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An improved practical Pd/C-catalyzed Sonogashira cross-coupling reaction for the synthesis of liquid crystals of trans-cyclohexyltolans

Hongyong Shang[a,b], Ruimao Hua[a*], Qingwei Zheng[a], Jianli Zhang[b], Xiao Liang[a,b] and Qiming Zhu[b]

An improved practical synthesis of liquid crystals of trans-cyclohexyltolans by Sonogashira cross-coupling reaction of 1-iodo-4-(trans-4-alkylcyclohexyl)benzene with aromatic terminal alkynes in the presence of Pd/C (palladium on activated carbon) as low as 0.03 mol% of Pd and CuI (2 mol%) in a mixture solvent of acetone–water (5 : 2 in volume) is described. The liquid crystals could be obtained in high yields as a solid with excellent purity by simple filtration, and the filtrate could be reused several times while still retaining high catalytic activity. Copyright © 2010 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: Pd/C; cuprous iodide; cross-coupling reaction; cyclohexyltolans; liquid crystals

Introduction

Palladium/copper-catalyzed Sonogashira cross-coupling reaction of terminal alkynes with aryl halides has evolved as a powerful method for constructing carbon–carbon bonds,[1–3] and has been applied as the key step in the synthesis of liquid crystals involving the structural unit of diarylacetylene. $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ are two catalysts commonly used in the industrial production of liquid crystals. However, their disadvantages include the occurrence of several side-reactions such as oxidative homocoupling, dimerization and trimerization of terminal alkynes, as well as dehalogenative hydrogenation of aryl halides. The formation of a considerable amount of by-products from the above-mentioned side-reactions usually resulted not only in the tedious purification of liquid crystals, but also in the decrease in quality of the liquid crystals, and low economic efficiency.

In recent years, we have been interested in the synthesis of *trans*-cyclohexyltolan-type liquid crystals, which have the properties of low viscosity coefficients, higher phase transition temperature and higher optical anisotropy (Δn),[4–7] by the Sonogashira cross-coupling reaction of 1-iodo-4-(*trans*-4-alkylcyclohexyl)benzene with aromatic terminal alkynes catalyzed by $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ with CuI as co-catalyst in both the academic and industrial settings.[8–10] One of the most important topics in our research group is the development of an alternative catalyst system which aims to suppress side reactions, improve liquid crystal quality, and decrease production cost.

It is well known that Pd/C can be used as a catalyst in carbon-carbon coupling reactions to replace homogeneous palladium catalysts.[11–13] Since the first example of Sonogashira cross-coupling reaction catalyzed by Pd/C was reported,[14] a few reports on the Sonogashira cross-coupling reactions catalyzed by Pd/C have appeared in the literature.[15–18] Pd/C is considered to be the most suitable catalyst in industrial processes because of its low cost and stability. Therefore, recent attempts have been made in our research group to improve the Sonogashira cross-coupling reaction of 1-iodo-4-(*trans*-4-alkylcyclohexyl)benzene with aromatic terminal alkynes to synthesize the *trans*-cyclohexyltolan-type liquid crystals catalyzed by Pd/C and CuI, and our results are reported in this paper (Scheme 1).

Results and Discussion

Table 1 concludes the catalytic activity of Pd/C under different reaction conditions in the reaction of 1-iodo-4-(*trans*-4-propylcyclohexyl)benzene (**1a**) with 4-methoxyphenyl acetylene (**2a**). When a mixture of **1a** and **2a** (1.1 equiv.) in THF was refluxed in the presence of 5% Pd/C (0.0006 equiv), CuI (0.05 equiv), PPh_3 (0.006 equiv) and Et_3N (3.0 equiv) under nitrogen for 3 h, the desired coupling product **3a** was obtained in 75% GC yield (entry 1, GC yield was based on the amount of **1a** employed by adding the internal standard material). In this case, the conversion of **1a** was 80%. When DMF was used as a solvent (at 90 °C) to replace THF, the yield of **3a** could be slightly improved (entry 2). The use of a solvent mixture of DMF and H_2O (1 : 1 in volume, at 93 °C) resulted in the complete conversion of **1a**, and the GC yield

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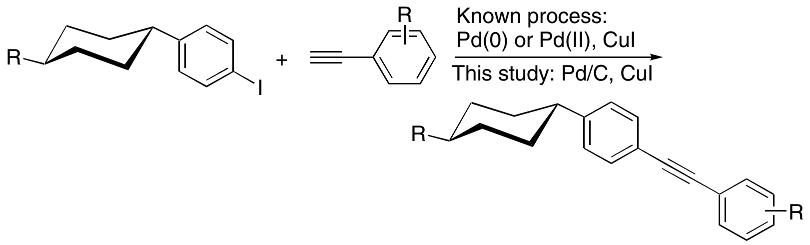
* *Correspondence to: Ruimao Hua, Tinghua University, Department of Chemistry, Tsinghua University, Beijing 100084, China. E-mail: ruimao@mail.tsinghua.edu.cn*

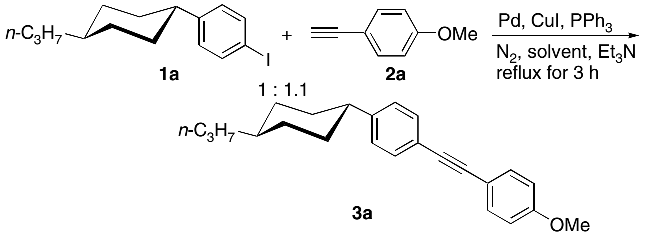
a *Department of Chemistry, Tsinghua University, Beijing 100084, China*

b *Shijiazhuang (Developed Zone) Yongsheng Huatsing Liquid Crystal Co. Ltd, Shijiazhuang 050091, China*



Scheme 1. Synthesis of liquid crystals by Sonogashira cross-coupling reaction.

Table 1. Cross-coupling reaction of 1-iodo-4-(*trans*-4-propylcyclohexyl)benzene (**1a**) with 4-methoxyphenyl acetylene (**2a**)[a]



Entry	Catalyst (Pd mol%)	Solvent	Other conditions	GC yield (%)[b]
1	Pd/C (0.06)	THF	CuI (5 mol%), PPh_3 (0.6 mol%) Et_3N (3 equiv), reflux (64 °C)	75
2	Pd/C (0.06)	DMF	CuI (5 mol%), PPh_3 (0.6 mol%) Et_3N (3 equiv), reflux (90 °C)	80
3	Pd/C (0.06)	DMF/H_2O (1 : 1 v/v)	CuI (5 mol%), PPh_3 (0.6 mol%) Et_3N (3 equiv), reflux (93 °C)	90
4	Pd/C (0.06)	DMF/H_2O (5 : 2 v/v)	CuI (2 mol%), PPh_3 (0.6 mol%) Et_3N (3 equiv), reflux (93 °C)	> 99
5	Pd/C (0.03)	acetone/H_2O (5 : 2 v/v)	CuI (2 mol%), PPh_3 (0.6 mol%) Et_3N (3 equiv), reflux (63 °C)	> 99 (93)
6	Pd/C (0.03)	acetone/H_2O (5 : 2 v/v)	CuI (1 mol%), PPh_3 (0.6 mol%) Et_3N (3 equiv), reflux (63 °C)	96

[a] Reactions were carried out using 25.0 mmol of **1a**, 27.5 mmol of **2a** in 70 mL of solvent under reflux for 3 h.
[b] GC yield based on **1a** used. Number in parenthesis was isolated yield.

of **3a** was increased to 90% (entry 3). A quantitative yield of **3a** could be achieved when a mixture solvent of DMF and H_2O in a ratio of 5 : 2 (in volume) was used, even if the amount of CuI was reduced to 0.02 equivalent (entry 4). It was found that a mixture solvent of acetone and water in a ratio of 5 : 2 (in volume) was the better solvent for the present cross-coupling reaction and the amount of Pd/C could be reduced to 0.0003 equiv. without any significant decrease in the yield of **3a**. As shown in entries 5 and 6, although 0.0003 equiv. of Pd/C and 0.01 equiv. of CuI also worked sufficiently, the use of 0.0003 equiv. of Pd/C and 0.02 equiv. of CuI realized the quantitative yield with good reproducibility. It is most notable that, when the reaction mixture was cooled to room temperature, **3a** was precipitated as crystals, and it could be isolated in 93% yield with high purity by simple filtration (entry 5). It is also important to point out that under theses reaction conditions only trace amounts of 1,4-diaryl-1,3-diyne and dimer of **2a** could be found in the filtrate.

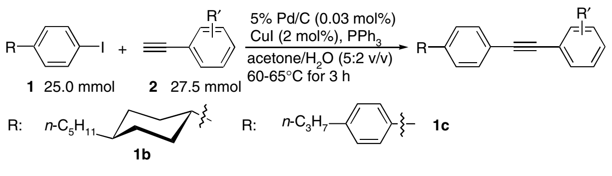
Table 2 shows the results of the cross-coupling reactions of aryl iodides **1a** and **1b** with aromatic terminal alkynes **2a**–**d** under the reaction conditions indicated in entry 5 of Table 1. Aromatic terminal alkynes bearing both an electron-donating group and an electron-withdrawing group(s) in the benzene ring underwent the cross-coupling reactions smoothly, affording the desired coupling products **3b**–**e** in 80–89% isolated yields with high purity. Under the same reaction conditions, the cross-coupling reaction of **1c** with **2a** also proceeded efficiently to give the corresponding coupling product **3f** in 83% isolated yield.

The high catalytic activity of the present catalyst system is considered to result from the leaching of Pd from Pd/C and complete solubility of Pd as homogeneous catalyst under the chosen reaction conditions. Indeed, the filtrate could be directly reused as the palladium catalyst source after filtering out the coupling products. As an example, after separation of **3a** by filtration from the reaction mixture indicated in entry 5 of Table 1, the additional amounts of **1a** (25.0 mmol), **2a** (27.5 mmol) and Et_3N (3 equiv.) were added, and the mixture was refluxed for 9 h. When the reaction mixture was cooled to room temperature, **3a** was again isolated in 89% yield by filtration.

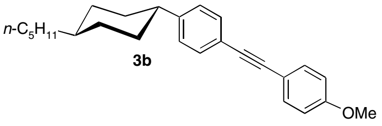
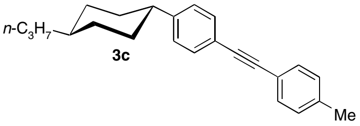
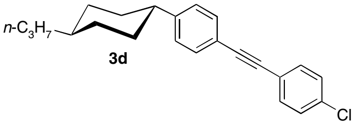
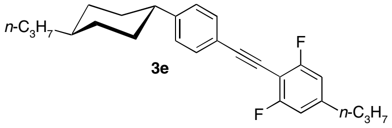
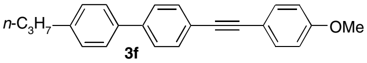
Conclusion

In conclusion, we have demonstrated that Pd/C in a mixture solvent of acetone and water (5 : 2 in volume) shows excellent

Table 2. Synthesis of liquid crystals via Sonogashira cross-coupling reaction[a]



R′ = *p*-Me, **2b**; *p*-Cl, **2c**; 2, 6-difluro-4-*n*-propyl, **2d**

Product	Isolated yield (%)	Purity (%)[b]
 **3b**	89	99.4
 **3c**	85	99.8
 **3d**	80	98.2
 **3e**	88	99.8
 **3f**	83	99.8

[a] Reaction conditions: Pd (0.03 mol%, 5% on activated carbon, 66% water wet), CuI (2 mol%), PPh_3 (0.6 mol%), Et_3N (75.0 mmol), acetone (50 mL), H_2O (20 mL), 60–65 °C (under refluxing) for 3 h.
[b] Determined by GC.

catalytic activity for the Sonogashira cross-coupling reaction of 1-iodo-4-(*trans*-4-alkylcyclohexyl)benzene with aromatic terminal alkynes to afford liquid crystals of *trans*-cyclohexyltolans. The advantages of the present catalytic system include cost-effectiveness, a simple procedure for product isolation, high yields and excellent purity, as well as the reuse of the filtrate as the catalyst source. Compared with previously reported systems, the present system is cheaper and more practical, and seems promising in future industrial, large-scale production of liquid crystals.

Experimental

General Methods

All organic starting materials are chemically pure and were used without further purification. ^1H and ^{13}C NMR spectra were recorded on Joel JNM-ECA300 spectrometers at 300 and 75 MHz, respectively. ^1H chemical shifts (δ) were referenced to TMS, and ^{13}C NMR chemical shifts (δ) were referenced to internal solvent resonance. GC analyses of organic compounds were performed on an Agilent 6890N instrument. Mass spectra were obtained on a Shimadzu GCMS-QP2010S. Element analyses were obtained with a Flash EA 1112 Element Analyzer.

Typical Experimental Procedure for the Synthesis of *trans*-Cyclohexyltolan (3a) (Table 1, entry 5)

A mixture of 1-iodo-4-(*trans*-4-propylcyclohexyl)benzene (**1a**) (8.2 g, 25.0 mmol), 4-methoxyphenyl acetylene (**2a**) (3.65 g, 27.5 mmol), 5% Pd/C (0.05 g, 66% water wet, 0.03 mol%), CuI (0.1 g, 2 mol%), PPh_3 (0.04 g, 0.6 mol%) and Et_3N (7.6 g, 75.0 mmol) in acetone (50 ml) and H_2O (20 ml) under nitrogen was refluxed (at *ca* 64 °C) for 3 h. After the reaction mixture was cooled to room temperature, **3a** (7.72 g, 23.3 mmol, 93%, purity is 99.7%) as white precipitate was isolated by filtration.

For GC analysis, a parallel reaction was carried out, and the solvents and volatiles were directly removed under vacuum. The obtained residue was resolved in toluene (200 ml) and biphenyl (0.77 g, 5.0 mmol) was added as internal standard for GC analysis. It was found that **3a** was formed in almost quantitative yield.

Compounds **3e** and **3f** are new, and were characterized by ^1H, ^{13}C-NMR, mass spectra and elemental analysis. Other known coupling products were characterized by ^1H, ^{13}C-NMR and mass spectra. The spectroscopic data of **3e** and **3f** are reported below.

*1-(2,6-Difluoro-4-n-propylphenylethynyl)-4-(4-n-propylcyclohexyl) benzene **3e***

White solid, mp 74.5–76.3 °C; ^1H NMR (300 MHz, $CDCl_3$) δ7.48 (d, 2H, $J = 8.3$ Hz, 2 × *CH* arom.), 7.18 (d, 2H, $J = 7.9$ Hz, 2 × *CH* arom), 6.73 (d, 2H, $J = 7.9$ Hz, 2 × *CH* arom), 2.56 (t, 2H, $J = 7.6$ Hz, $CH_3CH_2\mathit{CH_2}$), 2.50–2.42 (m, 1H, *CH*), 1.87–1.80 (m, 4H, 2 × $\mathit{CH_2}$), 1.66–1.58 (m, 2H, $\mathit{CH_2}$), 1.50–1.16 (m, 7H, 3 × $\mathit{CH_2}$ and *CH*), 1.10–0.85 (m, 8H, $\mathit{CH_2}$ and 2 × $\mathit{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8 (dd, $J^1{}_{C-F} = 256.7$ Hz, $J^3{}_{C-F} = 6.45$ Hz, *ipso*-C of CF), 148.9 (*ipso*-C arom), 145.8 (t, $J^2{}_{C-F} = 8.6$ Hz, *ipso*-C arom), 131.8 (C arom), 127.0 (C arom), 120.2 (*ipso*-C arom), 111.4–111.1 (m, *ipso*-C and C arom), 99.8 (t, $J^3{}_{C-F} = 20.1$ Hz, *C*–C), 98.7 (C–*C*), 44.8 (CH), 39.8 (CH), 37.9 (CH_2), 37.1 (CH_2), 34.3 (2C, 2 × CH_2), 33.6 (2C, 2 × CH_2), 23.9 (CH_2), 20.2 (CH_2), 14.5 ($CH_3CH_2CH_2$), 13.7 ($CH_3CH_2CH_2$); GCMS *m/z* (% rel. inten.) 380 (M^+, 100), 351 (3), 295 (15), 282 (30), 267 (8), 253 (41), 240 (13), 207 (9), 169 (3), 115 (2), 81 (6); anal. calcd for $C_{26}H_{30}F_2$: C, 82.11; H, 7.89. Found: C, 82.67; H, 7.91.

*4-(4-Methoxyphenylethynyl)-4′-n-propyl-biphenyl **3f***

White solid, m.p. 154.7–156.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.45 (m, 8H, 8 × *CH* arom.), 7.24 (d, 2H, $J = 7.9$ Hz, 2 × *CH* arom), 6.86 (d, 2H, $J = 8.6$ Hz, 2 × *CH* arom), 3.79 (s, 3H, $O\mathit{CH_3}$), 2.62 (t, 2H, $J = 7.2$ Hz, $CH_3CH_2\mathit{CH_2}$), 1.70–1.63 (m, 2H, $CH_3\mathit{CH_2}CH_2$), 0.96 (t, 3H, $J = 7.2$ Hz, $\mathit{CH_3}CH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7 (*ipso*-C arom), 142.4 (*ipso*-C arom), 140.7 (*ipso*-C arom), 137.8 (*ipso*-C arom), 133.2 (C arom), 131.9 (C arom), 129.1 (C arom), 126.9 (C arom), 122.3 (*ipso*-C arom), 115.6 (*ipso*-C arom), 114.1 (C arom), 90.1 (*C*–C), 88.3 (C–*C*), 55.4 (OCH_3), 37.8 ($CH_3CH_2CH_2$), 24.7 ($CH_3CH_2CH_2$), 14.0 ($CH_3CH_2CH_2$); GCMS *m/z* (% rel. inten.) 326 (M^+, 97), 297 (70), 282 (23), 254 (23), 237 (9), 207 (100), 149 (30), 127 (14), 96 (15); anal. calcd for $C_{24}H_{22}O$: C, 88.34; H, 6.75. Found: C, 88.47; H, 6.61.

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Supporting Information

Supporting information of the general method, characterization data and charts of ^{1}H- and ^{13}C-NMR for all the products may be found in the online version of this article.

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