Linear free-energy correlation analysis of the electronic effects of the substituents in the Sonogashira coupling reaction

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Abstract: Relative rate constants (k_{rel}) for the Sonogashira coupling were determined in competitive reactions between iodobenzene and a series of *para*- and *meta*-substituted iodobenzenes and compared to the charge on iodine and the *z*-component of the quadrupole moment of the iodine-bearing carbon. We use an Hammett correlation analysis and the computational data to provide further evidence that the rate limiting step of the Sonogashira reaction is the initial oxidative addition of Pd to the carbon–iodine bond.

Key words: Sonogashira, competitive reactions, Hammett correlation.

Résumé : On a déterminé les constantes de vitesses relatives (k_{rel}) pour le couplage de Sonogashira dans des réactions compétitives entre l'iodobenzène et une série d'iodobenzènes substitués en positions *méta* et *para* et on a les a comparées à la charge sur l'iode et au composant *z* du moment quadripolaire du carbone portant l'iode. On a utilisé une analyse par corrélation de Hammett et des données de calculs théoriques pour obtenir d'autres bases pour établir que l'étape cinétiquement limitante de la réaction de Sonogashira est l'addition initiale oxydante du palladium sur la liaison carbone–iode.

Mots-clés : Sonogashira, réactions compétitives, corrélation de Hammett.

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Introduction

Preparations of aryl alkynes have been described in the literature using the Sonogashira reaction since 1975 (1). As this coupling reaction has become the most important method for the synthesis of terminal aryl alkynes that have found use as building blocks in materials chemistry and natural product synthesis, amongst others, numerous variations in reaction conditions have been reported (2), and the efforts have culminated in a recent review (3). The original reaction involved the presence of a palladium catalyst, a base, and cuprous iodide. Studies investigating the nature of the aryl halide, the base, the solvent, and the palladium catalyst have all been reported with changes to the reaction that result in improved yields and reduced reaction times (4). In fact, the Sonogashira reaction was developed from earlier reports by Stephens and Castro who used cuprous acetylides to couple with phenyl halides (5). In their report, they indicate that electron-withdrawing groups in the *para*-position increase

the ease of substitution with respect to electron-donating groups in the following manner: *p*-nitro > H > *p*-methoxy. Subsequent reports of Sonogashira coupling reactions have described improved yields when electron-withdrawing substituents, such as carboxaldehydes, nitro groups, and esters, are used (6).

The Sonogashira reaction is one of a family of coupling reactions; these reactions are proposed to proceed via an oxidative addition–reductive elimination via the use of d^{10} or d^8 catalysts such as Pd^0 or Pd^{2+} (1, 7, 8) or Ni^0 or Ni^{2+} (9, 10). The mechanisms of other reactions in this family, such as the Heck reaction (11, 12), Stille coupling (13), and Suzuki reaction (8, 9, 14) have been investigated previously, with a focus on the oxidative addition. Those studies focussed primarily on changes in reactivity resulting from changes in *para*-substitution. All but one (11) obtained a positive Hammett ρ value, indicating that the reaction involves an oxidative addition as the rate-determining step. Even in the case where a negative value (ρ = –1.6) was obtained, the researchers suggest that the oxidative addition is rate-limiting (11) and proceeds through a three-center reaction model, based on work presented for a d^9 iridium catalyst (15, 16).

In light of these studies, and having previously reported competitive Sonogashira reactions between iodobenzenes with electron-donating and electron-withdrawing groups in the *para*-position, which support the observations by Stephens and Castro (17), we would like to report on an extension of this research. A kinetic competition experiment between iodobenzene and a large number of *para*- and *meta*-

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substituted iodobenzenes is presented. The majority of studies presented in the literature have focused on *para*-substitution, and we present a number of new *meta*-substituted compounds to extend the scope of the study. Furthermore, a computational study was undertaken to analyze the relationship of the kinetic data with the electron density within the quantum theory of atoms in molecules (18).

Results and discussion

The substituted iodobenzenes were chosen for their availability and to ensure a range of electron-donating and electron-withdrawing substituents. The intermolecular competition was carried out using 1 equiv. each of iodobenzene and the substituted iodobenzene and 0.05 equiv. of the trimethylsilylacetylene. The Pd catalyst and CuI catalyst were present in 0.02 and 0.06 mol equiv., respectively. The choice of reaction conditions (catalyst, solvent, and base) was based on established reaction conditions that allow the Sonogashira coupling to occur for a wide variety of substituents (4). The alkyne was present at a level of 0.05 equiv. to establish pseudo first-order reaction conditions with respect to the aryl iodides. Biphenyl was used as an internal standard in the GC analysis and was added after the desired reaction time. The yields of the aryl alkynes were determined using this internal standard with the relative areas of the GC peaks (aryl alkyne : biphenyl) being compared to the response factors that had been previously obtained using pure samples of the products of known concentrations with known amounts of biphenyl added. To obtain pure samples of the aryl alkynes, samples of each of the aryl alkynes, **3** and **4a–4r**, were synthesized using an excess of the alkyne to ensure sufficient yields (Scheme 1). The relative rate constants for the substituted iodobenzenes were determined from the yield of products and are reported in Table 1. No products other than **3** and **4** could be detected by GC. A reaction containing iodobenzene in the presence of the catalysts (no alkyne present) was run to ensure that homocoupling of the aryl iodides did not occur. The products of oxidative homocoupling of the alkyne [bis(trimethylsilyl)butadiyne], Buchwald–Hartwig type amination of **3g** and **3r**, or Ulmann ether coupling could not be detected by GC.

The relative rate constants follow a predictable trend with the exception of the *m*-OH and *m*-NH$_2$ substituents. In both of these cases, the resonance effects of the substituents greatly overwhelm the inductive effects. Even more strikingly, *m*-OH appears to have a greater electron-donating effect than *p*-OH as evidenced by the relative rate constants, k_{rel} values of 0.0948 and 0.199, respectively. It is interesting to note that the effect of substituting a proton with a methyl group (**4p** to **4o** vs. **4r** to **4q**) has a more pronounced effect for the oxygen-containing substituent than for the nitrogen-containing substituent, with the *p*-OCH$_3$ group leading to a rate enhancement over the *p*-OH group of 2.6 times, while the rate increase of *p*-N(CH$_3$)$_2$ is only 1.5 times that of the
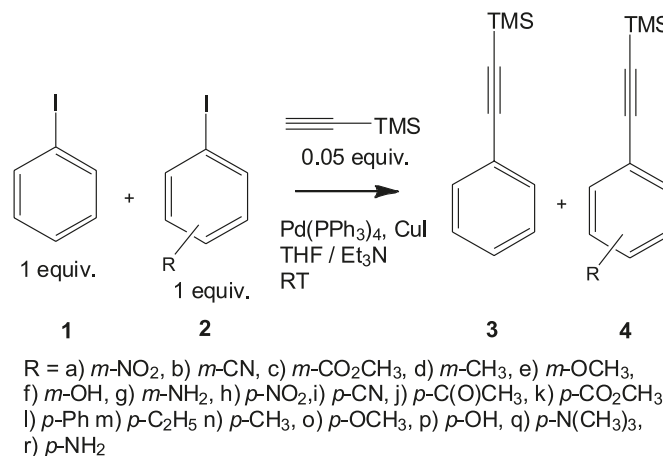
Scheme 1.

R = a) *m*-NO$_2$, b) *m*-CN, c) *m*-CO$_2$CH$_3$, d) *m*-CH$_3$, e) *m*-OCH$_3$, f) *m*-OH, g) *m*-NH$_2$, h) *p*-NO$_2$,i) *p*-CN, j) *p*-C(O)CH$_3$, k) *p*-CO$_2$CH$_3$ l) *p*-Ph m) *p*-C$_2$H$_5$ n) *p*-CH$_3$, o) *p*-OCH$_3$, p) *p*-OH, q) *p*-N(CH$_3$)$_3$, r) *p*-NH$_2$

Table 1. Relative rate constants of the Sonogashira coupling reaction.

4 (R =)	$k_{rel}{}^a$
a) *m*-NO$_2$	9.60
b) *m*-CN	6.44
c) *m*-CO$_2$CH$_3$	4.03
d) *m*-CH$_3$	0.904
e) *m*-OCH$_3$	0.434
f) *m*-OH	0.0948
g) *m*-NH$_2$	0.0417
h) *p*-NO$_2$	36.7
i) *p*-CN	22.5
j) *p*-C(O)CH$_3$	3.54
k) *p*-CO$_2$CH$_3$	1.41
l) *p*-Ph	0.619
m) *p*-C$_2$H$_5$	0.855
n) *p*-CH$_3$	0.846
o) *p*-OCH$_3$	0.514
p) *p*-P–OH	0.199
q) *p*-N(CH$_3$)$_2$	0.035
r) *p*-NH$_2$	0.023

^{a}Relative rate constants k_{rel} are calculated from the GC ratios: See supplementary material for the kinetic treatment.[2]

p-NH$_2$ group. If the anomalous rates for the hydroxyl and primary amino groups are a result of coordination with the metal catalyst, removing two potential bonding sites from **4r** to **4q** vs. one site from **4p** to **4o** should have shown the greater effect. However, the overall effectiveness of the coordination in **4p** must have a greater relative influence on reactivity.
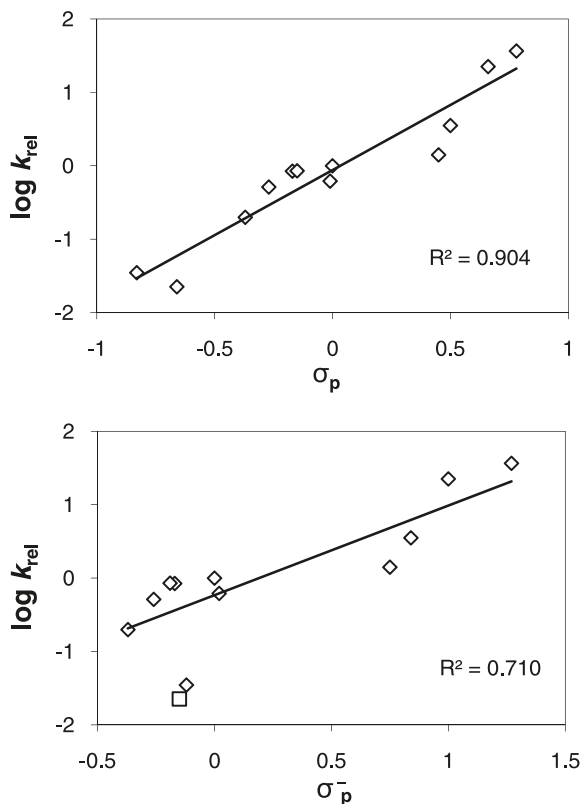
We next correlated the relative rate constants with the Hammett substituent constants (19) and found the best correlation with σ_p (Table 2; Fig. 1). The Hammett reaction constant ρ shows a higher sensitivity to substituent change than with the standard Hammett reaction (dissociation of benzoic acid), which is reasonable for a reaction site directly

Table 2. Hammett correlation data of relative rate (Log k_{rel}).

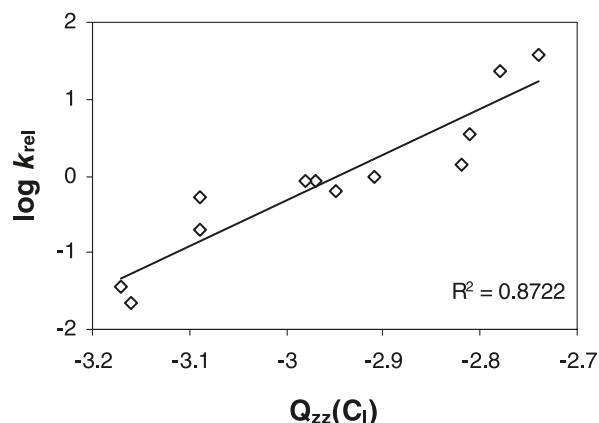| Substituent constant[11]	ρ^a	$R^{2\ b}$
σ^+_p	1.229	0.854
σ_p	1.803	0.904
σ^-_p	1.089	0.710

Fig. 1. Plot of (*a*) log k_{rel} against σ and (*b*) log k_{rel} against σ^- relationships for *para*-substitution (excluding the point for *p*-NH$_2$, □).

Fig. 2. Plot of the log of the rate against the *z*-component of the quadrupole moment of the iodine-bearing carbon for *para*-substitution.

on a ring carbon atom, i.e., closer to the perturbing substituent. The positive value (1.8) indicates an increase in electron density at the rate-limiting step, suggesting a nucleophilic attack. In comparison, this ρ value is closest to that presented by Fauvarque et al. (7). Their conditions are significantly different, having completed an electrochemical kinetic study in which the results were obtained in the absence of copper. In their study, they attribute the rate-limiting step to the oxidative addition of the Pd to the aryl halide (7). In the study by Weissman and Milstein, an investigation of Suzuki coupling with aryl bromides, the best fit was with σ^-_p ($R^2 = 0.97$) with a ρ value of close to 1, which they attribute to conjugation with electron donors (14). They present data for only four *para*-substituted compounds, one of which is a strong resonance donor (14). Our data stem from a greater range of compounds, including strong resonance withdrawers; we do not see an effect that would indicate a strong direct resonance in either direction, i.e., anomalously high or low values of k_{rel} for withdrawers or donors.

The ease with which a nucleophilic attack on a ring carbon of the iodobenzenes occurs should be reflected in the
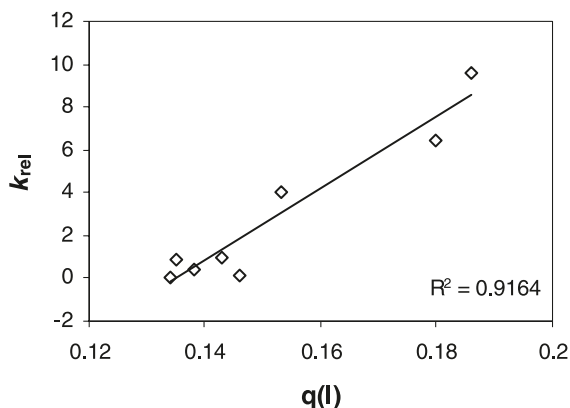
atomic properties of that carbon. Analyzing the electron density within the quantum theory of atoms in molecules (18), we obtained the charge on the ipso-C atom that bears the iodine atom, $q(C_I)$, and the *z*-component of the quadrupole moment of C_I, given as $Q_{zz}(C_I)$, as it has been correlated with the π-density on carbon atoms in aromatic systems (18). For comparison and because the first step in the suggested mechanism (see below) involves the C–I bond of the iodobenzenes, the charge on iodine, $q(I)$, and its quadrupole moment component $Q_{zz}(I)$ were obtained as well.
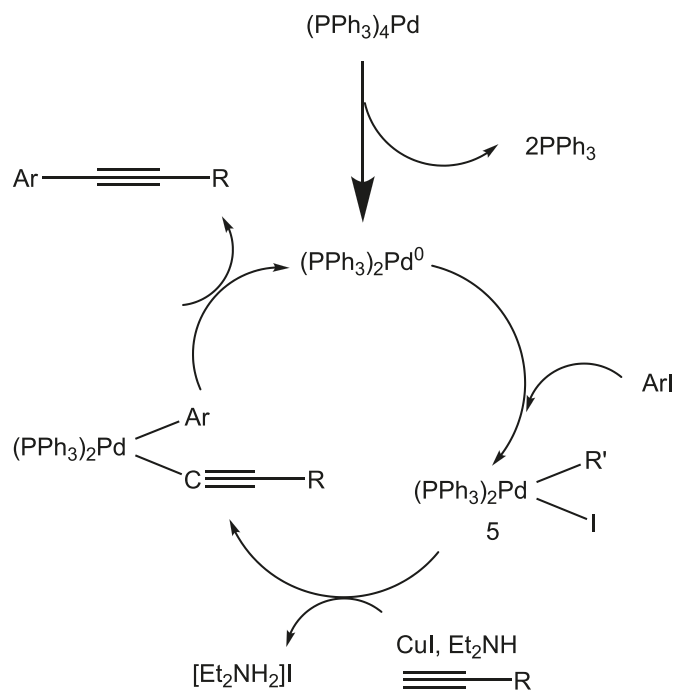
It is known that substituent effects in electrophilic aromatic substitutions cannot be explained through total atomic charges of the carbon atoms, because the σ and π contributions to the density are not affected uniformly by different substituents; while CH$_3$ is both σ and π electron-donating and CN is both σ and π withdrawing, OH is σ withdrawing and π donating (20). On the other hand, the negative values of Q_{zz}, indicative of a charge accumulation at the atom above and below the molecular plane, i.e., where one would expect π-density, are known to parallel the observed reactivity (20). These findings should also hold for the nucleophilic aromatic substitution. As expected in the iodobenzenes, therefore, while $q(C_I)$ for *meta*- or *para*-substitution does not correlate with a Hammett substituent constant, $Q_{zz}(C_I)$ shows a strong correlation with σ_p ($R^2 = 0.9604$). In contrast, $q(I)$ correlates equally well with both σ_m ($R^2 = 0.9060$) and σ_p ($R^2 = 0.9043$). For relationships involving k_{rel} and log k_{rel}, we find that, for *para*-substitution, log k_{rel} correlates only with $Q_{zz}(C_I)$ (Fig. 2), while, for *meta*-substitution, the best correlation is found for k_{rel} with $q(I)$ (Fig. 3).

The palladium cycle in the proposed mechanism of the Sonogashira reaction involves an oxidative addition (to give intermediate **5**) followed by a reductive elimination (to give product) (Fig. 4) (1). Electron density on the reactive site is most likely to be impacted in one of these two steps, since addition of the alkyne/ligand exchange on Pd would rely on the electronic effects being transmitted through the metal. Both the correlation of log k_{rel} with σ_p and with $Q_{zz}(C_I)$ indicate that the first insertion step is rate-limiting for the *para*-substituted iodobenzenes. The positive reaction constant of 1.8 indicates an increased electron density in the rate-

Fig. 3. Plot of the rate against the charge of the iodine atom for *meta*-substitution.

Conclusion

Both the experimental and computational results provide evidence that the rate-limiting step of the Sonogashira reaction is the oxidative addition of the metal catalyst. The evidence to support this rate-limiting step is not as compelling with the *meta*-substituted iodobenzenes as with the *para*-substituted iodobenzenes.

Experimental

Solvents and reagents were used as purchased unless otherwise noted. THF was dried over sodium. Pd(PPh$_3$)$_4$ was synthesized according to literature procedure (21) and stored under nitrogen at –4 °C.

Fig. 4. Proposed mechanism of the Sonogashira reaction (1).

General procedure for the Sonogashira coupling reactions– Preparation of aryl alkynes 3 and 4a–4r for use as standards

Iodobenzene, **1**, or the substituted iodobenzene, **2a–2r** (1.0 mmol), Pd(PPh$_3$)$_4$ (0.02 mmol, 23 mg), CuI (0.06 mmol, 11 mg), triethylamine (0.21 mL), and trimethylsilylacetylene (2.5 mmol, 245 mg, 0.353 mL) were combined in THF (2.5 mL) and stirred under argon at room temperature, 21 °C, overnight. The reaction was filtered through Celite, the solvent removed in vacuo, and the residue was purified by silica gel chromatography (hexanes/EtOAc = 90:10) to give products **3** and **4a–4r**. All of the products are known and were characterized or confirmed by spectral data, which is provided along with a Chemical Abstracts number for reference. The pure products were used to determine the detector response factors according to standard methods, using biphenyl as the internal standard.

Trimethyl[(3-nitrophenyl)ethynyl]silane, 4a [Chem. Abstr. 183322-33-0]

^{1}H NMR (200 MHz, CDCl$_3$) δ: 8.32 (s, 1H), 7.75 (dt, J = 7.8, 1.4 Hz, 1H), 7.49 (t, J = 6.6 Hz, 1H), 7.45 (t, J = 6.6 Hz, 1H) 0.26 (s, 9H).

3-[(Trimethylsilyl)ethynyl]benzonitrile, 4b [Chem. Abstr. 190771-22-3]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.74 (s, 1H), 7.66 (dt, J = 6.4, 1.2 Hz, 1H), 7.58 (dt, J = 6.4, 1.2 Hz, 1H), 7.42 (t, J = 6.4 Hz, 1H), 0.26 (s, 9H).

Methyl 3-[(trimethylsilyl)ethynyl]benzoate, 4c [Chem. Abstr. 77123-59-2]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.88 (s, 1H), 7.71 (d, J = 6 Hz, 1H), 7.31 (d, J = 6 Hz, 1H), 7.12 (t, J = 6 Hz, 1H), 3.92 (s, 3H), 0.27 (s, 9H).

Trimethyl[(3-methylphenyl)ethynyl]silane, 4d [Chem. Abstr. 40230-90-8]

^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.36 (s, 1H), 7.40 (t, J = 7.3 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 7.1 Hz, 1H), 2.32 (s, 3H), 0.26 (s, 9H).

limiting step; the largest increase in electron density at the reaction site, according to Sonogashira's proposed mechanism, would occur to give **5** (Fig. 4). Furthermore, this proposed rate-limiting step is supported by the correlation of the rate with $Q_{zz}(C_I)$, i.e., a strong correlation existing with the undisturbed iodobenzenes. When we turned our attention to the *meta*-substituents, a correlation could be found between k_{rel} and σ$_m$ (R^2 = 0.8849); when log k_{rel} was used, a correlation was not obtained (R^2 = 0.6768). Even though k_{rel} for the *meta*-substituted iodides correlates with q(I), a correlation supporting the first step of the reaction as being rate-determining is not as obvious. Since the final step of the reaction would result in a decreased electron density at the carbon, it should, therefore, result in a reaction constant with a negative value, which was not observed.

Trimethyl[(3-methoxyphenyl)ethynyl]silane, 4e [Chem. Abstr. 40230-92-0]

^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.39 (dt, J = 9.0, 2.4 Hz, 1H), 7.26 (s, 1H), 7.13 (t, J = 9.0 Hz, 1H), 7.06 (dt, J = 8.5, 2.4 Hz, 1H), 3.36 (s, 3H), 0.37 (s, 9H).

3-[(Trimethylsilyl)ethynyl]phenol, 4f [Chem. Abstr. 388061-72-1]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.16 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 6.81 (d, J = 6.0 Hz, 1H), 5.10 (s, 1H), 0.27 (s, 9H).

3-[(Trimethylsilyl)ethynyl]aniline, 4g [Chem. Abstr. 110598-30-6]

^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.65 (t, J = 8.0 Hz, 1H), 6.86 (dt, J = 8.0, 3.0 Hz, 1H), 6.78 (s, 1H), 6.63 (dt, J = 8.0, 3.0 Hz, 1H), 3.50 (s, 2H), 0.27 (S, 9H).

Trimethyl[(4-nitrophenyl)ethynyl]silane, 4h [Chem. Abstr. 75867-38-8]

^{1}H NMR (200 MHz, CDCl$_3$) δ: 8.18 (d, J = 6.6 Hz, 2H), 7.50 (d, J = 6.7 Hz, 2H), 0.31 (s, 9H).

4-[(Trimethylsilyl)ethynyl]benzonitrile, 4i [Chem. Abstr. 75867-40-2]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.59 (d, J = 6.4 Hz, 2H), 7.53 (d, J = 6.4 Hz, 2H), 0.26 (s, 9H).

1-[4-[(Trimethylsilyl)ethynyl]phenyl]ethanone, 4j [Chem. Abstr. 75883-03-3]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.89 (d, J = 5.2 Hz, 2H), 7.54 (d, J = 5.2 Hz, 2H), 2.61 (s, 3H), 0.27 (s, 9H).

Methyl 4-[(trimethylsilyl)ethynyl]benzoate, 4k [Chem. Abstr. 75867-41-3]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.97 (d, J = 6.8 Hz, 2H), 7.52 (d, J = 6.8 Hz, 2H), 3.92 (s, 3H), 0.26 (s, 9H).

([1,1′-Biphenyl]-4-ylethynyl)trimethylsilane, 4l [Chem. Abstr. 75867-42-4]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.49 (d, J = 6.0 Hz, 2H), 7.44 (m, 4H), 7.34 (t J = 6.0 Hz, 2H), 7.26 (t, J = 6.0 Hz, 1H), 0.19 (s, 9H). ^{13}C NMR (125 MHz, CDCl$_3$) δ: 141.1, 140.3, 132.4, 128.8, 127.6, 127.0, 126.9, 122.0, 105.0, 94.8, 0.3.

Trimethyl[(4-ethylphenyl)ethynyl]silane, 4m [Chem. Abstr. 393857-27-7]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.39 (d, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 2H), 2.62 (q, J = 7 Hz, 2H), 1.21 (t, J = 7.5 Hz, 3H), 0.27 (s, 9H).

Trimethyl[(4-methylphenyl)ethynyl]silane, 4n [Chem. Abstr. 4186-14-5]

^{1}H NMR (500 MHz, CDCl$_3$) δ:7.11 (d, J = 3.2 Hz, 2H), 6.83 (d, J = 3.2 Hz, 2H), 2.34 (s, 3H), 0.26 (s, 9H).

Trimethyl[(4-methoxyphenyl)ethynyl]silane, 4o [Chem. Abstr. 3989-14-8]

^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.42 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 3.60 (s, 3H), 0.70 (s, 9H).

4-[(Trimethylsilyl)ethynyl]phenol, 4p [Chem. Abstr. 88075-18-7]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.35 (d, J = 3.5 Hz, 2H), 7.53 (d, J = 3 Hz, 2H), 5.30 (s, 1H), 0.23 (s, 9H).

N,N-Dimethyl-4-[(trimethylsilyl)ethynyl]aniline, 4q [Chem.Abstr. 40230-97-5]

^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.31 (d, J = 9.0 Hz, 2H), 6.55 (d, J = 9.0 Hz, 2H), 2.92 (s, 6H), 0.21 (s, 9H).

4-[(Trimethylsilyl)ethynyl]aniline, 4r [Chem. Abstr. 75867-39-9]

^{1}H NMR (200 MHz, CDCl$_3$) δ: 7.27 (d, J = 6.8 Hz, 2H), 6.57 (d, J = 6.8 Hz, 2H), 3.80 (bs, 2H), 0.22 (s, 9H).

General procedure for the competitive coupling reactions

The intermolecular competition was carried out using iodobenzene (1.0 mmol, 204 mg, 0.11 mL) and the substituted iodobenzene, **2a**–**2r** (1.0 mmol), Pd(PPh$_3$)$_4$ (0.02 mmol, 23 mg), CuI (0.06 mmol, 11 mg), triethylamine (0.21 mL), and trimethylsilylacetylene (0.05 mmol, 5 mg, 7 μL) combined in THF (2.5 mL) and stirred under argon at room temperature, 21 °C. After a standard reaction time of 5 h, a GC of the mixture was run (internal standard biphenyl), and the relative rates of reactivity were calculated. The reported rates are an average of a minimum of two experiments.

GC conditions

The reaction mixtures were analyzed by a flame ionization detector (FID) and DB-5 High Temp column. The initial oven temperature was 50 °C, which was ramped by 5 °C/min to the final temperature of 200 °C, which was held for 5 min. At least two GC runs were performed for each sample to ensure reproducibility.

Computational details

All geometry optimizations were performed with Gaussian03 (22), using the Perdew–Burke–Ernzerhof (PBE0) hybrid density functional (23–25) with the 6–31+G(d) basis set for all atoms except for iodine and the Midi! basis set (26) for iodine. All geometries were confirmed to be minima by frequency calculations. In case of rotational isomerism (m-CO$_2$CH$_3$, m-OCH$_3$, and m-OH), the lower-energy conformer, determined through either electronic energies or Gibbs free energies, given in Fig. S2 in the supplementary information was used in the analyses.[2] Wave functions were analyzed with the Proaim module from the AIMPAC (27) series of programs for charges (q) and quadrupole moments (Q_{zz}); both are obtained from integrations of the electron density over the atomic basin. For p-C$_2$H$_5$ (torsional angle 90°) and p-Ph (torsional angle 40°), wave functions were also obtained for the planarized geometries and these were used in the analyses. Total energies as well as the q and Q_{zz} data used in the correlations are given in Table S1 of the supplementary information.[2]

Acknowledgments

References

1. K. Sonogashira, Y. Tohda, and K. Hagihara. Tetrahedron Lett. **16**, 4467 (1975).
2. E. Negishi and L. Anastasia. Chem. Rev. **103**, 1979 (2003).
3. R. Chinchilla and C. Nájera. Chem. Rev. **107**, 874 (2007).
4. S. Thorand and N. Krause. J. Org. Chem. **63**, 8551 (1998).
5. R.D. Stephens and C.E. Castro. J. Org. Chem. **28**, 3313 (1963).
6. S. Takashi, Y. Kuroyama, K. Sonogashira and N. Hagihara. Synthesis, 627 (1980).
7. J.-F. Fauvarque, F. Pfluger, and M. Troupel. J. Organomet. Chem. **208**, 419 (1981).
8. C. Amatore and F. Pfluger. Organometallics, **9**, 2276 (1990).
9. D. Zim, V.R. Lando, J. Dupont, and A.L. Monteiro. Org. Lett. **3**, 3049 (2001).
10. S. Saito, S. Oh-tani, and N. Miyaura. J. Org. Chem. **62**, 8024 (1997).
11. R. Benhaddou, S. Czernecki, G. Ville, and A. Zegar. Organometallics, **7**, 2435 (1988).
12. A.S. Gruber, D. Zim, G. Ebeling, A.L. Monteiro, and J. Dupont. Org. Lett. **2**, 1287 (2000).
13. D. Milstein and J.K. Stille. J. Am. Chem. Soc. **101**, 4992 (1979).
14. H. Weissman and D. Milstein. Chem. Commun. 1901 (1999).
15. R. Ugo, A. Pasini, A. Fusi, and S. Cenini. J. Am. Chem. Soc. **94**, 7364 (1972).
16. R.J, Mureinik, M. Weitzberg, and J. Blum. Inorg. Chem. **18**, 915 (1979).
17. C. Gottardo and A. Aguirre. Tetrahedron Lett. **43**, 7091 (2002).
18. R.F.W. Bader. Atoms in molecules: A quantum theory. Clarendon Press, Oxford, UK. 1990.
19. Substituent constants were taken from: (*a*) C. Hansch, A. Leo, and R.W. Taft. Chem. Rev. **91**, 165 (1991); (*b*) D.H. McDaniel and H.C. Brown. J. Org. Chem., **23**, 420 (1958).
20. R.F.W. Bader and C. Chang. J. Phys. Chem. **93**, 2946 (1989).
21. F.R. Hartley. The chemistry of platinum and palladium: with particular reference to complexes of the elements. John Wiley & Son, New York. 1973.
22. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery, Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A.D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, and J.A. Pople. Gaussian 03 [computer program], Revision C.02. Gaussian, Inc., Wallingford CT. 2004.
23. J.P. Perdew, K. Burke, and M. Ernzerhof. Phys. Rev. Lett. **77**, 3865 (1996).
24. J.P. Perdew, K. Burke, and M. Ernzerhof. Phys. Rev. Lett., **78**, 1396 (1997).
25. J.P. Perdew, M. Ernzerhof, and K.Burke. J. Chem. Phys. **105**, 9982 (1996).
26. R.E. Easton, D.J. Giesen, A. Welch, C.J. Cramer, and D.G. Truhlar. Theor. Chim. Acta **93**, 281 (1996).
27. Available from Professor R.F.W. Bader, McMaster University, Hamilton, ON L8S 4M1, Canada, and from the AIMPAC website (www.chemistry.mcmaster.ca/aimpac, last accessed on February 6, 2008).