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Pd(0)-Catalyzed Tandem One-Pot Reaction of Biphenyl Ketones/Aldehydes to the Corresponding Di-substituted Aryl Olefins

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Synthesis of di-substituted aryl olefins via a Pd(0)-catalyzed cross-coupling reaction of biphenyl ketones/aldehydes, tosylhydrazide, and aryl bromides (or benzyl halides) was developed. This methodology was achieved by one-pot two-step reactions involving the preparation of *N*-tosylhydrazones by reacting tosylhydrazide with biphenyl ketones/aldehydes, followed by coupling with aryl bromides (or benzyl halides) in the presence of $Pd(PPh_3)_4$ and lithium *t*-butoxide to produce various di-substituted aryl olefins in moderate to good yields.

Keywords one-pot reaction, biphenyl ketone, *N*-tosylhydrazones, di-substituted olefins, palladium catalyzed

Introduction

N-Tosylhydrazones are highly versatile synthetic intermediates that have attracted considerable interest in a variety of research fields in recent years.[1] In 2007, Barluenga group reported the first Pd-catalyzed cross-coupling reactions of *N*-tosylhydrazones as the nucleophilic component with aryl halides. Under mild conditions, di- and tri-substituted olefins can be synthesized in good yields.[2] Subsequently, the scope of this transformation has been greatly extended by using different substrates, coupling reagents, or catalysts.[3,4] But almost none of the investigations have used biphenyl-4-carbonyl compounds as substrates. Also, tosylhydrazones as starting materials must be prepared by reaction of tosylhydrazide with a corresponding ketone or aldehyde. Thus, using *N*-tosylhydrazones as starting materials is not ideal due to the multi-step response, complex operation, and the comparatively high cost. Only a few researchers have directly used carbonyl compounds as nucleophilic coupling partners in this reaction.[5-7]

One-pot multistep transformation as an ideal synthetic strategy for the molecular complexity from readily available starting compounds provides a means to improve the economic and environmental aspects of the chemical processes by minimizing the use of chemicals, the waste production and the processing time.[8] Herein, we developed an efficient method for the synthesis of 4-(1-phenylvinyl)-1,1'-biphenyl derivatives and (*E*)-4-styryl-1,1'-biphenyl derivatives through a Pd(0)-catalyzed coupling reaction of biphenyl-4-carbonyl compounds and *p*-toluenesulfonyl hydrazide substrates coupled directly with aryl halides or benzyl halides. In this one-pot two-step transformation, the di-substituted aryl olefins, obtained as final products, are important synthetic compounds in the preparation of organic materials, functional molecules, and natural products. For example (Scheme 1), in 2010, Hartmann group found that the change of the substituents on 4-(1-([1,1'-biphenyl]-4-yl)vinyl) pyridine resulted in several strong CYP17 (cytochrome P450, family 17) inhibitors, which are promising therapy for prostate cancer.[9] In 2008, Anderson group reported a series of biphenyl compounds, which are potent inhibitors for the emerging infectious disease cryptosporidiosis.[10]

Experimental

Materials and instruments

All the reactions were carried out under a nitrogen atmosphere using magnetic stirring unless otherwise noted. ^{1}H NMR spectral data were recorded on a BRUKER AVANCE III HD 400 spectrometer using TMS as internal standard and $CDCl_3$ as solvent. EI-Mass spectrum was measured on an LC/Q-TOF MS (Micromass, England). Column chromatography was performed with silica gel (200—300 mesh) purchased from Qingdao Haiyang Chemical Co., Ltd. All the other reagents were of analytical grade quality, purchased commercially and used as received.

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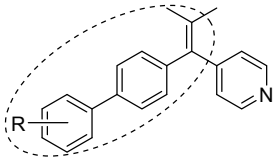
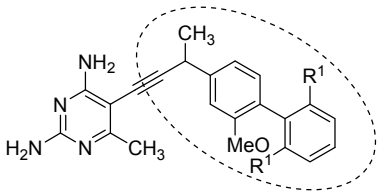
Scheme 1 Alkenylbiphenyls as potent drug molecoles



(R = *m*-BocNH, *p*-BocNH, *m*,*p*-diBocNH, *m*,*p*-diNH$_2$)

Biphenylmethylene 4-Pyridine Compounds by Hartmann's group



(R^1, R^2 = H, Me, IPr)

Biphenyl Inhibitors by Anderson's group

General procedure for the Pd(0)-catalyzed tandem one-pot reaction

Through "One Pot" process, the Schlenk tube (25 mL) equipped with a stir bar was charged with the substituted 4-acetylbiphenyl (or 4-phenylbenzaldehyde) and tosylhydrazide. The intermediate needn't be separated after heating at 100 ℃ for 2 h under a N_2 atmosphere. Aryl halides, LiO^tBu, $Pd(PPh_3)_4$ (5 mol%) and 1,4-dioxane were added under a N_2 atmosphere. The mixture was then stirred at 100 ℃ for 12 h. The solution was quenched with water and extracted with EtOAc (10 mL×3). The combined EtOAc extracts were dried over anhydrous $MgSO_4$ and filtrated, then the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with petroleum ether (PE) and dichloromethane (DCM) as the eluent to obtain the desired products.

4-Methyl-4'-(1-(*p*-tolyl)vinyl)-1,1'-biphenyl (5b)

Product **5b** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. White solid, 84% yield (120 mg). m.p. 119.4−120.2 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55−7.52 (m, 3H), 7.40 (d, J=8.0 Hz, 2H), 7.30−7.22 (m, 5H), 7.17−7.14 (m, 2H), 5.46 (s, 1H), 5.43 (s, 1H), 2.39 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.7, 140.6, 140.5, 138.8, 138.0, 137.7, 137.2, 129.6, 129.0, 128.8, 128.4, 127.0, 126.8, 113.7, 21.3. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}$ $[M+H]^+$ 285.1638, found 285.1636.

3-Methyl-4'-(1-(*p*-tolyl)vinyl)-1,1'-biphenyl (5c)

Product **5c** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. White solid, 73% yield (104 mg). m.p. 120.8−121.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56−7.52 (m, 2H), 7.43−7.38 (m, 4H), 7.34−7.25 (m, 3H), 7.15 (d, J=8.0 Hz, 3H), 5.44 (d, J=9.2 Hz, 2H), 2.39 (d, J=16.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.6, 140.8, 140.7, 140.6, 138.7, 138.4, 137.6, 129.0, 128.8, 128.7, 128.3, 128.1, 127.9, 126.9, 124.2, 113.7, 21.6, 21.3. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}$ $[M+H]^+$ 285.1638, found 285.1638.

2-Methyl-4'-[1-(*p*-tolyl)vinyl]-1,1'-biphenyl (5d)

Product **5d** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. Yellow liquid, 69% yield (98 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, J=8.4 Hz, 2H), 7.30−7.28 (m, 2H), 7.27 (d, J=4.0 Hz, 2H), 7.26−7.23 (m, 4H), 7.16 (t, J=5.2 Hz, 2H), 5.48 (s, 1H), 5.44 (s, 1H), 2.37 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.8, 141.7, 141.5, 140.1, 138.8, 137.7, 135.5, 130.5, 129.9, 129.1, 129.0, 128.4, 128.0, 127.4, 125.9, 113.8, 21.3, 20.7. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}$ $[M+H]^+$ 285.1638, found 285.1637.

4-Methoxy-4'-(1-(*p*-tolyl)vinyl)-1,1'-biphenyl (5e)

Product **5e** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. White solid, 64% yield (96 mg). M.p. 145.1−146.2 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57−7.47 (m, 5H), 7.38 (d, J=8.4 Hz, 2H), 7.28 (s, 1H), 7.15 (d, J=8.0 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 5.45 (d, J=1.2 Hz, 1H), 5.42 (d, J=1.2 Hz, 1H), 3.83 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3, 149.7, 140.1, 138.8, 137.7, 133.4, 129.0, 128.8, 128.4, 128.2, 126.5, 114.37, 114.36, 113.6, 55.5, 21.3. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{21}O$ $[M+H]^+$ 301.1587, found 301.1587.

4-Propyl-4'-(1-(*p*-tolyl)vinyl)-1,1'-biphenyl (5f)

Product **5f** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. Yellow solid, 81% yield (126 mg). M.p. 99.1−102.1 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55−7.51 (m, 4H), 7.39 (d, J=8.4 Hz, 2H), 7.29−7.22 (m, 4H), 7.15 (d, J=8.0 Hz, 2H), 5.44 (d, J=10.8 Hz, 2H), 2.64−2.60 (m, 2H), 2.37 (s, 3H), 1.69 (d, J=7.6 Hz, 1H), 1.66 (d, J=7.2 Hz, 1H), 0.97 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.7, 142.0, 140.6, 138.8, 138.2, 137.7, 130.8, 130.4, 129.0, 128.8, 128.4, 127.0, 126.8, 113.7, 37.9, 24.7, 21.3, 14.0. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{25}$ $[M+H]^+$ 313.1951, found 313.1951.

4-Fluoro-4'-(1-(*p*-tolyl)vinyl)-1,1'-biphenyl (5g)

Product **5g** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. Yellow solid, 96% yield (138 mg). M.p. 99.8−101.8 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58−7.54 (m, 2H), 7.52−7.48 (m, 2H), 7.40 (d, J=8.0 Hz, 2H), 7.26 (t, J=7.6 Hz, 2H), 7.18−7.09 (m, 4H), 5.45 (d, J=4.4 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.9, 149.6, 140.8, 139.5, 138.7, 137.8, 130.8, 129.1, 128.9, 128.3, 126.8, 115.7, 113.9, 21.3. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{18}F$ $[M+H]^+$

289.1387, found 289.1387.

4-(1-(*p*-Tolyl)vinyl)-4'-(trifluoromethyl)-1,1'-biphenyl (5h)

Product **5h** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. White solid, 84% yield (142 mg). m.p. 149.8—151.2 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, J=0.4 Hz, 4H), 7.55 (d, J=8.6 Hz, 2H), 7.44 (d, J=8.6 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 7.16 (d, J=8.0 Hz, 2H), 5.47 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.4, 144.4, 141.8, 139.1, 138.5, 137.9, 129.1, 129.0, 128.3, 127.4, 127.1, 125.9, 114.2, 21.3. HRMS (ESI): *m*/*z* calcd for $C_{22}H_{18}F_3$ $[M+H]^+$ 339.1355, found 339.1353.

2,4-Difluoro-4'-(1-(*p*-tolyl)vinyl)-1,1'-biphenyl (5i)

Product **5i** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. Yellow liquid, 92% yield (141 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46—7.43 (m, 2H), 7.42—7.36 (m, 3H), 7.26 (d, J=8.0 Hz, 2H), 7.14 (d, J=8.0 Hz, 2H), 6.93—6.85 (m, 2H), 5.45 (d, J=1.2 Hz, 1H), 5.44 (d, J=1.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.5, 141.2, 138.5, 137.7, 134.4, 134.4, 131.5, 131.4, 129.1, 128.3, 125.2, 125.0, 114.1, 111.8, 104.51, 104.49, 21.3. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{17}F_2$ $[M+H]^+$ 307.1293, found 307.1293.

4-(1-(3-Methoxyphenyl)vinyl)-1,1'-biphenyl (5k)

Product **5k** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. Yellow liquid, 84% yield (121 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63—7.52 (m, 5H), 7.44—7.37 (m, 5H), 7.24 (t, J=8.0 Hz, 1H), 6.98—6.91 (m, 2H), 5.48 (d, J=16.8 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.6, 149.6, 143.1, 140.8, 140.7, 140.4, 129.3, 128.9, 128.8, 127.5, 127.1, 127.0, 121.1, 114.5, 114.2, 113.4, 55.4. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}O$ $[M+H]^+$ 287.1430, found 287.1431.

4-(1-(2-Methoxyphenyl)vinyl)-1,1'-biphenyl (5l)

Product **5l** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. Yellow liquid, 96% yield (137 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63—7.56 (m, 3H), 7.50 (d, J=8.4 Hz, 2H), 7.42—7.35 (m, 5H), 7.26 (dd, J=1.6, 7.5 Hz, 1H), 7.01—6.97 (m, 1H), 6.91 (d, J=8.0 Hz, 1H), 5.78 (d, J=1.6 Hz, 1H), 5.33 (d, J=1.6 Hz, 1H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.2, 146.6, 140.9, 140.11, 140.06, 131.4, 131.1, 130.6, 129.2, 128.9, 127.3, 127.1, 126.9, 120.8, 115.5, 111.4, 55.8. HRMS (ESI): *m*/*z* calcd for $C_{21}H_{19}O$ $[M+H]^+$ 287.1430, found 287.1430.

4-(1-(4-Chlorophenyl)vinyl)-1,1'-biphenyl (5m)

Product **5m** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. White solid, 60% yield (86 mg). m.p. 118.1—118.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (s, 1H), 7.58 (s, 1H), 7.55 (d, J=8.4 Hz, 2H), 7.42 (t, J=7.6 Hz, 2H), 7.38—7.32 (m, 3H), 7.32—7.28 (m, 4H), 5.50 (d, J=0.8 Hz, 1H), 5.43 (d, J=0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.7, 140.9, 140.7, 140.0, 133.8, 129.8, 129.0, 128.7, 128.5, 127.6, 127.2, 127.1, 114.8. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{16}Cl$ $[M+H]^+$ 291.0935, found 291.0936.

4-[1-(3-Chlorophenyl)vinyl]-1,1'-biphenyl (5n)

Product **5n** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. White solid, 53% yield (78 mg). m.p. 76.9—77.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60—7.53 (m, 4H), 7.41 (t, J=7.6 Hz, 2H), 7.39—7.31 (m, 4H), 7.30—7.26 (m, 1H), 7.25—7.20 (m, 2H), 5.52 (s, 1H), 5.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.6, 143.5, 140.9, 140.7, 139.8, 134.3, 129.6, 128.9, 128.7, 128.5, 128.0, 127.5, 127.12, 127.11, 126.7, 115.4. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{16}Cl$ $[M+H]^+$ 291.0935, found 291.0935.

4-(1-(4-Nitrophenyl)vinyl)-1,1'-biphenyl (5p)

Product **5p** was obtained by flash column chromatography on silica gel with PE∶DCM=10∶1 as the eluent. White solid, 56% yield (85 mg). m.p. 135.2—136.1 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, J=9.2 Hz, 2H), 7.63—7.58 (m, 4H), 7.54 (d, J=8.8 Hz, 2H), 7.46 (t, J=7.6 Hz, 2H), 7.39—7.35 (m, 3H), 5.69 (d, J=0.4 Hz, 1H), 5.60 (d, J=0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.2, 148.1, 147.5, 141.4, 140.5, 139.1, 129.2, 129.0, 128.7, 127.7, 127.3, 127.2, 123.7, 117.3. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{16}NO_2$ $[M+H]^+$ 302.1176, found 302.1176.

1-(1-([1,1'-Biphenyl]-4-yl)vinyl)naphthalene (5q)

Product **5q** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. White solid, 80% yield (122 mg). m.p. 107.2—108.3 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85—7.78 (m, 3H), 7.53 (d, J=7.2 Hz, 2H), 7.48—7.31 (m, 10H), 7.29 (d, J=7.2 Hz, 1H), 6.01 (s, 1H), 5.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.9, 140.7, 140.5, 140.1, 139.9, 133.8, 132.0, 128.9, 128.3, 128.1, 127.44, 127.36, 127.19, 127.16, 127.1, 126.6, 126.1, 125.9, 125.6, 116.3. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{19}$ $[M+H]^+$ 307.1481, found 307.1481.

2-(1-([1,1'-Biphenyl]-4-yl)vinyl)naphthalene (5r)

Product **5r** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. White solid, 55% yield (84 mg). m.p. 131.9—132.8 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, J=9.6 Hz, 4H), 7.62 (d, J=7.2 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H), 7.51 (dd, J=8.4, 1.6 Hz, 1H), 7.48—7.41 (m, 6H), 7.34 (t, J=7.2 Hz, 1H), 5.60 (d, J=3.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.8, 140.84, 140.76, 140.6, 139.0, 133.5, 133.1, 128.9, 128.9, 128.3, 127.9,

127.8, 127.52, 127.49, 127.2, 127.1, 126.6, 126.3, 126.2, 115.0. HRMS (ESI): *m/z* calcd for $C_{24}H_{19}$ $[M+H]^+$ 307.1481, found 307.1481.

3-(1-([1,1'-Biphenyl]-4-yl)vinyl)thiophene (5s)

Product **5s** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. Yellow solid, 28% yield (37 mg). m.p. 82.4—83.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62—7.55 (m, 4H), 7.48—7.41 (m, 4H), 7.36—7.28 (m, 2H), 7.24—7.11 (m, 2H), 5.53 (s, 1H), 5.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.3, 142.6, 140.84, 140.77, 140.5, 128.9, 128.6, 127.5, 127.4, 127.2, 127.0, 125.6, 123.5, 113.6. HRMS (ESI): *m/z* calcd for $C_{18}H_{15}S$ $[M+H]^+$ 263.0889, found 263.0889.

2-(1-([1,1'-Biphenyl]-4-yl)vinyl)thiophene (5t)

Product **5t** was obtained by flash column chromatography on silica gel with PE∶DCM=20∶1 as the eluent. Yellow solid, 23% yield (31 mg). m.p. 79.5—80.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65—7.56 (m, 4H), 7.53—7.48 (m, 2H), 7.46—7.41 (m, 2H), 7.37—7.32 (m, 1H), 7.24 (dd, J=1.6, 4.8 Hz, 1H), 7.02—6.93 (m, 2H), 5.60 (d, J=0.8 Hz, 1H), 5.30 (d, J=0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.8, 143.1, 141.1, 140.8, 140.1, 128.9, 128.9, 127.5, 127.4, 127.2, 127.0, 126.7, 125.2, 113.8. HRMS (ESI): *m/z* calcd for $C_{18}H_{15}S$ $[M+H]^+$ 263.0889, found 263.0890.

(*E*)-3-Methyl-4'-styryl-1,1'-biphenyl (8c)

Product **8c** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid, 83% yield (112 mg). m.p. 160.8—162.6 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60—7.51 (m, 6H), 7.44—7.33 (m, 5H), 7.27 (d, J=7.2 Hz, 1H), 7.16 (d, J=10.8 Hz, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.8, 140.6, 138.5, 137.5, 136.4, 128.85, 128.84, 128.80, 128.4, 128.2, 127.9, 127.8, 127.5, 127.0, 126.7, 124.2, 21.7. HRMS (ESI) *m/z* calcd for $C_{21}H_{19}$ $[M+H]^+$ 271.1481, found 271.1480.

(*E*)-4-Fluoro-4'-styryl-1,1'-biphenyl (8e)

Product **8e** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid, 46% yield (63 mg). m.p. 218.2—219.3 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65—7.47 (m, 8H), 7.37 (t, J=7.6 Hz, 2H), 7.28 (d, J=7.2 Hz, 1H), 7.18—7.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6 (d, J=246.8 Hz), 139.5, 137.4, 136.9, 136.5, 129.0, 128.9, 128.6 (d, J=8.0 Hz), 128.2, 127.9, 127.4, 127.1, 126.7, 115.8 (d, J=1.6 Hz). HRMS (ESI) *m/z* calcd for $C_{20}H_{16}F$ $[M+H]^+$ 275.1231, found 275.1230.

(*E*)-4-(2-Methylstyryl)-1,1'-biphenyl (8f)

Product **8f** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid, 61% yield (82 mg). m.p. 93.8—95.1 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63—7.57 (m, 7H), 7.39 (dt, J=7.2, 23.2 Hz, 4H), 7.21—7.16 (m, 3H), 7.02 (d, J=16.0 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.8, 140.4, 136.9, 136.5, 136.0, 130.6, 129.6, 129.0, 127.7, 127.48, 127.45, 127.12, 127.05, 126.7, 126.4, 125.5 20.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{19}$ $[M+H]^+$ 271.1481, found 271.1482.

(*E*)-4-(3-Methylstyryl)-1,1'-biphenyl (8g)

Product **8g** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid, 78% yield (105 mg). m.p. 126.1—127.9 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61—7.54 (m, 6H), 7.42 (t, J=6.8 Hz, 2H), 7.32 (d, J=11.2 Hz, 3H), 7.14—6.98 (m, 4H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.8, 140.3, 138.3, 137.4, 136.6, 130.6, 129.7, 129.0, 128.9, 128.7, 128.6, 128.1, 127.5, 127.4, 127.0, 123.9, 21.6. HRMS (ESI) *m/z* calcd for $C_{21}H_{19}$ $[M+H]^+$ 271.1481, found 271.1488.

(*E*)-4-(4-Fluorostyryl)-1,1'-biphenyl (8i)

Product **8i** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid, 44% yield (61 mg). m.p. 126.1—127.1 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63—7.56 (m, 6H), 7.51—7.43 (m, 4H), 7.36 (d, J=7.2 Hz, 1H), 7.11—7.01 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5 (d, J=247.3 Hz), 140.8, 140.5, 136.4, 133.7 (d, J=3.3 Hz), 129.0, 128.14 (d, J=8.0 Hz), 128.13, 127.7, 127.52, 127.50, 127.1, 127.0, 115.8 (d, J=21.7 Hz). HRMS (ESI) *m/z* calcd for $C_{20}H_{16}F$ $[M+H]^+$ 275.1231, found 275.1236.

(*E*)-4-(4-(Trifluoromethoxy)styryl)-1,1'-biphenyl (8j)

Product **8j** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid, 60% yield (102 mg). m.p. 176.1—177.2 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63—7.52 (m, 7H), 7.45 (t, J=7.6 Hz, 2H), 7.36 (dd, J=7.0, 1.6 Hz, 1H), 7.27—7.18 (m, 3H), 7.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.8, 140.7, 136.3, 136.1, 129.4, 129.0, 127.8, 127.57, 127.56, 127.3, 127.2, 127.1, 121.36, 121.35. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}F_3O$ $[M+H]^+$ 341.1148, found 341.1153.

(*E*)-4-(3,4-Difluorostyryl)-1,1'-biphenyl (8k)

Product **8k** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid, 45% yield (66 mg). m.p. 171.8—172.8 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63—7.54 (m, 6H), 7.45 (t, J=7.6 Hz, 2H), 7.37—7.30 (m, 2H), 7.21—7.12 (m, 2H), 7.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.9, 140.7, 135.9, 129.4, 129.0, 127.7, 127.6, 127.2, 127.1, 126.7, 122.9, 122.8, 117.7, 117.5, 114.9, 114.7. HRMS (ESI) *m/z* calcd for $C_{20}H_{15}F_2$ $[M+H]^+$ 293.1136, found 293.1130.

(*E*)-4-(4-Chlorostyryl)-4'-fluoro-1,1'-biphenyl (8l)

Product **8l** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid,

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72% yield (111 mg). m.p. 170.1－171.4 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60－7.52 (m, 6H), 7.45 (d, J= 8.4 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H), 7.14 (d, J=8.8 Hz, 2H), 7.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.4, 139.7, 135.9, 133.4, 129.0, 128.8, 128.64, 128.57, 127.8, 127.6, 127.4, 127.2, 116.0. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{15}ClF$ $[M+H]^+$ 309.0841, found 309.0836.

(*E*)-4'-(4-Chlorostyryl)-3-methyl-1,1'-biphenyl (8m)

Product **8m** was obtained by flash column chromatography on silica gel with PE as the eluent. White solid, 67% yield (101 mg). m.p. 171.4－172.8 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (q, J=8.4 Hz, 4H), 7.43 (t, J=9.6 Hz, 4H), 7.33 (t, J=8.0 Hz, 3H), 7.17 (d, J=7.6 Hz, 1H), 7.09 (d, J=2.0 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.9, 138.6, 136.0, 133.3, 129.0, 128.9, 128.3, 127.84, 127.80, 127.6, 127.5, 127.4, 127.08, 127.07, 124.2, 77.5. HRMS (ESI) *m*/*z* calcd for $C_{21}H_{18}Cl$ $[M+H]^+$ 305.1092, found 305.1095.

Results and Discussion

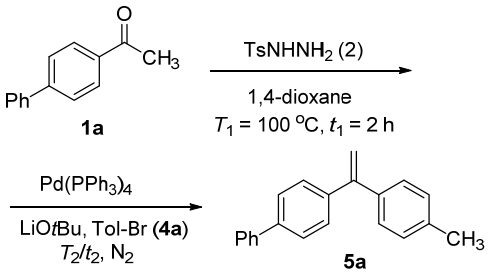
Initially, we chose *N*-tosylhydrazones (**3a**, 0.5 mmol), *p*-bromotoluene (1.0 mmol) as the model reaction in the presence of $Pd(PPh_3)_4$ (5 mol%) as the catalyst, Li*O*^{t}Bu (1.0 mmol) as the base, and 1,4-dioxane as the solvent. Upon optimizing the reaction conditions, we further investigated the substrate scope of this catalytic reaction. A series of substrates were investigated with the product yields in the range of 34% － 95%.[11] Because *N*-tosylhydrazones are easily accessed by the reaction of tosylhydrazide with a corresponding ketone, we focused our studies on examining whether this reaction could be directly conducted in a one-pot manner using 4-acetylbiphenyl as the starting material and without the need to isolate the tosylhydrazone intermediate. As shown in Table 1, upon further experiments, we found the following combination to be the most suitable reaction conditions: 4-acetylbiphenyl (**1a**, 0.5 mmol), *p*-toluenesulfonyl hydrazide (**2a**, 0.55 equiv.), 1-bromo-4-methylbenzene (**4a**, 1.0 mmol), $Pd(PPh_3)_4$ (5 mol%), and Li*O*^{t}Bu (1.0 equiv.) at T_1=100 ℃ (t_1=2 h) and T_2= 100 ℃ (t_2=12 h) in 1,4-dioxane (3 mL) in a nitrogen atmosphere.

Upon optimizing the reaction conditions, we further investigated the substrate scope of this one-pot two-step coupling reaction. As shown in Table 2, the substrate **1a** without substituent group has an 80% yield (**5a**). Other biphenyl ketone substrates, which have electron-donating groups (methyl, methoxy, and *n*-propyl), all had moderate to good yields (**5b**－**5f**). Among them, the substrate with a methyl group at the *para*-position, had the highest yield (**5b** vs. **5c**, **5d**). The substrates with electron withdrawing groups (*p*-fluorine, *p*-trifluoromethyl, and *o*,*m*-di-fluorine) all had good to excellent yields (**5g**－**5i**).

Next, a series of substituted aryl halides were examined under the optimized reaction conditions. As shown in Table 3, (*o*-, *m*-, and *p*-Br)-anisoles were used as coupling partners to provide the corresponding products (**5j**－**5l**) in good to excellent yields (66%－96%). For these, the *ortho*-methoxy substituted product obtained a high yield, while the *para*-methoxy substituted product had only 66% yield. The substrates with electron withdrawing groups (chlorine, cyano, and nitro) all had medium yields (**5m**－**5p**). The *β*-naphthyl compound (**5r**) had moderate yields as well. On the contrary, the *α*-naphthyl compound had a good yield (**5q**). Further, the coupling reaction involving the heterocyclic substrate was also investigated. 1- or 2-bromothiophene reacted with 4-acetylbiphenyl to give the corresponding products (**5s** and **5t**) with 23% and 28% yields, respectively.

We then used biphenyl formaldehyde and benzyl bromides as coupling partners in the one-pot two-step transformation (Table 4). Instead of terminal alkenes, substituted alkenes were found to be the final product. After optimizing the reaction conditions,[10] biphenyl formaldehyde and *o*-, *m*-, and *p*-methyl substituted biphenyl formaldehyde with benzyl bromide produced **8a**－**8d** in good yields. The *m*-, and *p*-methyl substrate were much better than the *o*-methyl substrate. Electron-withdrawing groups, such as the *p*-fluorine substituted substrate, gave only medium yield (**8e**). The substituted benzyl bromides with the *o*- and *m*-methyl group, *p*-chlorine, *p*-fluorine, *p*-trifluoromethoxy, and *m*, *p*-difluorine groups all had medium yields (**8f**－**8k**). There was not an obvious difference between the electron donating and electron withdrawing groups.

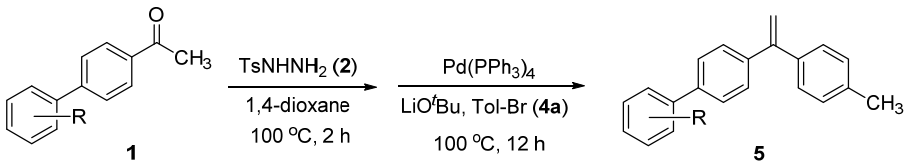
Table 1 Optimization of the reaction conditions[a]

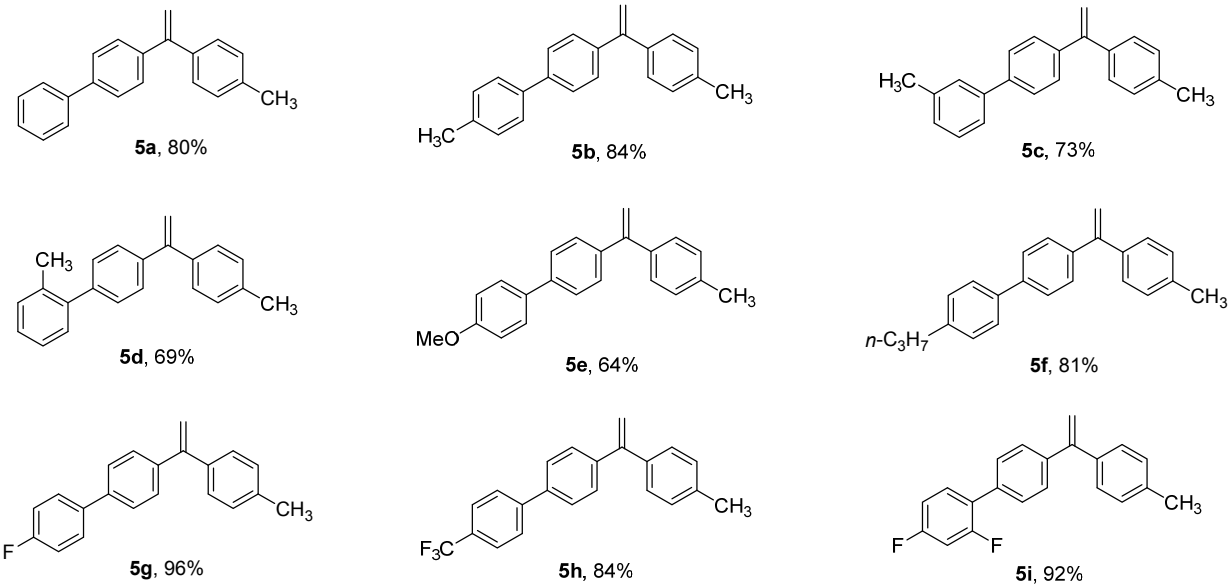


Entry	$TsNHNH_2$ (equiv.)	T_2/℃	t_2/h	Yield[b]/%
1	1.1	90	10	65
2	1.1	100	12	80
3	1.1	110	10	54
4[c]	1.1	100	12	76
5	1.2	100	12	81
6	1.2	100	14	82
7	1.2	100	16	76

[a] Reaction conditions: 4-acetylbiphenyl **1a** (0.5 mmol), $TsNHNH_2$ **2** (0.55 mmol), 1-bromo-4-methylbenzene **4a** (1.0 mmol), $Pd(PPh_3)_4$ (5 mol%), Li*O*^{t}Bu (1.0 mmol), 1,4-dioxane (3 mL) in N_2 atmosphere. [b] Isolated yield. [c] $Pd(PPh_3)_4$ (10 mol%).

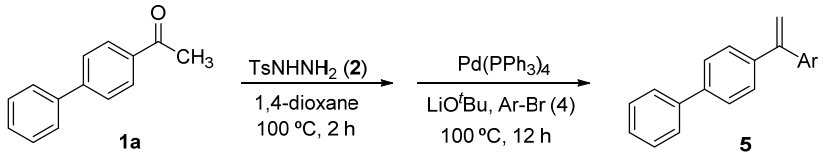
Table 2 One-pot coupling of substituted 4-acetylbiphenyl with Tol-Br

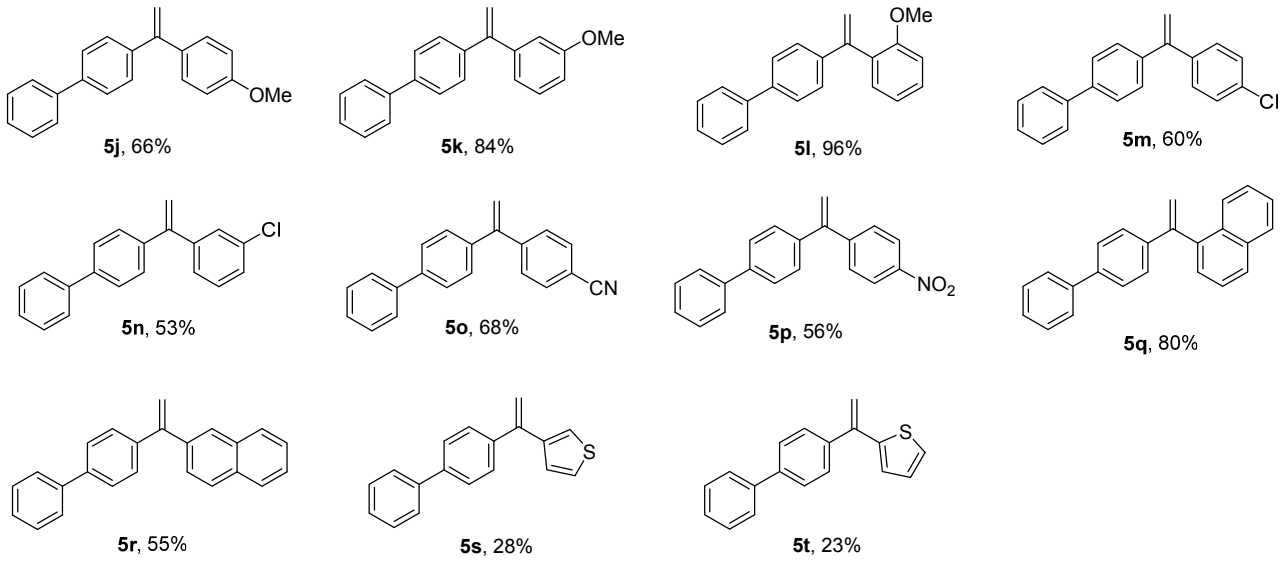




Reaction conditions: substituted 4-acetylbiphenyl (0.5 mmol), $TsNHNH_2$ (0.55 mmol), $Pd(PPh_3)_4$ (5 mol%), LiO^tBu (1.0 mmol), 1,4-dioxane (3 mL) in N_2 atmosphere. The yields of isolated products are given.

Table 3 One-pot coupling of 4-acetylbiphenyl with aryl bromides





Reaction conditions: 4-acetylbiphenyl (0.5 mmol), $TsNHNH_2$ (0.55 mmol), aryl bromide (2 equiv.), $Pd(PPh_3)_4$ (5 mol%), LiO^tBu (2 equiv.), 1,4-dioxane (3 mL) in N_2 atmosphere. The yields of isolated products are given.

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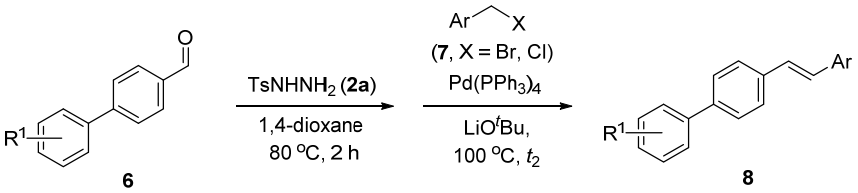
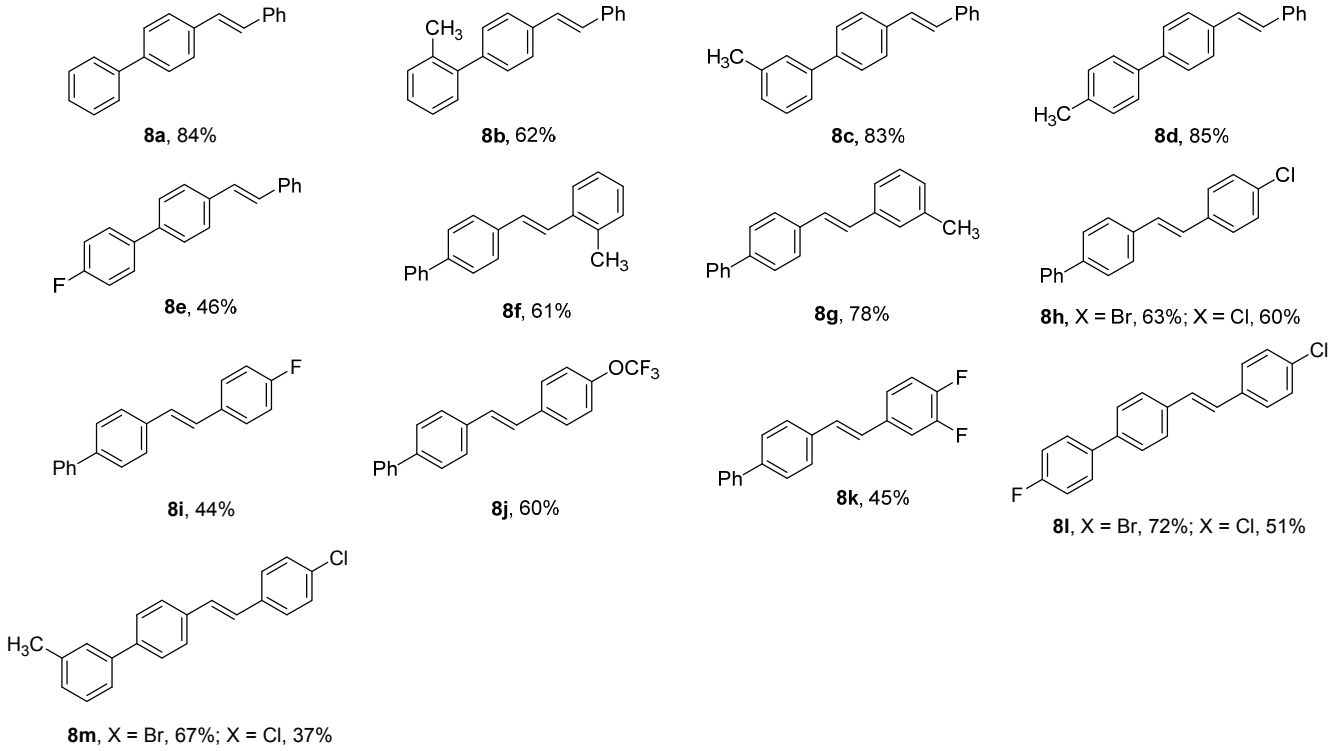
Table 4 One-pot coupling of biphenyl formaldehyde with benzyl halides

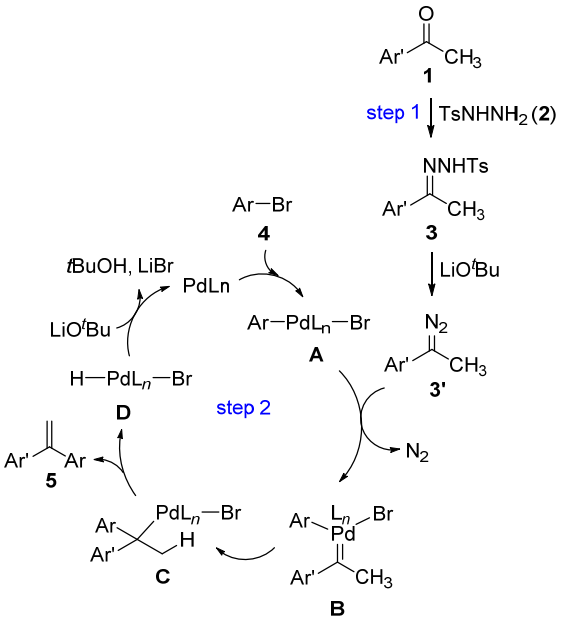




Reaction conditions: [1,1'-biphenyl]-4-carbaldehyde derivative (0.5 mmol), $TsNHNH_2$ (0.6 mmol), benzyl halides (2 equiv.), $Pd(PPh_3)_4$ (5 mol%), LiO^tBu (2 equiv.), 1,4-dioxane (3 mL) in N_2 atmosphere. The yields of isolated products are given.

We proposed a reaction mechanism for this transformation (Scheme 2) which is consistent with that reported in the literature.[1h] Herein, we took the reaction of aryl ketones with aryl bromides as an example. This is a two-step reaction, and during the first step, the aryl ketone **1** reacted with *N*-tosylhydrazide **2** to form the *N*-tosylhydrazone **3** intermediate. Because of the easy accessibility of *N*-tosylhydrazone, this step easily proceeded without the need of a catalyst. Then during the second step, *N*-tosylhydrazone **3** was treated with base (LiO^tBu), and yielded the carbene precursor **3′**. The aryl bromides reacted with the Pd-catalyst by oxidative addition to form **A**. Palladium-carbene **B** was formed through the reaction of **A** with **3′**. The formation of **C** was through the migratory insertion process from compound **B**. Through the *β*-hydride elimination, the final product **5** was released to generate **D**. After being treated with base (LiO^tBu), the Pd(0)-catalyst returned to the original state, and was able to participate in the next catalytic cycle.

Scheme 2 Possible reaction mechanism



Conclusions

To summarize, a simple and efficient method for the synthesis of alkenylbiphenyls via a Pd(0)-catalyzed coupling reaction was developed. Potential substrates

for this reaction are diverse, exhibiting a superior functional-group tolerance. Through the one-pot two-step process, moderate to good yields were obtained. Herein we present our preliminary results, which have led to the development of an optional synthesis route for di-substituted aryl olefins. Further studies to investigate the use of hydrazones in other transformations are currently underway in our laboratory.

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