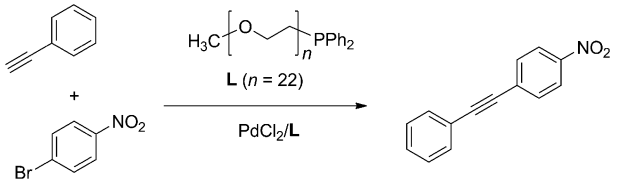


Figure 2. The effect of temperature on the Sonogashira reaction. *Reagents and conditions*: 4-bromo-1-nitrobenzene (0.5 mmol), phenylacetylene (0.75 mmol), Et_3N (1 mmol), $PdCl_2$ (0.3 mol-%), H_2O (1 mL), **L**/Pd = 2:1 (molar ratio), 1 h.

Generally, the nature of the base is an important factor that determines the efficiency of the Sonogashira cross-coupling reaction.[7f,10b] Therefore, various bases were evaluated for the coupling of 4-bromo-1-nitrobenzene with phenylacetylene in this thermoregulated system. The results are summarized in Table 1. Among the inorganic bases tested, stronger bases (Table 1, entry 5) gave better results than weaker bases (Table 1, entries 6–8). Several organic amines, such as morpholine, pyridine, and Et_3N (Table 1, entries 1, 3, and 4) afforded better results than those with inorganic bases (Table 1, entries 5–8). It is noteworthy that Et_3N achieved the highest isolated yield (Table 1, entry 1). These results indicate that the steric effect of Et_3N might be the main reason for the high activity. Thus, more hindered $(n\text{Pr})_3N$ was further investigated (Table 1, entry 2). Unfortunately, use of the latter base did not improve on the result obtained with Et_3N, which is consistent with reports by Lipshutz and co-workers.[10b]

Table 1. The effect of base on the Sonogashira reaction.[a]

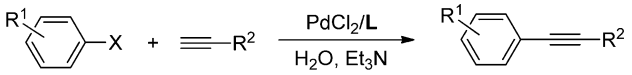


Entry	Base	Yield [%][b]
1	**Et_3N**	**92**
2	$(n\text{Pr})_3N$	64
3	morpholine	34
4	pyridine	28
5	NaOH	9
6	$K_3PO_4{\cdot}7H_2O$	trace amount
7	K_2CO_3	trace amount
8	Na_2CO_3	trace amount

[a] Reagents and conditions: 4-bromo-1-nitrobenzene (0.5 mmol), phenylacetylene (0.75 mmol), base (1 mmol), $PdCl_2$ (0.3 mol-%), H_2O (1 mL), **L**/Pd = 2:1 (molar ratio), 80 °C, 1 h. [b] Isolated yield.

Initially, we applied the optimized conditions for the Sonogashira cross-coupling reaction of a range of aryl iodides with arylacetylene in the presence of 0.3 mol-% $PdCl_2$ at 80 °C in 1 mL water. As illustrated in Table 2, the results showed that the coupling of aryl iodides with arylacetylene took place smoothly to give a near quantitative yield of diarylacetylene (Table 2, entries 1–6). Since aryl bromides are less expensive and more readily available than aryl iodides, we examined the coupling reaction of aryl bromides under the optimized conditions and were pleased to find that the present thermoregulated protocol can be applied to the Sonogashira coupling of various alkynes with aryl bromides, resulting in formation of the desired cross-coupling products in good to excellent yields with a low catalyst loading of 0.3 mol-%. As shown in Table 2, aryl bromides containing an electron-withdrawing group such as 4-NO_2 and 4-$COCH_3$, reacted smoothly with electron-poor, electron-neutral, or electron-rich aryl alkynes to provide the corresponding cross-coupling products in high yields (Table 2, entries 7–14). However, 4-bromobenzonitrile gave a less satisfactory result (Table 2, entry 15). Aryl bromides containing an electron-donating group were further investigated. As illustrated in Table 2, 4-bromoanisole was less reactive in this system. Nonetheless, good yields were obtained by extending the reaction time to 6 h (Table 2, entries 16–18). For example, the coupling between 4-bromoanisole and phenylacetylene gave the desired product in 79% yield

Table 2. Sonogashira reaction between aryl halides and terminal alkynes in water.[a]



X = Cl, Br, I; R^2 = Aryl or Alkyl

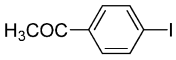
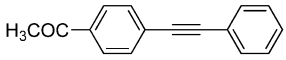
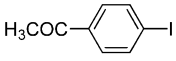
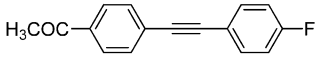
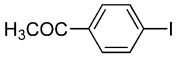
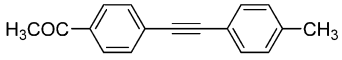
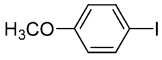
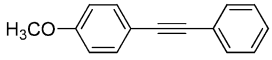
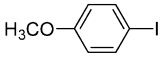
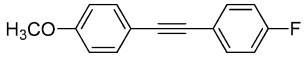
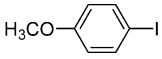
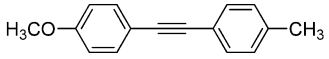
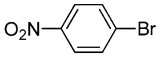
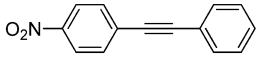
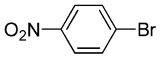
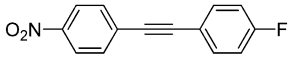
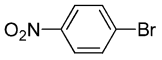
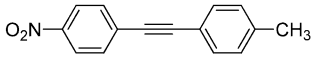
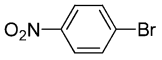
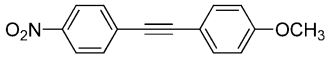
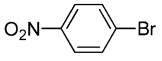
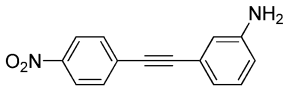
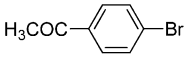
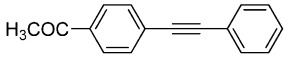
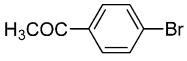
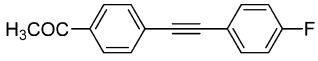
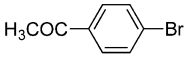
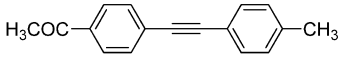
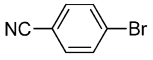
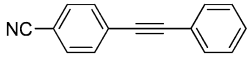
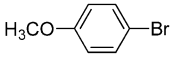
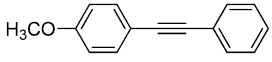
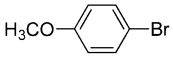
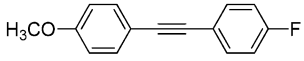
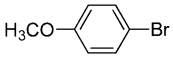
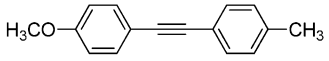
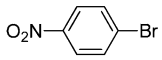
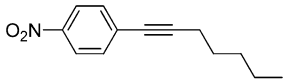
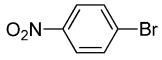
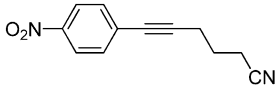
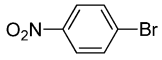
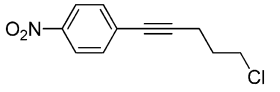
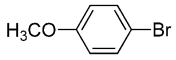
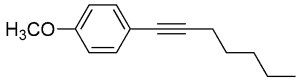
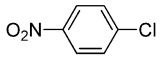
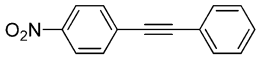
Entry	Aryl halide	Product	Time [h]	Yield [%][c]
1			1	96
2			1	95
3			1	93
4			2	95
5			2	96
6			2	92
7			1.5	98
8			2	97
9			3	96
10			3	98
11			1	97
12			4	92
13			4	89
14			4	83
15			4	72
16			6	79
17			6	71
18			6	62

Table 2. *(Continued)*

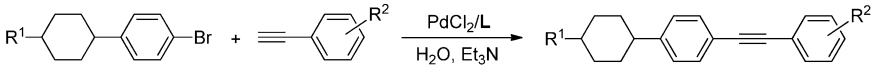
Entry	Aryl halide	Product	Time [h]	Yield [%][c]
19			2	98
20			1	96
21			1	97
22			6	77
23			8	12[b]

[a] Reagents and conditions: aryl bromide (0.5 mmol), terminal alkyne (0.75 mmol), Et_3N (1 mmol), $PdCl_2$ (0.3 mol-%), H_2O (1 mL), **L**/Pd = 2:1 (molar ratio), 80 °C. [b] 0.5 mol-% $PdCl_2$. [c] Isolated yield.

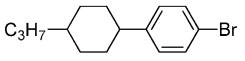
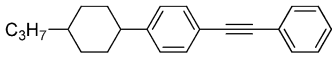
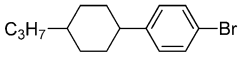
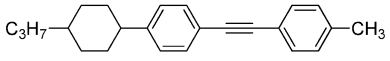
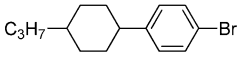
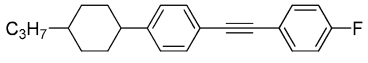
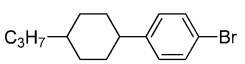
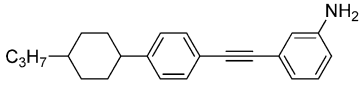
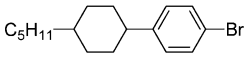
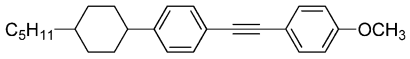
(Table 2, entry 16). According to literature reports, the reactivity of alkylacetylenes is usually lower than those of aryl alkynes.[21] To our delight, the catalytic system was also effective towards the couplings of alkylacetylenes bearing aliphatic substituents, giving the corresponding product in excellent yields (Table 2, entries 19–22). For example, 4-bromo-1-nitrobenzene underwent the Sonogashira coupling with 1-heptyne to afford the desired product in 98% yield (Table 2, entry 19). The results suggest that alkylacetylenes containing electron-withdrawing groups, such as cyano and chloro (Table 2, entries 20–21), were more reactive than 1-heptyne (Table 2, entry 19). However, efforts to activate aryl chlorides in this thermoregulated system to reach a high yield were unsuccessful, even after prolonging the reaction time to 8 h and using a palladium loading of 0.5 mol-% (Table 2, entry 23).

Diarylacetylenes are of particular interest in the synthesis of liquid crystals due to their unique physical properties, [22] and the use of the Sonogashira cross-coupling reaction to access liquid crystals containing a diarylacetylene structural

Table 3. The synthesis of liquid crystals.[a]



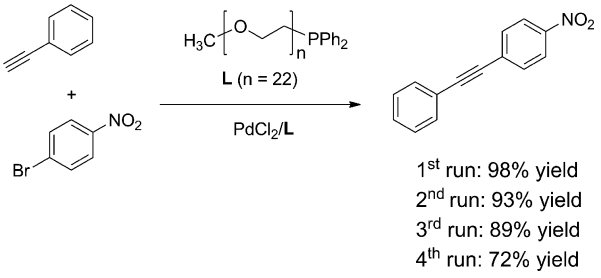
R^1 = *n*-C_3H_7, *n*-C_5H_{11}; R^2 = CH_3O, CH_3, NH_2, F

Entry	Ar–Br	Product	Time [h]	Yield [%][b]
1			5	74
2			8	67
3			8	78
4			8	83
5			8	71

[a] Reagents and conditions: aryl bromide (0.5 mmol), arylacetylene (0.75 mmol), Et_3N (1 mmol), $PdCl_2$ (1 mol-%), H_2O (1 mL), **L**/Pd = 2:1 (molar ratio), 80 °C. [b] Isolated yield.

unit has gained much attention. Present methods require either copper co-catalyst or organic co-solvent, and suffer from limited substrate scope.[23] To the best of our knowledge, there is no report on the synthesis of liquid crystals containing a diarylacetylene unit through a copper-free Sonogashira coupling in water. Thus, we applied this thermoregulated Sonogashira reaction system to the synthesis of *trans*-cyclohexyltolan-type liquid crystals. In Table 3, results of the Sonogashira coupling of aryl alkynes with 1-bromo-4-(*trans*-4-propylcyclohexyl)benzene are reported. Aryl alkynes bearing electron-poor, electron-neutral, and electron-rich groups proceeded smoothly, affording the corresponding product in good yields at a palladium loading of 1 mol-% (Table 3, entries 1–4). 1-Bromo-4-(*trans*-4-pentylcyclohexyl)benzene was also successfully coupled with 4-methoxyphenylacetylene to give the desired product in 71% yield (Table 3, entry 5).

To evaluate the reusability of the thermoregulated ligand–palladium catalyst, recycling studies were carried out for the cross-coupling of 4-bromo-1-nitrobenzene with phenylacetylene in water (1 mL) at 80 °C for 1.5 h using a palladium loading of 0.3 mol-% (Scheme 1). After the reaction was complete and cooled to room temperature, the product was extracted with ethyl ether and the water phase containing the catalyst was loaded with the reactants and bases for the next run. As shown in Scheme 1, the catalyst can be recycled three times. However, a clear loss of catalytic activity was observed in the fourth run. The cause of the decrease in catalytic activity is under investigation.



Scheme 1. Recycling experiments.

Conclusions

We have demonstrated that the thermoregulated ligand–palladium-catalyst system gives good activity for the Sonogashira coupling with a wide range of substrates using water as sole medium. Further work to develop more efficient thermoregulated ligands is underway in our laboratory.

Experimental Section

General Remarks: All the reactions were carried out under nitrogen. All aryl halides and terminal alkynes were purchased from Alfa Aesar or Avocado. Other chemicals were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded with a Bruker Advance II 400 spectrometer. ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal standard. Mass spectroscopy data of the products were collected with a MS-EI instrument. All products were isolated by short chromatography on a silica gel (200–300 mesh) using petroleum ether (60–90 °C), unless otherwise noted. Compounds described in the literature were characterized by ^{1}H NMR spectroscopy and compared to the reported data.

Synthesis of $Ph_2P(CH_2CH_2O)_nCH_3$ (n = 22) (L): The ligand $Ph_2P(CH_2CH_2O)_nCH_3$ (n = 22) (**L**, *C*p: 93 °C) was prepared from $CH_3(OCH_2CH_2)_nOSO_2CH_3$ (n = 22) and $LiPPh_2$ according to the reported method.[20] ^{1}H NMR (400 MHz, D_2O): δ = 2.39 (t, J = 7.6 Hz, 2 H), 3.37 (s, 3 H), 3.55–3.65 (m, 95 H), 7.31–7.50 (m, 10 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 28.64 (d), 58.75 (s), 68.16 (d), 69.88–71.70 (m), 128.17 (s), 128.30 (d), 132.40 (d), 138.08 (d) ppm. ^{31}P NMR (400 MHz, D_2O): δ = –22.70 ppm.

General Procedure for the Sonogashira Reaction of Aryl Halides with Terminal Alkynes: A solution of $PdCl_2$ (0.27 mg, 0.0015 mmol) and ligand **L** (3.6 mg, 0.003 mmol) in deoxygenated H_2O (1 mL) was stirred at room temperature for 30 min under nitrogen. Et_3N (1 mmol, 101 mg), aryl halide (0.5 mmol), and terminal alkyne (0.75 mmol) were then successively added. The reaction mixture was heated in an oil bath under nitrogen with magnetic stirring. After cooling to room temperature, the reaction mixture was added to brine (15 mL) and extracted three times with diethyl ether (3 × 15 mL). The solvent was concentrated under vacuum and the product was isolated by short column chromatography on a silica gel (200–300 mesh).

Catalyst Recycling for the Sonogashira Reaction: When the reaction was completed, the reaction mixture was cooled to room temperature and extracted with ethyl ether (2 mL). Et_3N (1 mmol, 101 mg), 4-bromo-1-nitrobenzene (0.5 mmol) and phenylacetylene (0.75 mmol) were added to the aqueous phase that was separated from the previous catalytic run under nitrogen, and reacted at 80 °C.

3-[(4-Nitrophenyl)ethynyl]aniline: 115.5 mg (97% yield); yellow solid (m.p. 180–181 °C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.20–8.23 (m, 2 H, Ar-H), 7.63–7.66 (m, 2 H, Ar-H), 7.17 (t, J = 8.0 Hz, 1 H, Ar-H), 6.87–6.97 (m, 2 H, Ar-H), 6.70–6.73 (m, 1 H, Ar-H), 3.74 (s, 2 H, NH_2) ppm. ^{13}C NMR: δ = 146.92 (C_{ar}), 146.45 (C_{ar}), 132.25 (2×C_{ar}), 130.42 (C_{ar}), 129.49 (C_{ar}), 123.62 (2×C_{ar}), 122.77 (C_{ar}), 122.25 (C_{ar}), 117.83 (C_{ar}), 116.28 (C_{ar}), 95.10 (C≡C), 86.97 (C≡C) ppm. MS (EI): m/z (%) = 238 (100) [M^+], 238, 208, 180, 141, 104, 90, 76.

1-(Heptynyl)-4-nitrobenzene: 106.5 mg (98% yield); yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.15 (d, J = 8.0 Hz, 2 H, Ar-H), 7.51 (d, J = 8.0 Hz, 2 H, Ar-H), 2.44 (t, J = 7.2 Hz, 2 H, CH_2), 1.60–1.67 (m, 2 H, CH_2), 1.34–1.47 (m, 4 H, CH_2), 0.93 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 146.76 (C_{ar}), 132.42 (2×C_{ar}), 131.41 (C_{ar}), 123.66 (2×C_{ar}), 97.00 (C≡C), 79.48 (C≡C), 31.30 (CH_2), 28.29 (CH_2), 22.37 (CH_2), 19.72 (CH_2), 14.14 (CH_3) ppm. MS (EI): m/z (%) = 217 (100) [M^+], 217, 187, 158, 144, 130, 115, 77.

6-(4-Nitrophenyl)hex-5-ynenitrile: 103.1 mg (96% yield); yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.16 (d, J = 8.8 Hz, 2 H, Ar-H), 7.54 (d, J = 8.8 Hz, 2 H, Ar-H), 2.67 (t, J = 6.8 Hz, 2 H, CH_2), 2.58 (t, J = 7.2 Hz, 2 H, CH_2), 1.97–2.04 (m, 2 H, CH_2) ppm. ^{13}C NMR: δ = 146.97 (C_{ar}), 132.43 (2×C_{ar}), 130.29 (C_{ar}), 123.60 (2×C_{ar}), 119.05 (CN), 93.09 (C≡C), 80.88 (C≡C), 24.33 (CH_2), 18.74 (CH_2), 16.39 (CH_2) ppm. MS (EI): m/z (%) = 214 (100) [M^+], 214, 184, 167, 149, 130, 77, 63, 51, 39.

1-(5-Chloropentynyl)-4-nitrobenzene: 108.6 mg (97% yield); yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.16 (d, J = 8.4 Hz, 2 H, Ar-H), 7.52 (d, J = 8.8 Hz, 2 H, Ar-H), 3.71 (t, J = 6.4 Hz, 2 H, CH_2), 2.67 (t, J = 6.8 Hz, 2 H, CH_2), 2.06–2.12 (m, 2 H, CH_2) ppm. ^{13}C NMR: δ = 146.89 (C_{ar}), 132.45 (2×C_{ar}), 130.73 (C_{ar}), 123.63 (2×C_{ar}), 94.40 (C≡C), 80.20 (C≡C), 43.70 (CH_2), 31.19 (CH_2), 17.12 (CH_2) ppm. MS (EI): *m*/*z* (%) = 223 (100) [M^+], 223, 193, 188, 157, 142, 102, 88, 77, 63, 51, 39.

1-(Phenylethynyl)-4-(4-propylcyclohexyl)benzene: 112.4 mg (74% yield); light-yellow solid (m.p. 87–88 °C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.53–7.51 (m, 2 H, Ar-H), 7.45 (dd, J = 8.4, 1.6 Hz, 2 H, Ar-H), 7.35–7.31 (m, 3 H, Ar-H), 7.19 (d, J = 8.4 Hz, 2 H, Ar-H), 2.50–2.43 (m, 1 H, *c*Hex-H), 1.90–1.85 (m, 4 H, CH_2CH_2), 1.49–0.99 (m, 9 H, *c*Hex-H), 0.90 (t, J = 8.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 148.35 (C_{ar}), 131.58 (3×C_{ar}), 128.32 (2×C_{ar}), 128.06 (C_{ar}), 126.92 (2×C_{ar}), 123.55 (C_{ar}), 120.57 (C_{ar}), 89.65 (C≡C), 88.69 (C≡C), 44.60 ($C_{c\mathrm{Hex}}$), 39.72 ($C_{c\mathrm{Hex}}$), 37.01 (CH_2), 34.17 (2×$C_{c\mathrm{Hex}}$), 33.50 (2×$C_{c\mathrm{Hex}}$), 20.06 (CH_2), 14.45 (CH_3) ppm. MS (EI): *m*/*z* (%) = 302 (100) [M^+], 302, 217, 204, 191, 165, 115, 91, 55.

3-{[4-(4-Propylcyclohexyl)phenyl]ethynyl}aniline: 131.8 mg (83% yield); brown solid (m.p. 95–96 °C). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.43 (d, J = 8.0 Hz, 2 H, Ar-H), 7.18 (d, J = 8.0 Hz, 2 H, Ar-H), 7.12 (t, J = 8.0 Hz, 1 H, Ar-H), 6.93 (d, J = 8.0 Hz, 1 H, Ar-H), 6.84 (s, 1 H, Ar-H), 6.66–6.63 (m, 1 H, Ar-H), 3.67 (s, 2 H, NH_2), 2.47–2.43 (m, 1 H, *c*Hex-H), 1.90–1.85 (m, 4 H, CH_2CH_2), 1.49–0.99 (m, 9 H, *c*Hex-H), 0.90 (t, J = 8.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 148.24 (C_{ar}), 146.24 (C_{ar}), 131.56 (2×C_{ar}), 129.25 (C_{ar}), 126.88 (2×C_{ar}), 124.22 (C_{ar}), 122.07 (C_{ar}), 120.65 (C_{ar}), 117.82 (C_{ar}), 115.17 (C_{ar}), 89.04 (C≡C), 88.90 (C≡C), 44.59 ($C_{c\mathrm{Hex}}$), 39.70 ($C_{c\mathrm{Hex}}$), 37.00 (CH_2), 34.15 (2×$C_{c\mathrm{Hex}}$), 33.50 (2×$C_{c\mathrm{Hex}}$), 20.04 (CH_2), 14.42 (CH_3) ppm. MS (EI): m/z (%) = 317 (100) [M^+], 317, 232, 206, 193, 165, 97, 55.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra of all cross-coupling products.

Acknowledgments

The authors thank the National Natural Science Foundation of China (NSFC) (grant numbers 20976024, 20923006, 21076034), Fundamental Research Funds for the Central Universities (grant number DUT11LK15), Dalian University of Technology (grant numbers DUTTX2009102, JG0916), and the Ministry of Education (Program for New Century Excellent Talents in University) for financial support.

[1] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; b) K. Sonogashira, *J. Organomet. Chem.* **2002**, *653*, 46–49; c) E.-I. Negishi, L. Anastasia, *Chem. Rev.* **2003**, *103*, 1979–2017; d) R. Chinchilla, C. Nájera, *Chem. Rev.* **2007**, *107*, 874–922; e) H. Doucet, J.-C. Hierso, *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871; f) H. Plenio, *Angew. Chem. Int. Ed.* **2008**, *47*, 6954–6956.

[2] a) P. Appukkuttan, E. Van der Eycken, *Eur. J. Org. Chem.* **2008**, 1133–1155; b) J. H. Cho, C. D. Prickett, K. H. Shaughnessy, *Eur. J. Org. Chem.* **2010**, 3678–3683; c) I. Malik, Z. Ahmed, S. Reimann, I. Ali, A. Villinger, P. Langer, *Eur. J. Org. Chem.* **2011**, *11*, 2088–2093; d) B. de Carné-Carnavalet, A. Archambeau, C. Meyer, J. Cossy, B. Folléas, J.-L. Brayer, J.-P. Demoute, *Org. Lett.* **2011**, *13*, 956–959.

[3] U. Létinois-Halbes, P. Pale, S. Berger, *J. Org. Chem.* **2005**, *70*, 9185–9190.

[4] B. Panda, T. K. Sarkar, *Tetrahedron Lett.* **2010**, *51*, 301–305.

[5] a) K. W. Anderson, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2005**, *44*, 6173–6177; b) F. Li, T. S. A. Hor, *Adv. Synth. Catal.* **2008**, *350*, 2391–2400; c) A. John, M. M. Shaikh, P. Ghosh, *Dalton Trans.* **2009**, 10581–10591.

[6] a) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3166; b) S. Roy, H. Plenio, *Adv. Synth. Catal.* **2010**, *352*, 1014–1022; c) J. D. Senra, L. F. B. Malta, M. E. H. M. da Costa, R. C. Michel, L. C. S. Aguiar, A. B. C. Simas, O. A. C. Antunes, *Adv. Synth. Catal.* **2009**, *351*, 2411–2422; d) B. Soberats, L. Martínez, M. Vega, C. Rotger, A. Costa, *Adv. Synth. Catal.* **2009**, *351*, 1727–1731; e) H. Firouzabadi, N. Iranpoor, M. Gholinejad, *J. Mol. Catal. A: Chem.* **2010**, *321*, 110–116; f) M. Bakherad, A. Keivanloo, Z. Kalantar, S. Jajarmi, *Tetrahedron Lett.* **2011**, *52*, 228–230; g) D. Rosario-Amorin, M. Gaboyard, R. Clérac, S. Nlate, K. Heuzé, *Dalton Trans.* **2011**, *40*, 44–46.

[7] a) Y. Liang, Y.-X. Xie, J.-H. Li, *J. Org. Chem.* **2006**, *71*, 379–381; b) D. A. Fulmer, W. C. Shearouse, S. T. Medonza, J. Mack, *Green Chem.* **2009**, *11*, 1821–1825; c) A. Carpita, A. Ribecai, *Tetrahedron Lett.* **2009**, *50*, 204–207; d) R. Luque, D. J. Macquarrie, *Org. Biomol. Chem.* **2009**, *7*, 1627–1632; e) M. Bakherad, A. Keivanloo, B. Bahramian, S. Jajarmi, *Appl. Catal. A* **2010**, *390*, 135–140; f) R. Thorwirth, A. Stolle, B. Ondruschka, *Green Chem.* **2010**, *12*, 985–991.

[8] a) Y. Liu, S.-S. Wang, W. Liu, Q.-X. Wan, H.-Y. Wu, G.-H. Gao, *Curr. Org. Chem.* **2009**, *13*, 1322–1346; b) R. Singh, M. Sharma, R. Mamgain, D. S. Rawat, *J. Braz. Chem. Soc.* **2008**, *19*, 357–379; c) H. Gao, L. McNamee, H. Alper, *Org. Lett.* **2008**, *10*, 5281–5284; d) P. G. de Lima, O. A. C. Antunes, *Tetrahedron Lett.* **2008**, *49*, 2506–2509; e) J. R. Harjani, T. J. Abraham, A. T. Gomez, M. T. Garcia, R. D. Singer, P. J. Scammells, *Green Chem.* **2010**, *12*, 650–655; f) V. Singh, R. Ratti, S. Kaur, *J. Mol. Catal. A: Chem.* **2011**, *334*, 13–19.

[9] Y. Akiyama, X. Meng, S. Fujita, Y.-C. Chen, N. Lu, H. Cheng, F. Zhao, M. Arai, *J. Supercrit. Fluids* **2009**, *51*, 209–216.

[10] a) C. Wolf, R. Lerebours, *Org. Biomol. Chem.* **2004**, *2*, 2161–2164; b) B. H. Lipshutz, D. W. Chung, B. Rich, *Org. Lett.* **2008**, *10*, 3793–3796; c) M. Bakherad, A. Keivanloo, B. Bahramian, M. Hashemi, *Tetrahedron Lett.* **2009**, *50*, 1557–1559; d) M.-J. Jin, D.-H. Lee, *Angew. Chem. Int. Ed.* **2010**, *49*, 1119–1122.

[11] a) C. A. Fleckenstein, H. Plenio, *Chem. Eur. J.* **2007**, *13*, 2701–2716; b) S. Mori, T. Yanase, S. Aoyagi, Y. Monguchi, T. Maegawa, H. Sajiki, *Chem. Eur. J.* **2008**, *14*, 6994–6999; c) R. J. Brea, M. P. López-Deber, L. Castedo, J. R. Granja, *J. Org. Chem.* **2006**, *71*, 7870–7873.

[12] a) P. Appukkuttan, E. Van der Eycken, *Eur. J. Org. Chem.* **2003**, 4713–4716; b) J. Gil-Moltó, C. Nájera, *Eur. J. Org. Chem.* **2005**, 4073–4081; c) K. M. Dawood, W. Solodenko, A. Kirschning, *ARKIVOC* **2007**, *5*, 104–124; d) G. Chen, X. Zhu, J. Cai, Y. Wan, *Synth. Commun.* **2007**, *37*, 1355–1361.

[13] H. Kawanami, K. Matsushima, M. Sato, Y. Ikushima, *Angew. Chem. Int. Ed.* **2007**, *46*, 5129–5132.

[14] M. Osawa, H. Nagai, M. Akita, *Dalton Trans.* **2007**, 827–829.

[15] M. Lamblin, L. Nassar-Hardy, J.-C. Hierso, E. Fouquet, F.-X. Felpin, *Adv. Synth. Catal.* **2010**, *352*, 33–79.

[16] a) D. E. Bergbreiter, *Chem. Rev.* **2002**, *102*, 3345–3384; b) D. E. Bergbreiter, S. D. Sung, *Adv. Synth. Catal.* **2006**, *348*, 1352–1366; c) A. Corma, H. García, A. Leyva, *J. Catal.* **2006**, *240*, 87–99; d) H. Azoui, K. Baczko, S. Cassel, C. Larpent, *Green Chem.* **2008**, *10*, 1197–1203; e) Y. Wang, J. Zhang, W. Zhang, M. Zhang, *J. Org. Chem.* **2009**, *74*, 1923–1931; f) A. Behr, L. Johnen, N. Rentmeister, *Adv. Synth. Catal.* **2010**, *352*, 2062–2072; g) T. Terashima, M. Ouchi, T. Ando, M. Sawamoto, *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 373–379; h) K. Li, Y. Wang, J. Jiang, Z. Jin, *Catal. Commun.* **2010**, *11*, 542–546.

[17] D. E. Bergbreiter, P. L. Osburn, A. Wilson, E. M. Sink, *J. Am. Chem. Soc.* **2000**, *122*, 9058–9064.

[18] S. Kim, K. Yamamoto, K. Hayashi, K. Chiba, *Tetrahedron* **2008**, *64*, 2855–2863.
[19] N. Lu, Y.-C. Chen, W.-S. Chen, T.-L. Chen, S.-J. Wu, *J. Organomet. Chem.* **2009**, *694*, 278–284.
[20] a) D. E. Bergbreiter, L. Zhang, V. M. Mariagnanam, *J. Am. Chem. Soc.* **1993**, *115*, 9295–9296; b) M. Solinas, J. Y. Jiang, O. Stelzer, W. Leitner, *Angew. Chem. Int. Ed.* **2005**, *44*, 2291–2295.
[21] a) D.-H. Lee, Y. H. Lee, J. M. Harrowfield, I.-M. Lee, H. I. Lee, W. T. Lim, Y. Kim, M.-J. Jin, *Tetrahedron* **2009**, *65*, 1630–1634; b) T. Teratani, A. Ohtaka, T. Kawashima, O. Shimomura, R. Nomura, *Synlett* **2010**, 2271–2274.
[22] H. Shang, R. Hua, Q. Zheng, J. Zhang, X. Liang, Q. Zhu, *Appl. Organomet. Chem.* **2010**, *24*, 473–476.
[23] a) B. Chen, G. Sun, S. Xu, *Liq. Cryst.* **2004**, *31*, 421–429; b) X.-B. Chen, Z.-W. An, L. Jia, A.-A. Gao, *Chin. J. Chem.* **2005**, *23*, 970–976.

Received: March 16, 2011
Published Online: June 7, 2011

