Palladium-Catalyzed Desulfitative Sonogashira–Hagihara Cross-Couplings of Arenesulfonyl Chlorides and Terminal Alkynes

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Dedicated to Joe Richmond on the occasion of his 60th birthday.

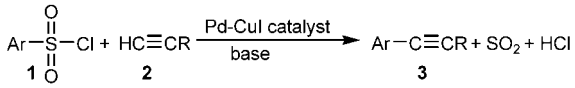
Abstract: For the first time, conditions have been found for the palladium-catalyzed desulfitative carbon-carbon cross-coupling of arenesulfonyl chlorides with aryl- and alkylacetylenes. $Pd_2(dba)_3$/P(*t*-Bu)$_3$ and CuI provide the best catalyst for reactions in refluxing THF and in the presence of K_2CO_3.

Keywords: alkynes; arenesulfonyl chlorides; C–C cross coupling; homogeneous catalysis; palladium; tri(*t*-butyl)phosphine ligand

Introduction

Palladium-catalyzed cross-coupling reactions are extremely useful synthetic tools.[1,2] The typical Sonogashira–Hagihara reaction is applied for the coupling of terminal alkynes and aryl halides, utilizing catalytic palladium, a copper co-catalyst and a base.[3] The process has been applied to produce antimycotics,[4] antibiotics,[5] liquid crystals, polymers, and optical or electronic materials.[6] Aryl bromides and aryl iodides are used normally as arylation agents.[7] Unactivated alkyl bromides can also undergo cross-couplings with alkynes provided that N-heterocyclic carbenes are used as ligands for the palladium.[8] Several groups have developed efficient procedures for the Sonogashira reaction.[9,10]

The most widely employed co-catalysts are copper salts. Unfortunately, they have the disadvantage to induce Glaser-type homocouplings of the alkynes.[11] Taking this into account, Sonogashira reactions that do not utilize co-catalysts have also been explored.[12] Practical procedures have been proposed by Herrmann and coworkers,[13] as well as Merck researchers.[14] They utilize palladium complexes with electron-rich ligands such as P(*t*-Bu)$_3$, and a base. Very recently, Gelman and Buchwald showed that the use of copper co-catalyst inhibits the reaction between aryl chlorides and tosylates with terminal alkynes.[15] Arene- and alkanesulfonyl chlorides are readily available compounds, but have rarely been used as coupling partners in transition metal-catalyzed cross-coupling reactions with organometallic species to construct carbon-carbon bonds. Arenesulfonyl chlorides have been engaged in carbon-vinylation,[16] carbon-carbonylation,[17] and homo-couplings.[18] Recently, we have disclosed the palladium-catalyzed Stille, carbonylative Stille,[19] Suzuki–Miyaura[20] and Heck–Mizoroki[21] desulfitative cross-coupling reactions with sulfonyl chlorides. We report here that arenesulfonyl chlorides can be cross-coupled with terminal aryl- and alkylacetylenes with desulfitation in the presence of palladium and copper catalysts (Scheme 1).



Scheme 1.

Results and Discussion

Our initial exploratory studies engaged *para*-toluenesulfonyl chloride (TsCl) and phenylacetylene. With 5 mol % of $PdCl_2(PhCN)_2$, 5 mol % CuI as co-catalyst and bases such as Et_3N and K_2CO_3 (Table 1, entries 1 and 2), low yields (=10%) of the product of desulfitative cross-coupling were obtained. Under these conditions, the major product was diphenylbuta-1,3-diyne[11] resulting from the oxidative homocoupling of phenylacetylene (Scheme 2).

Adding P(*t*-Bu)$_3$ as co-ligand led to an increase of the formation of the desired product of cross-coupling (entries 3 and 4). Recently it was reported[10a] that

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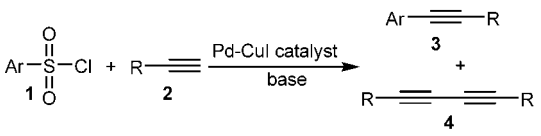


Scheme 2.

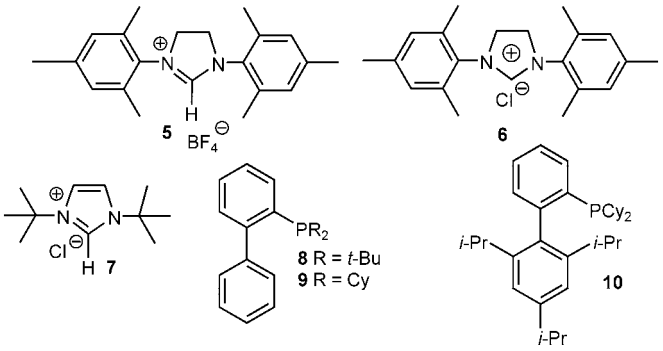
Na_2PdCl_4 and P(*t*-Bu)$_3$ generate a good catalyst for the Sonogashira cross-coupling of aryl chlorides and terminal alkynes. In our case (entries 5 and 6) the yield of 1-(4-methylphenyl)-2-phenylacetylene never surpassed 11%. Exchanging Na_2PdCl_4 for $Pd(OAc)_2$ led to worse results (entry 7). In the presence of [(π-allyl)PdCl]$_2$ and P(*t*-Bu)$_3$ (4:15 mol %) cross-coupling occurred with a yield of 30%, together with a 59% yield of the product of homocoupling of phenylacetylene (entry 8). Similar results were obtained with $Pd_2(dba)_3$/P(*t*-Bu)$_3$ (entries 10–12, 20 and 21). As the later system is less expensive than [(π-allyl)PdCl]$_2$/P(*t*-Bu)$_3$ we continued our exploration with it. We varied the base (entries 11–18) and the amount of co-catalyst CuI (entries 10 and 11, 19–21) and found that CuI is necessary for the cross-coupling and that K_2CO_3 is a better base than Et_3N as it improves the competition between the desired cross-coupling and undesired homocoupling reactions. We have also explored the role of diaminocarbene ligands generated by α-elimination from salts **5–7** (Scheme 3). But, as seen from Table 1 (entries 22–24), this led to no cross-coupling at all! With phosphines other than P(*t*-Bu)$_3$, the yield of product of cross-coupling remained very poor (entries 9, 25–27). We have also examined the role of the solvent and have found that THF is far better than toluene and acetonitrile.

The best conditions found for the desulfitative cross-coupling of TsCl and phenylacetylene were then applied to other substrates (Table 2) including sulfonyl chlorides with electron-rich or electron-poor aromatic systems, and various terminal alkynes. As expected, yields of cross-coupling products **3** increased when using an excess of alkynes **2**, as it compensates for the competitive

Table 1. Screening for Pd-catalyst, co-ligands and bases.[a]

Entry	Catalyst (mol %)	Co-ligand (mol %)	Base	CuI (mol %)	Yield [%] of	
					3	**4**[b]
1	$PdCl_2(PhCN)_2$ (5)	–	Et_3N	5	ca.10	78
2	$PdCl_2(PhCN)_2$ (5)	–	K_2CO_3	5	<6	62
3	$PdCl_2(PhCN)_2$ (5)	P(*t*-Bu)$_3$ (10)	Et_3N	5	25	62
4	$PdCl_2(PhCN)_2$ (5)	P(*t*-Bu)$_3$ (10)	K_2CO_3	5	28	60
5	Na_2PdCl_4 (7)	P(*t*-Bu)$_3$ (15)	Et_3N	10	<5	30
6	Na_2PdCl_4 (7)	P(*t*-Bu)$_3$ (15)	Et_3N	10	11	13[c]
7	$Pd(OAc)_2$ (7)	P(*t*-Bu)$_3$ (15)	Et_3N	10	8	25
8	[(π-allyl)PdCl]$_2$ (4)	P(*t*-Bu)$_3$ (15)	Et_3N	10	30	59
9	Pd_2dba_3 (3)	PPh_3 (10)	Et_3N	5	<9	43
10	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	Et_3N	10	25	68
11	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	K_2CO_3	5	28	35
12	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	K_2CO_3	10	30	50
13	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	Na_2CO_3	10	9	22
14	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	Li_2CO_3	10	<8	34
15	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	DABCO	10	4	45
16	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	DBU	10	6	24
17	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	EtN(*i*-Pr)$_2$	10	10	60
18	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	-[d]	10	<10	50
19	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	Et_3N	–	3	60
20	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	Et_3N	15	29	60[e]
21	Pd_2dba_3 (3)	P(*t*-Bu)$_3$ (10)	K_2CO_3	15	30	45[e]
22	[(π-allyl)PdCl]$_2$ (3)	**5** (10)	Et_3N	10	0	<40
23	Pd_2dba_3 (3)	**6** (10)	K_2CO_3	10	0	<16
24	Pd_2dba_3 (3)	**7** (10)	K_2CO_3	10	0	<2
25	Pd_2dba_3 (3)	**8** (10)	Et_3N	10	<13	40
26	Pd_2dba_3 (3)	**9** (10)	Et_3N	10	<10	40
27	Pd_2dba_3 (3)	**10** (10)	Et_3N	10	<15	27

[a] All experiments in boiling THF (unless noted), 0.15–0.2 molar, 1:1.3 mixtures of TsCl and PhC≡CH, 5–20 h (until disappearance of TsCl by TLC, yields of **3** based on TsCl after flash chromatography on silica gel.
[b] Yields based on phenylacetylene.
[c] In toluene.
[d] *N*-Methylmorpholine.
[e] Same reaction but in MeCN at 65 °C, 10 h, the yield in **3** was <5% (*ca.* 70% **4**).



Scheme 3. Co-ligand precursors and co-ligands.

homocoupling reactions. Recently Ho et al.[22] found that homocoupling of alkynes can be retarded under argon atmosphere diluted with H_2. In our case (Table 2, entry 1) a 1:1 mixture of Ar/H_2 led to slightly better results. Phase-transfer catalysts such as Bu_4NBr or Bu_4NCl did not improve the yields in products **3**. This contrasts with several reports[16,21,23] stating that these ammonium salts can induce better yield in Heck-type reactions. In one case (Table 2, entry 6) 40 mol % of $MeN(oct)_3Cl$ led to a lower yield of product of cross-coupling than in the absence of the phase-transfer catalyst.

At least two possible mechanisms can be operative for our desulfitative Sonogashira–Hagihara cross-coupling reactions. In one of them, the palladium catalyst $L_2Pd^{(0)}$ undergoes oxidative addition into the S–Cl bond of the arenesulfonyl chloride. A fast desulfitation occurs with the formation of an $ArPdL_2Cl$ species that reacts, as in the usual Sonogashira–Hagihara reaction, with the alkynylcopper intermediate (CuC≡CR); then reductive elimination produces ArC≡CR and the initial catalyst $L_2Pd^{(0)}$ (Figure 1). An alternative mechanism is to invoke an oxidative addition of the latter catalyst into the C–S bond of the $ArSO_2Cl$ reagent, followed by desulfitation.

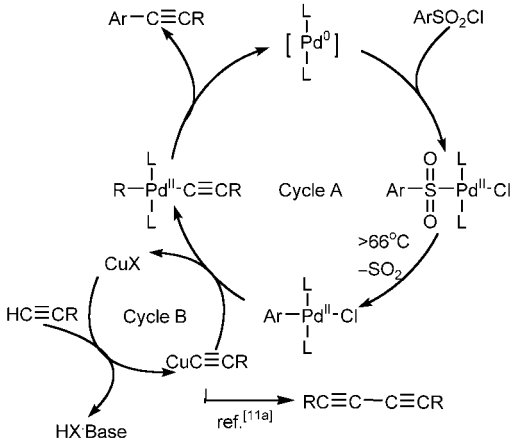


Figure 1. Probable catalytic cycle for the desulfitative Sonogashira–Hagihara cross-coupling of arenesulfonyl chlorides and terminal alkynes.

Conclusion

Arenesulfonyl chlorides undergo desulfitative Stille, carbonylative Stille, Suzuki–Miyaura and Heck–Mizor-

Table 2. Sonogashira–Hagihara desulfitative cross-coupling of arenesulfonyl chlorides **1** and terminal alkynes **2** by using Pd_2dba_3/P(*t*-Bu)$_3$/CuI.[a]

Entry	Ar in $ArSO_2Cl$ (**1**)	R in HC≡CR (**2**)	Yield [%] in ArC≡CR (**3**) based on **1** using	
			1.3 equivs. of **2**[b]	2 equivs. of **2**[c]
1	4-methylphenyl	phenyl	30 [34][d]	40
2	4-methylphenyl	*t*-butyl	45	60
3	4-methylphenyl	1-hexyl	50	63
4	1-naphthyl	*t*-butyl	55 [52][e] [38][f]	65
5	1-naphthyl	1-hexyl	57 [40][e]	72
6	1-naphthyl	1-hexyl	57[g] [28][h] [57][i]	–
7	1-naphthyl	tri(isopropyl)silyl	35 [50][d]	60
8	4-fluorophenyl	1-hexyl	40 [43][d]	52
9	4-nitrophenyl	tri(isopropyl)silyl	41	59
10	3-cyanophenyl	1-hexyl	–	52
11	3-cyanophenyl	*t*-butyl	–	50

[a] See details in Experimental Section.
[b] Yields of purified products, after flash chromatography.
[c] Yields were determined through gas chromatography.
[d] 1:1 Ar/H_2 atmosphere.
[e] Et_3N instead of K_2CO_3.
[f] 5 instead of 15 mol % of CuI.
[g] 4 mol % [(π-allyl)PdCl]$_2$ and 15 mol % P(*t*-Bu)$_3$ instead of the usual conditions.
[h] With $MeN(Oct)_3Cl$ (40 mol %).
[i] Slow addition of HC≡CR, 2–4 h.

oki cross-coupling reactions. We have shown in this paper that they can also be cross-coupled with terminal alkynes. The best catalyst found so far for the desulfitative Sonogashira–Hagihara cross-coupling reactions is $Pd_2(dba)_3$/P(*t*-Bu)$_3$/CuI using K_2CO_3 as base, and boiling THF as medium. Competition of the homocoupling of the acetylene cannot be avoided, but its effect on the yields of products of cross-coupling can be reduced by slow addition of 2 equivalents of the alkyne to the reaction mixture.

Experimental Section

General Remarks

Unless stated otherwise, reactions were conducted in flame-dried glassware under a vacuum. THF was distilled before use from sodium and benzophenone. Catalysts and ligands were purchased from Strem Chemical, Inc. All commercially available reagents were used without further purification. Solvents after reactions and extraction were evaporated in a rotatory evaporator under vacuum (solvents were removed by cooling at $-20\,^{\circ}C$, in the case of low boiling point or low molecular mass products). TLC for reaction monitoring was performed on 60 F_{254} (Merck) with detection by UV light and charring with $KMnO_4$. ^1H and ^{13}C NMR spectra were recorded by using a Bruker DPX-400 or Bruker ARX-400 spectrometer at 400 MHz and 100.6 MHz, respectively, and are reported relative to Me_4Si ($\delta = 0.0$) or to the solvents residual ^1H-signal ($CDCl_3$, $\delta_H = 7.27$). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (J in hertz) and integration. Data for ^{13}C NMR spectra reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS (MALDI-TOF) mass spectra were taken on a Kratos Analytical Instruments system.

Typical Experimental Procedure for Desulfitative Sonogashira–Hagihara Cross-Coupling Reactions (Table 2)

A round-bottom flask was dried under vacuum, and to the flask were added the corresponding arenesulfonyl chloride (1.00 mmol), Pd_2dba_3 (0.03 mmol), CuI (0.15 mmol) and also an internal standard (4,4′-dimethyldiphenyl, 0.25 mmol) under a nitrogen atmosphere (glove-box). The flask was connected to a vacuum line and filled with Ar (three times), then THF (4 mL) was added under Ar. Next, P(*t*-Bu)$_3$ [0.1 mmol, P(*t*-Bu)$_3$ sold by Strem Chemicals in a Sure/Seal bottle as a 10 wt % solution in hexane], K_2CO_3 (2.5 mmol) or Et_3N (2.5 mmol, in 1 mL of THF), were added in that order. The alkyne (1.3 to 2.0 mmol) was added *via* a syringe under reflux and the mixture stirred for 5–10 h. After cooling to 20 °C, the mixture was diluted with Et_2O and washed with H_2O. The aqueous layer was extracted again with Et_2O (3 times). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure (solvents were removed under reflux and cooling to $-20\,^{\circ}C$ in the case of low boiling point or low molecular mass products). The residue was analyzed by gas chromatography or/and purified by flash chromatography on silica gel.

1-(4-Methylphenyl)-2-phenylacetylene (Table 2, entry 1):[24] ^1H NMR ($CDCl_3$): $\delta = 7.44$ (d, 2H, $J = 8.0$ Hz, ArH), 7.41–7.33 (m, 5H, ArH), 7.17 (d, 2H, $J = 8.0$ Hz, ArH), 2.38 (s, 3H, CH_3).

1-(4-Methylphenyl)-2-*t*-butylacetylene (Table 2, entry 2):[25] ^1H NMR ($CDCl_3$): $\delta = 7.24$ (d, 2H, $J = 7.7$ Hz, ArH), 7.09 (d, 2H, $J = 7.7$ Hz, ArH), 2.43 (s, 3H, CH_3), 1.39 [s, 9H, $C(CH_3)_3$].

1-(4-Methylphenyl)-2-hexylacetylene (Table 2, entry 3):[26] ^1H NMR ($CDCl_3$): $\delta = 7.24$ (d, 2H, $J = 7.7$ Hz, ArH), 7.09 (d, 2H, $J = 7.7$ Hz, ArH), 2.60 (t, 2H, $J = 7.0$ Hz, CH_2), 1.74 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 1.4 (m, 4H, $2 \times CH_2$), 0.96 (t, 3H, $J = 7.0$ Hz, CH_3).

1-(*t*-But-1-yn-1-yl)naphthalene (Table 2, entry 4):[27] ^1H NMR ($CDCl_3$): $\delta = 8.35$ (d, 1H, $J = 8.6$ Hz, ArH), 7.85 (d, 1H, $J = 8.0$ Hz, ArH), 7.79 (d, 1H, $J = 8.0$ Hz, ArH), 7.54 (m, 1H, ArH), 7.64 (d, 1H, $J = 7.4$ Hz, ArH), 7.42 (t, 1H, $J = 8.0$ Hz, ArH), 7.3 (m, 1H, ArH), 1.47 [s, 9H, 7.0, $C(CH_3)_3$].

1-(Oct-1-yn-1-yl)naphthalene (Table 2, entry 5):[28] ^1H NMR ($CDCl_3$): $\delta = 8.38$ (d, 1H, $J = 8.3$ Hz, ArH), 7.86 (d, 1H, $J = 7.7$ Hz, ArH), 7.80 (d, 1H, $J = 8.3$ Hz, ArH), 7.65 (d, 1H, $J = 7.0$ Hz, ArH), 7.56 (m, 2H, ArH), 7.42 (t, 1H, $J = 7.3$ Hz, ArH), 2.60 (t, 2H, $J = 7.0$ Hz, CH_2), 1.74 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 1.4 (m, 4H, $2 \times CH_2$), 0.96 (t, 3H, $J = 7.0$ Hz, CH_3).

1-(1-Naphthyl)-2-(triisopropylsilyl)acetylene (Table 2, entry 7): R_f: 0.42 (pentane); oil; IR (film): $\nu = 2942$, 2890, 2864, 2152, 1462, 1392, 1074, 1014, 996, 881, 798, 772, 736 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 8.42$ (d, 1H, $J = 8.3$ Hz, ArH), 7.85 (t, 2H, $J = 8.8$ Hz, ArH), 7.75 (d, 1H, $J = 7.4$ Hz, ArH), 7.61 (t, 1H, $J = 7.7$ Hz, ArH), 7.54 (t, 1H, $J = 7.7$ Hz, ArH), 7.44 (t, 1H, $J = 7.7$ Hz, ArH), 1.23 [m, 21H, $3 \times CH(CH_3)_2$]; ^{13}C NMR: $\delta = 133.5$, 133.1, 131.0, 128.8, 128.3, 126.8, 126.4, 126.3, 125.2, 121.2, 104.9, 95.8, 18.8, 11.4; MS: *m/z* (rel. int.) = 308 (M^+, 43), 265 (67), 237 (17), 223 (43), 209 (58), 195 (100), 179 (32), 165 (22), 105 (23), 85 (8); HRMS (MALDI-TOF): calcd. for $C_{21}H_{28}Si$: 308.1960; found: 308.1967.

1-(4-Fluorophenyl)-2-hexylacetylene (Table 2, entry 8): R_f: 0.39 (pentane); oil; IR (film): $\nu = 2955$, 2938, 2858, 2352, 1601, 1507, 1465, 1427, 1230, 835 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.38$ (td, 2H, $J = 8.6$, 3.2 Hz, ArH), 6.99 (t, 2H, $J = 8.6$ Hz, ArH), 2.40 (t, 2H, $J = 7.0$ Hz, CH_2), 1.53 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 1.3 (m, 4H, $2 \times CH_2$), 0.91 (t, 3H, $J = 7.0$ Hz, CH_3); ^{13}C NMR: $\delta = 162.4$, 133.7, 117.8, 115.7, 90.5, 79.8, 31.7, 28.9, 28.7, 22.9, 19.6, 14.4; MS: *m/z* (rel. int.) = 204 (M^+, 5), 189 (11), 147 (16), 133 (37), 119 (24), 105 (51), 91 (100), 79 (84); HRMS (MALDI-TOF): calcd. for $[C_{14}H_{17}F + K]^+$: 243.0951; found: 243.0959.

1-(4-Nitrophenyl)-2-(triisopropylsilyl)acetylene (Table 2, entry 9):[29] ^1H NMR ($CDCl_3$): $\delta = 8.20$ (d, 2H, $J = 8.9$ Hz, ArH), 7.63 (d, 2H, $J = 8.9$ Hz, ArH), 1.15–1.13 [m, 21H, $3 \times CH(CH_3)_2$].

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