Synthesis of Tri- and Tetrasubstituted Olefins by Palladium Cross-Coupling Reaction

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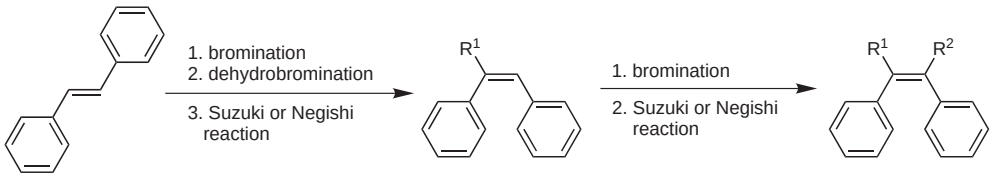
Abstract: Tri- and tetrasubstituted olefins were obtained in high yields and regioselectivities using stilbene as starting material. First, stilbene was converted into (*E*)-bromostilbene by a bromination–dehydrobromination sequence. Then, (*E*)-bromostilbene was coupled with arylboronic acids at room temperature and low loading of Pd catalyst precursor (0.5–0.05 mol%) to afford selectively (*E*)-1-aryl-1,2-phenylethylenes in high yields (87–98%). Bromination of triphenylethylene afforded directly the bromotriphenylethylene that also underwent coupling reactions with arylboronic acids under mild conditions to afford tetrarylethylene (88–90% yield). Under the same conditions attempted Suzuki cross-coupling reactions of (*E*)-bromostilbene or 1,1,2-triphenylethene with alkylboronic acids were unsuccessful. However, the alkyl group could be introduced under mild conditions and high yields by using a Pd-catalyzed Negishi coupling protocol.

Key words: cross-coupling reactions, Suzuki reaction, palladium

The construction of tri- and tetraarylolefins with a high degree of stereocontrol remains a significant challenge in organic synthesis. Amongst the several approaches described in the literature, Pd-catalyzed reactions have been widely applied in the synthesis of tri- and tetrasubstituted olefins.[1] The palladium-catalyzed cross-coupling of aryl halides with arylboronic acids (Suzuki reaction) is a well established and efficient method for the construction of C_{aryl}–C_{aryl} bonds and has found widespread use in organic and polymer synthesis. On the other hand, the Suzuki reaction with vinyl halide derivatives affording tri- and tetraarylolefins has attracted less attention.[2] For instance, the use of $[PdCl(C_3H_5)]_2$/Tecicyp {*cis*,*cis*,*cis*-1,2,3,4-tetrakis[(diphenylphosphanyl)methyl]cyclopentane} at low loadings enables the coupling of vinyl halides at 130 °C.[2a,3] We have recently applied the Suzuki reaction of arylboronic acids with vinyl bromides generated in situ from 1,2-dibromoethane and 1,2-dibromo-1-phenylethane to the synthesis of styrene derivatives and 1,1-diarylolefins, respectively.[4] We have also shown that 1,2-(dibromoethyl)arenes, easily obtained from the bromination of the corresponding styrene derivatives, can be transformed into 2-arylacrylic esters by a one-pot dehydrobromination–carbonylation sequence.[5] The use of styrene in this reaction is an advantage over the traditional carbonylation of expensive and less available alkynes. The latter are also the starting material for most of the palladium-catalyzed syntheses of tri- and tetrasubstituted olefins. Stilbene and substituted stilbenes are easily obtained from a Pd-catalyzed Heck reaction. Herein we report a method for the synthesis of tri- and tetrasubstituted olefins using stilbene as a platform (Scheme 1) using a bromination–dehydrobromination–Suzuki and Negishi cross-coupling reaction sequence.

We used N- and S-based palladacycles to produce stilbene on a 20-gram scale.[6] Bromination of the stilbene at 0 °C using CH_2Cl_2 as solvent gave the 1,2-dibromo-1,2-diphenylethane in 71%, that underwent dehydrobromination (K_2CO_3 as base in a 1:1 mixture of THF–MeOH at r.t.) furnishing the (*E*)-bromostilbene in 70–88% yield and 97–99% regioselectivity.[5]

An initial screening was performed in order to determine the best conditions for the Pd-catalyzed Suzuki cross-coupling of (*E*)-bromostilbene with 4-methoxyphenylboronic acid. We have found similar results to those obtained for the coupling of arylboronic acids with vinyl bromide, generated in situ from 1,2-dibromoethane: $Pd(OAc)_2/PPh_3$ as catalyst precursor, KOH as base, and a solvent mixture (MeOH–THF). However, the reaction can be carried out under milder conditions, such as at room temperature, with lower loadings of palladium (0.05–0.5 mol%). It is also important to note that under these conditions $Pd(OAc)_2$ without triphenylphosphine ligand gave also



Scheme 1 Synthesis of tri- and tetrasubstituted olefins from *trans*-stilbene

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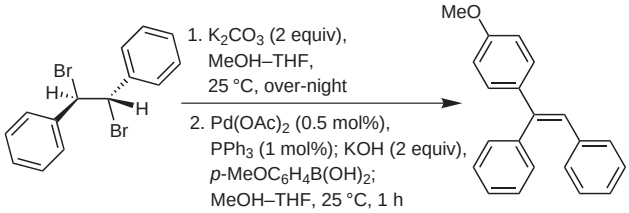
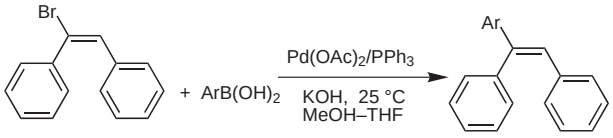
the expected coupling product. However, since higher reaction times and palladium loadings are necessary for the ligandless reaction we chose to follow our studies using a mixture of $Pd(OAc)_2/PPh_3$ as catalyst precursor. The best conditions so far developed were applied to a variety of arylboronic acids (Table 1). Under these conditions, the reaction proceeds smoothly and the (*E*)-1-aryl-1,2-diphenylethylenes were isolated in high yields. Long reaction times were necessary for the coupling with arylboronic acids containing electron-withdrawing groups (Table 1, entries 5–8). The regioselectivity was maintained in the cross-coupling reaction since it was the same as that observed for the starting stilbene (95–98%).

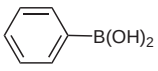
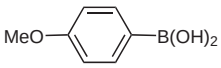
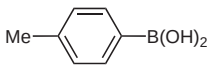
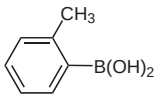
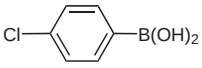
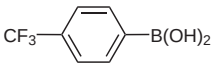
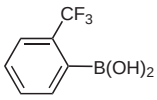
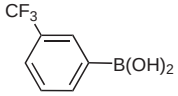
It is worthwhile to mention that dehydrobromination and coupling reaction occur in a basic media in a common solvent media (THF–MeOH) making a one-pot protocol possible (Scheme 2). Therefore, in a resealable Schlenk flask were placed 1,2-dibromo-1,2-diphenylethane, K_2CO_3, THF and methanol, and the mixture was stirred overnight at room temperature. The reaction mixture was filtered off and the reagents for the coupling reaction were added [*p*-methoxyphenylboronic acid, $Pd(OAc)_2$, PPh_3, and KOH]. The mixture was stirred at room temperature for one hour. After work-up, (*E*)-1,2-diphenyl-1-(*p*-methoxyphenyl)ethene was obtained in 91% yield and 98%, regioselectivity.



Scheme 2 Synthesis of trisubstituted olefins from 1,2-dibromo-1,2-diphenylethane

Table 1 Pd-Catalyzed Suzuki Cross-Coupling Reaction of (*E*)-Bromostilbene with Arylboronic Acids[a]



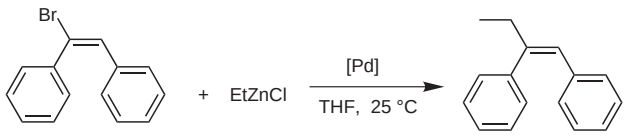
Entry	$ArB(OH)_2$	Time (h)[b]	Yield (%)[c]
1		1	94
2		1	98
3		1	95
4		1	96
5		15	97
6		15	87
7		15	90
8		15	93
9	$MeCH_2CH_2CH_2B(OH)_2$	24	NR
10	$MeB(OH)_2$	24	NR

[a] Reaction conditions: (*E*)-bromostilbene (1 mmol), arylboronic acid (1.2 mmol), KOH (2 mmol), $Pd(OAc)_2$ (0.005 mmol), PPh_3 (0.01 mmol), MeOH (2.5 mL), THF (2.5 mmol), 25 °C.
[b] Reaction times were not optimized.
[c] Isolated yields. NR = no reaction.

Since important arylated ethylenes such as Tamoxifen contain an ethyl group attached to the double bond,[2a] we have also investigated the cross-coupling reaction of (*E*)-bromostilbene with alkylboronic acids. Under the same conditions no conversion of starting material was observed when we used methyl- and butylboronic acid (Table 1, entries 9 and 10). Some coupling product (up to 10%) was obtained by raising the temperature to 100 °C and increasing the palladium loading [4 mol% $Pd(OAc)_2$] but the reduced product stilbene was the main product (up to 90%). It is know that alkylboronic acids are less prone to react with aryl halides than arylboronic acids.[7] On the other hand, it has been shown that (*E*)-bromostilbene could be converted into 1-aryl-1,2-diphenylethene by a cross-coupling reaction with arylzinc chloride in the presence of catalytic amounts of $Pd(PPh_3)_4$.[1] Therefore, we decided to insert an alkyl group by a Pd-catalyzed cross-coupling reaction of (*E*)-bromostilbene with alkyl zinc halides. We investigated the coupling of (*E*)-bromostilbene with ethylzinc chloride in THF at room temperature using different catalyst precursors and phosphine ligands (Table 2). Low yields were obtained in the absence of phosphine ligands (Table 2, entries 1 and 2). Dppf was the best ligand (Table 2, entries 3–6) when $Pd(OAc)_2$ was used as the catalyst precursor. Triphenylphosphine is a very cheap phosphine and the difference was not so pronounced when a phosphine–palladium complex was used (Table 2, entries 7 and 8). Therefore, the reaction was carried out using $PdCl_2(PPh_3)_2$ as catalyst precursor on a 1.5-mmol scale and the (*Z*)-1,2-diphenyl-1-butene was obtained in 90% isolated yield. Once again the regioselectivity was maintained in the cross-coupling reaction (Table 2, entry 9).

The synthesis of tetraarylethylenes was also possible by using the same Suzuki reaction protocol established for the synthesis of triarylethylenes. Bromotriphenylethylene, obtained from the bromination of triphenylethylene, underwent a coupling reaction with arylboronic acids using $Pd(OAc)_2/PPh_3$ as catalyst precursor at room temper-

Table 2 Pd-Catalyzed Cross-Coupling Reaction of (*E*)-Bromostilbene with Ethylzinc Chloride[a]



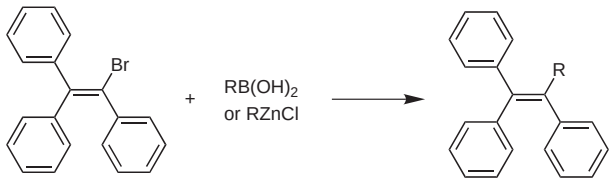
Entry	Catalyst	Ligand	Conv. (%)	Yield (%)[b]
1	$Pd(OAc)_2$	–	31	3
2	$Pd_2(dba)_3$	–	9	5
3	$Pd(OAc)_2$	PPh_3	45	41
4	$Pd(OAc)_2$	PCy_3	46	34
5	$Pd(OAc)_2$	P(*o*-Tol)$_3$	35	21
6	$Pd(OAc)_2$	dppf	77	73
7	$PdCl_2$(dppf)	–	85	68
8	$PdCl_2(PPh_3)_2$	–	65	64
9[c]	$PdCl_2(PPh_3)_2$	–	100	98 (90)

[a] Reaction conditions: (*E*)-bromostilbene (0.25 mmol), ethylzinc chloride (1.25 equiv), Pd (1 mol%), $Pd(OAc)_2/PR_3$ ratio = 1:2, $Pd(OAc)_2$/dppf ratio = 1:1, THF (4 mL), 25 °C, 1 h.
[b] GC yields. Isolated yields are giving in parentheses.
[c] Reactions conditions: (*E*)-bromostilbene (1.5 mmol), 15 h.

ature to afford tetraarylethylenes in high yields (Table 3, entries 1 and 2). On the other hand, the protocol obtained for the reaction of (*E*)-bromostilbene with ethyl zinc chloride was not directly transposable for the coupling of bromotriphenylethylene. Using $PdCl_2(PPh_3)_2$ as catalyst precursor, lower selectivities were observed for the reaction of bromotriphenylethylene with ethylzinc chloride, the reduced product (triphenylethylene) was obtained in the same proportion as the coupling product (Table 3, entry 3). The selectivity in coupling product was improved by using diphosphines instead of monophosphine ligands (Table 3, entries 3–10), but, since lower activities were observed, a higher temperature (100 °C) was necessary to achieve high conversion. Therefore, using BINAP as ligand and 2 mol% of palladium catalyst precursor, bromotriphenylethylene reacted cleanly with ethyl zinc chloride at 100 °C affording (*Z*)-1,1,2-triphenyl-1-butene in 97% selectivity and 91% yield after work-up.

In summary, we have found that a simple catalyst precursor prepared in situ from palladium acetate and triphenylphosphine can be used in the synthesis of tri- and tetraarylethylene, which were obtained in high yields and regioselectivities, using stilbene as starting material. The Suzuki cross-coupling reactions can be carried out at low catalyst loadings at room temperature. Alkyl groups could be introduced under mild conditions and high yields by using a Pd-catalyzed Negishi coupling protocol. The

Table 3 Synthesis of Tetrasubstituted Ethylenes



Entry	RM	Catalyst Precursor	Conv. (%)	Coupling product (%)[a]	Reduced product (R = H) (%)
1[b]	Ph-B(OH)$_2$	$Pd(OAc)_2/PPh_3$	100	100 (88)	–
2[b]	*p*-MeOC$_6$H$_4$B(OH)$_2$	$Pd(OAc)_2/PPh_3$	100	100 (90)	–
3[c,d]	EtZnCl	$PdCl_2(PPh_3)_2$	94	51	49
4[c,d]	EtZnCl	$Pd(OAc)_2/PCy_3$	76	46	54
5[c,e]	EtZnCl	$Pd(OAc)_2$/dppf	100	69	31
6[c,e]	EtZnCl	$Pd(OAc)_2$/dppe	53	55	45
7[c,e]	EtZnCl	$Pd(OAc)_2$/dppp	99	95	5
8[c,e]	EtZnCl	$Pd(OAc)_2$/dppb	100	92	8
9[c,e]	EtZnCl	$Pd(OAc)_2$/*p*-tolyl BINAP	100	90 (88)	10
10[c,e]	EtZnCl	$Pd(OAc)_2$/BINAP	100	97 (91)	3

[a] Isolated yields are given in parentheses.
[b] Reaction conditions: bromotriphenylethylene (1 mmol), arylboronic acid (1.2 mmol), KOH (2 mmol), $Pd(OAc)_2$ (0.5 mol%, 0.005 mmol), PPh_3 (0.01 mmol), MeOH (2.5 mL), THF (2.5 mmol), 25 °C, overnight.
[c] Reactions conditions: bromotriphenylethylene (0.25 mmol), Pd (2 mol%, 0.005 mmol), EtZnCl (0.3 mmol), overnight.
[d] At 25 °C.
[e] At 100 °C.

extension of these protocols for the selective synthesis of biologically active tri- and tetraarylated olefins is now under investigation in our group.

General Experimental Procedures

All reactions were carried out under argon atmosphere in oven dried resealable Schlenk tube. Iodobenzene was purchased from Acros, and styrene was purchased from Aldrich and dried before use. MeOH and THF were degassed and dried, respectively. Arylboronic acids were prepared according to the previously published procedure.[8] Chemicals were used without purification. NMR spectra were recorded on a Varian XL300 spectrometer, infrared spectra performed in a SHIMADZU FTIR-8300 spectrometer, and mass spectra obtained on a GC/MS Shimadzu QP-5050 (EI, 70eV). Gas chromatography analyses were performed on a HP column DB-17 GC with a FID and 30 m capillary column with a dimethylsiloxane stationary phase.

Typical for the Suzuki Coupling of 1-Bromo-1,2-diphenylethene and Arylboronic Acids

An oven-dried resealable Schlenk flask was charged with 1-bromo-1,2-diphenylethene (259 mg, 1 mmol), evacuated and black-filled with argon. Then, $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), PPh_3 (2.6 mg, 0.01 mmol), phenylboronic acid (146 mg, 1.2 mmol), KOH (112 mg, 2 mmol), MeOH (2.5 mL), THF (2.5 mL) were added. The reaction mixture was stirred at r.t. for 1 h. The solution was then taken up in Et_2O (30 mL) and washed with aq NaOH (1 M, 10 mL) and brine (2 × 5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel with cyclohexane, affording triphenylethene (241 mg, 94% yield).

Triphenylethylene: white solid, mp 68.6 °C (lit. mp 67–69 °C).[9] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.96 (s, 1 H), 7.01–7.33 (m, 15 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 126.71, 127.38, 127.47, 127.57, 127.92, 128.17, 128.60, 129.51, 130.35, 137.33, 140.32, 142.54, 143.38 ppm. IR (mull): 2924, 2854, 1463, 1377, 760, 695 cm^{-1}. GC-MS (IE, 70 eV): *m/z* (%) = 256 (100) [M$^+$], 178 (89), 120 (71), 126 (60), 179 (50), 113 (46), 51 (42), 165 (38), 255 (26).

Typical for the Negishi Coupling of 1-Bromo-1,2-diphenylethene and Ethyl Zinc Chloride

An oven-dried resealable Schlenk flask was charged with $ZnCl_2$ (273 mg, 2 mmol), THF (3 mL), diethyl zinc (2 mL of a 1 M solution in hexane, 2 mmol). The mixture was stirred at r.t. for 1 h before use. The mixture was transferred to an oven-dried resealable Schlenk flask containing 1-bromo-1,2-diphenylethene (388 mg, 1.5 mmol) in THF (5 mL). Finally, $Pd(PPh_3)_2Cl_2$ (10.5 mg, 0.015 mmol) was added and the reaction was stirred at r.t. for 2 h. The solvent was evaporated under reduced pressure, and the crude material was purified by flash chromatography on silica gel with hexane furnishing (*Z*)-1,2-diphenyl-1-butene (281 mg, 90% yield).

(*Z*)-1,2-Diphenyl-1-butene: white solid, mp 170.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.5 Hz, 3 H), 2.50 (q, *J* = 7.4 Hz, 2 H), 6.42 (s, 1 H), 6.90–7.40 (m 10 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 12.88, 33.52, 125.07, 126.00, 126.78, 127.76, 128.44, 128.51, 128.96, 137.53, 141.47, 144.93 ppm. IR (mull): 3079, 3056, 3023, 2967, 2931, 2873, 1599, 1494, 1445, 756, 697 cm^{-1}. GC-MS (IE, 70 eV): *m/z* (%) = 208 (52) [M$^+$], 115 (100), 91 (41), 178 (40), 179 (38), 129 (28), 193 (26), 89 (25).

1,1,2-Triphenyl-1-butene: white solid, mp 77.8 °C (lit. mp 78–79 °C).[1] ^{1}H NMR (300 MHz,$CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H), 2.48 (q, *J* = 7.5 Hz, 2 H), 6.86–7.34 (m, 15 H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 13.55, 28.96, 125.68, 126.11, 126.56, 127.31, 127.76, 128.10, 129.42, 129.65, 130.72, 138.78, 142.13, 142.16, 142.95, 143.47 ppm. IR (mull): 2952, 2925, 2854, 1461, 1376, 760, 700 cm^{-1}. GC-MS (IE, 70 eV): *m/z* (%) = 284 (43) [M$^+$], 78 (100), 77 (57), 51 (52), 91 (47), 191 (47), 39 (41), 165 (39).

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