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Pd/Cu catalyzed homo-coupling reactions of 2-iodo-3-iodomethyl-1,4-diarylnaphthalene in the presence of arylacetylene

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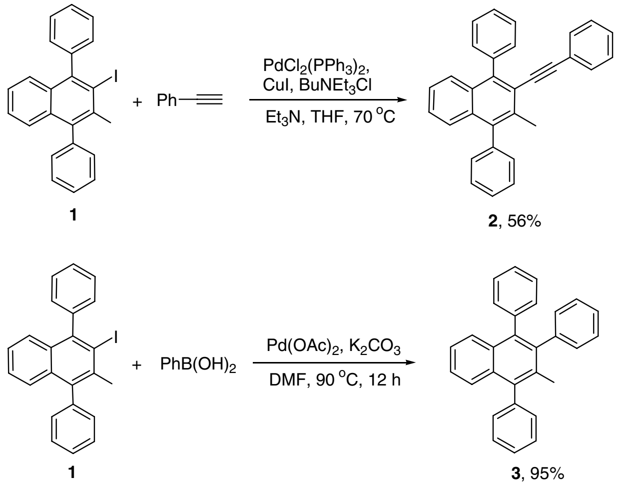
Abstract—Palladium/CuI catalyzed reactions of 2-iodo-3-iodomethyl-1,4-diarylnaphthalenes in the presence of arylacetylenes produced the corresponding sp^3–sp^3 homo-coupling products 1,2-bis(3-iodonaphthalen-2-yl)ethane in moderate to good yields.

Palladium catalyzed coupling of terminal alkynes with aryl and vinyl halides in the presence of catalytic CuI and an amino base (the Sonogashira reaction) is one of the important and widely used carbon–carbon bond-forming reactions in organic synthesis.[1,2] This method has been successfully applied in the synthesis of natural compounds,[3] biologically active molecules,[4] new organic materials for optical and microelectronic application,[5] dendrimeric, oligomeric, polymeric materials,[6] macrocycles with acetylene links,[7] polyalkynylated molecules, and, generally, as a route to new intriguing molecular architectures.[8] Previously, we reported the preparation of 2-iodo-3-methyl-1,4-diarylnaphthalene and 2-iodo-3-iodomethyl-1,4-diarylnaphthalene from the reaction of vinylidenecyclopropane with iodine (I_2) under different reaction conditions.[9] Therefore, we attempted the Sonogashira coupling reaction of these interesting compounds with arylacetylene in the presence of Pd and CuI catalysts. Herein, we wish to report our new finding in this coupling reaction.

Using $PdCl_2(PPh_3)_2$ (10 mol %) and CuI (10 mol %) as the catalysts as well as triethylamine (Et_3N) (1.5 equiv) as a base in the presence of $BuNEt_3Cl$ (10 mol %) (a standard Sonogashira coupling reaction conditions), the Sonogashira coupling reaction of 2-iodo-3-methyl-1,4-diarylnaphthalene with phenylacetylene afforded the corresponding product **2** in 56% yield at 70 °C (Scheme 1). In addition, under the standard conditions for Suzuki coupling reaction of **1** with phenylboronic acid, the corresponding Suzuki coupling reaction product **3** could be also obtained in 95% yield (Scheme 1).



Scheme 1. Sonogashira and Suzuki coupling reactions of **1** with phenylacetylene and phenylboronic acid.

Keywords: Vinylidenecyclopropane; Sonogashira coupling reaction; 2-Iodo-3-methyl-1,4-diarylnaphthalene; 2-Iodo-3-iodomethyl-1,4-diarylnaphthalene; $PdCl_2(PPh_3)_2$; CuI.

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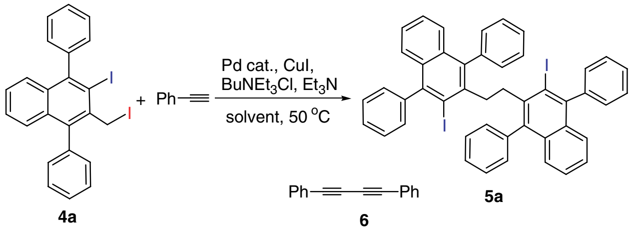
However, we found that the coupling reaction of 2-iodo-3-iodomethyl-1,4-diphenylnaphthalene **4a** (0.18 mmol) with phenylacetylene (0.24 mmol) produced an interesting sp^3–sp^3 homo-coupling product, 1,2-bis(3-iodo-1,4-diphenylnaphthalen-2-yl)ethane **5a**, along with the sp–sp homo-coupling product **6** under identical conditions rather than the corresponding Sonogashira coupling reaction product. This interesting finding prompted us to further clarify the scope and limitations of this unusual coupling reaction. Therefore, we carefully optimized the reaction conditions and the results of these experiments are summarized in Table 1. Using $PdCl_2(PPh_3)_2$ (10 mol %) or $Pd(PPh_3)_4$ (10 mol %) as the catalyst, **5a** was obtained in 85% yield under otherwise identical conditions (Table 1, entries 1 and 2). Other Pd catalysts are less effective in this reaction (Table 1, entries 3–5). Without Pd catalyst, no reaction occurred (Table 1, entry 6). In the absence of CuI, **5a** was formed in 18% yield, suggesting that CuI is essential in this reaction (Table 1, entry 7). Using 4-chlorophenylacetylene and 4-methoxyphenylacetylene as the acetylene source, **5a** was produced in 73% and 57% yields, respectively, further indicating that this coupling reaction did not incorporate arylacetylene moiety (Table 1, entries). Without phenylacetylene or in the presence of 10 mol % of phenylacetylene, either no reaction occurred or trace of **5a** was formed, suggesting that excess amount of phenylacetylene is required in this reaction to give the sp^3–sp^3 homo-coupling product **5a** in good yield. The examination of solvent effects revealed that THF is the solvent of choice (Table 1, entries 12–15). The best conditions are to carry out this reaction using $PdCl_2(PPh_3)_2$ (10 mol %) or $Pd(PPh_3)_4$ (10 mol %) and CuI (10 mol %) as the catalysts in THF in the presence of phenylacetylene and Et_3N. It should be noted that terminal arylacetylene is required in this reaction since no reaction occurred using 1,2-diphenylacetylene to replace phenylacetylene under the standard conditions and in all cases, the corresponding sp–sp homo-coupling product **6** was formed as a by-product.

Table 1. Coupling reaction of 2-iodo-3-iodomethyl-1,4-diphenylnaphthalene **4a** in the presence of arylacetylene



Entry	Pd cat.	Solvent	Time (h)	Yield [a] (%) 5a
1	$PdCl_2(PPh_3)_2$	THF	10	85
2	$Pd(PPh_3)_4$	THF	5	85
3	$PdCl_2(PhCN)_2$	THF	5	70
4	$Pd_2(dba)_3$	THF	5	38
5[b]	$Pd(OAc)_2$	THF	5.5	30
6	—	THF	72	NR
7[c]	$Pd(PPh_3)_4$	THF	20	18
8[d]	$Pd(PPh_3)_4$	THF	3.5	73
9[e]	$Pd(PPh_3)_4$	THF	7	57
10[f]	$Pd(PPh_3)_4$	THF	72	NR
11[g]	$Pd(PPh_3)_4$	THF	72	Trace
12	$PdCl_2(PPh_3)_2$	DCE	10	55
13	$PdCl_2(PPh_3)_2$	DMF	10	24
14	$PdCl_2(PPh_3)_2$	Toluene	10	33
15	$PdCl_2(PPh_3)_2$	MeCN	10	25

[a] Isolated yield.

[b] 10 mol % of PPh_3 was added.

[c] Without CuI.

[d] (4-Chlorophenyl)acetylene was used.

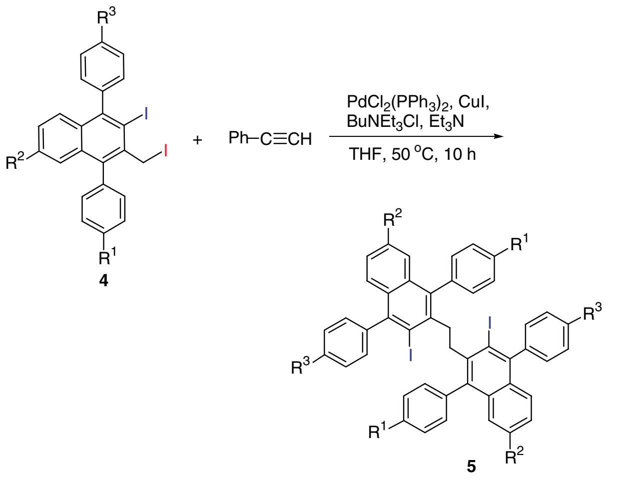
[e] (4-Methoxyphenyl)acetylene was used.

[f] No phenylacetylene was used.

[g] 10 mol % of phenylacetylene was used.

With these optimized reaction conditions identified, we next examined a variety of 2-iodo-3-iodomethyl-1,4-diarylnaphthalenes **4** in the presence of phenylacetylene and the results are summarized in Table 2. As can be seen from Table 2, the corresponding sp^3–sp^3 homo-coupling products 1,2-bis(3-iodo-1,4-diarylnaphthalen-2-yl)ethanes **5** were obtained in 44–70% yields within 10 h. For substrates **4b**, **4c**, and **4d**, in which R^1 or R^2 and R^3 are electron-withdrawing substituents, the corresponding sp^3–sp^3 homo-coupling products **5b**, **5c**, and **5d** were obtained in somewhat lower yields (Table 2, entries 1–3). In addition, similar result was obtained for substrate **4d** using $Pd(PPh_3)_4$ as a catalyst under the standard conditions (Table 2, entry 4).

Table 2. Homo-coupling reaction of 2-iodo-3-iodomethyl-1,4-diarylnaphthalenes **4** in the presence of phenylacetylene under the optimized conditions



Entry[a]	4 (R^1/R^2/R^3)	Yield[b] (%) 5
1	**4b** (Cl/H/H)	**5b**, 60
2	**4c** (Br/H/H)	**5c**, 44
3	**4d** (H/F/F)	**5d**, 50
4[c]	**4d** (H/F/F)	**5d**, 48
5	**4e** (Me/H/H)	**5e**, 70
6	**4f** (H/Me/Me)	**5f**, 64
7	**4g** (MeO/H/H)	**5g**, 70

[a] All reactions were carried out with **4a** (0.18 mmol), phenylacetylene (0.24 mmol), $PdCl_2(PPh_3)_2$ (0.018 mmol), CuI (0.018 mmol), $BuNEt_3Cl$ (0.018 mmol) and Et_3N (0.27 mmol) in THF (4.0 mL) at 50 °C for 10 h.

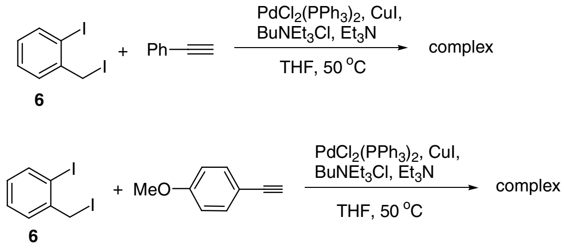
[b] Isolated yields.

[c] $Pd(PPh_3)_4$ was used as the catalyst.

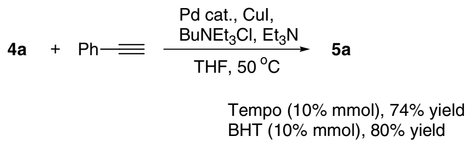
Furthermore, we also found that using 1-iodo-2-iodomethylbenzene **6** as a substrate, complex product mixtures were obtained in the presence of phenylacetylene or 4-methoxyphenylacetylene under identical conditions, suggesting that the fused aromatic ring in compound **4** plays an important role in this interesting homo-coupling reaction (Scheme 2).

To further understand this interesting sp^3–sp^3 homo-coupling reaction, two control experiments using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as the radical inhibitors were performed under the standard conditions, respectively (Scheme 3). We confirmed that this sp^3–sp^3 homo-coupling reaction under these optimized conditions was unaffected by the addition of these radical inhibitors, rendering unlikely the intervention of a radical or a biradical pathway.

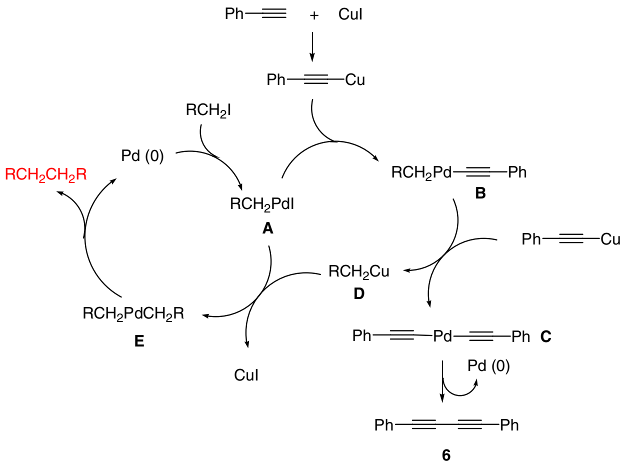
A plausible mechanism for this interesting homo-coupling reaction is tentatively outlined in Scheme 3.[10] The oxidative addition of RCH_2I with Pd(0) generates intermediate **A**, which undergoes transmetallation with alkynylcopper, generated from phenylacetylene with CuI in the presence of Et_3N, to afford intermediate **B** (Scheme 4). Transmetallation of intermediate **B** with alkynylcopper gives intermediate **C** and intermediate **D**, respectively. Reductive elimination from intermediate **C** produces sp–sp homo-coupling product **6** and regenerates Pd(0). Transmetallation of intermediate **A** with intermediate **D** produces intermediate **E** and regenerates CuI. Reductive elimination from intermediate **E** produces sp^3–sp^3 homo-coupling product **5** (Scheme 4). The absence of sp–sp^3 cross-coupling product which may be formed from intermediate **B** indicates that the next transmetallation followed by the successive processes to form the sp^3–sp^3 homo-coupling product is faster than the reductive elimination of intermediate **B** after the first transmetallation. At the present stage, though not being confirmed experimentally and computationally, we believe that the fused aromatic ring of substrates **4** blocks out the normal Sonogashira coupling reaction of iodoarene with phenylacetylene, and therefore, the sterically less hindered coupling reaction of benzyliodides takes place to give the sp^3–sp^3 homo-coupling product **5**.



Scheme 2. Reactions of 1-iodo-2-iodomethylbenzene **6** in the presence of phenylacetylene or 4-methoxyphenylacetylene under identical conditions.



Scheme 3. Homo-coupling reaction of **4a** in the presence of phenylacetylene, BHT and TEMPO.



Scheme 4. A plausible reaction mechanism.

In conclusion, we have identified an interesting Pd/Cu catalyzed reactions of 2-iodo-3-iodomethyl-1,4-diarylnaphthalenes in the presence of arylacetylenes to furnish the corresponding sp^3–sp^3 homo-coupling products 1,2-bis(3-iodonaphthalen-2-yl)ethane **5** in moderate to good yields rather than the normal Sonogashira cross-coupling products with arylacetylenes.[11] The specially fused aromatic ring structure plays a key role for this unusual homo-coupling reaction under the standard conditions. Efforts are underway to further elucidate the reaction mechanism and to understand the scope and limitations of this process.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.112.

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11. *Typical reaction procedures*: To a stirred mixture of CuI (3.4 mg, 0.018 mmol), benzyltriethylammonium chloride (4.1 mg, 0.018 mmol), bis(triphenylphosphine)-palladium chloride (12.9 mg, 0.018 mmol) and Et$_3$N (37.6 μL, 0.27 mmol) in anhydrous THF (4.0 mL), **4a** (100 mg, 0.18 mmol) and phenylacetylene (26 μL, 0.24 mmol) were added under an argon atmosphere. The reaction mixtures were stirred in oil bath at 50 °C for 10 h. Then the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: petroleum) to give **5a** as a white solid, mp 266–270 °C; IR (CH$_2$Cl$_2$): ν 3056, 2925, 2853, 1619, 1604, 1541, 1513, 1499, 1491, 1442, 1422, 1399, 1263, 1231, 1197, 1157, 1017, 976, 870, 837, 824, 762, 701 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$, TMS): δ 3.28 (4H, s, CH$_2$), 6.61 (4H, d, $J = 7.2$ Hz, ArH), 7.03–7.08 (6H, m, ArH), 7.17–7.35 (12H, m, ArH), 7.47–7.51 (6H, m, ArH); ^{13}C NMR (75 MHz, CDCl$_3$): δ 38.8, 109.0, 125.7, 125.9, 126.7, 126.8, 127.4, 127.5, 127.9, 128.3, 130.0, 131.8, 132.8, 137.6, 139.47, 139.49, 145.2, 145.7; MS (EI) *m/z* (%): 838 (100) [M$^+$]; Anal. Calcd for C$_{46}$H$_{32}$I$_2$: C, 65.89; H, 3.85. Found: C, 66.12; H, 4.11.