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Structure–Reactivity Relationships in Negishi Cross-Coupling Reactions

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Dedicated to Professor Mieczysław Mąkosza on the occasion of his 75th birthday

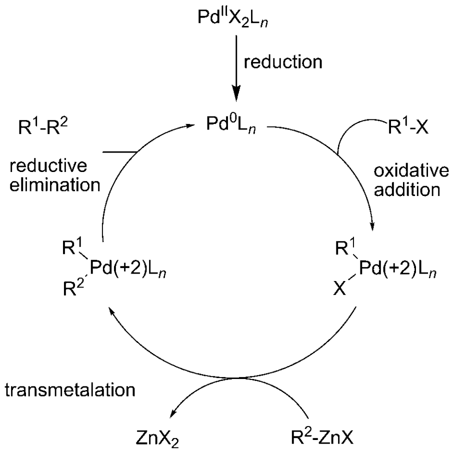
Abstract: Competition experiments have been performed to determine the relative reactivities of substituted bromobenzenes and of different arylzinc reagents in the [Pd(PPh$_3$)$_4$]-catalyzed Negishi cross-coupling reaction in THF at 25 °C. The cross-coupling reactions are accelerated by electron acceptors in the bromobenzenes, the effect of which increases in the order *ortho* < *meta* < *para*. On the other hand, electron acceptors in the arylzinc halides diminish the reaction rates. Hammett correlations show that substituent variations in the bromobenzenes ($\rho = +2.5$) have a larger effect than substituent variations in the arylzinc halides ($\rho = -0.98$).

Keywords: C–C bond formation · Hammett equation · kinetics · reaction mechanisms · substituent effects

Introduction

Pd-catalyzed cross-coupling reactions of unsaturated halides with organometallic reagents belong to the best methods for the formation of C(sp^2)–C(sp^2) bonds.[1] Among many organometallics used in these cross-couplings, organozinc reagents have proven to be particularly useful, as they react under very mild conditions,[2,3] and are compatible with many functionalities.[4] Therefore, they can be used for the synthesis of polyfunctional molecules without the need of protecting groups.

So far most mechanistic studies on cross-coupling reactions have focused on other organometallic reagents, especially organostannanes.[5] The conclusions that arise from studies on Stille reactions have been considered to be representative also for palladium- and nickel-catalyzed cross-coupling reactions with other organometallic nucleophiles as well as for carbon–heteroatom bond formations. The general catalytic cycle, consisting of an oxidative addition, a transmetalation, and a reductive elimination step, furnishes the coupling product and regenerates the active catalyst (Scheme 1).



Scheme 1. Catalytic cycle of the palladium-catalyzed Negishi reaction.

We were interested in gaining a more detailed insight into the mechanism of the Negishi cross-coupling reaction by studying the influence of the substitution pattern of both the zinc reagent and the aryl halide on the rates of the various steps.[6]

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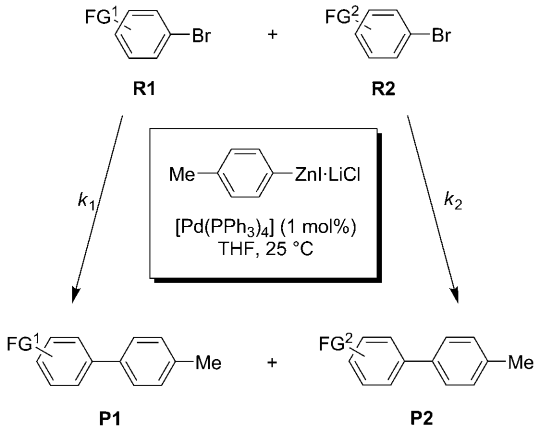
Results and Discussion

Relative reactivities of bromoarenes in the oxidative addition step: The influence of substituents on the reactivities of aryl bromides in Negishi cross-coupling reactions has been determined by competition experiments. For this purpose, mixtures of two differently substituted aryl bromides were combined with less than one equivalent of 4-tolylzinc iodide/lithium chloride in the presence of catalytic amounts of a palladium complex. Commercially available aryl bromides were chosen as electrophiles, and [Pd(PPh$_3$)$_4$], a common and widely used catalyst, as palladium source. The yield of the resulting biaryls was derived by gas chromatographic determination of the product ratio [**P1**]/[**P2**] obtained after quenching with aqueous NH$_4$Cl (Scheme 2). All reactions were run in THF at 25 °C.



Scheme 2. Determination of the relative reactivities of bromoarenes.

The relative reactivities of the aryl bromides **R1** and **R2** with 4-tolylzinc iodide have been calculated by Equation (1),[7] which also holds under conditions where the ratio [**R1**]/[**R2**] varies during the course of the reaction. Substitution of [**R1**]$_0$ and [**R2**]$_0$ by the terms in Equations (2) and (3) (mass balance) yields Equation (4), which calculates the competition constant κ from the gas chromatographically determined ratios [**P1**]$_t$/[[**R1**]$_t$ and [**P2**]$_t$/[[**R2**]$_t$.

Abstract in German: *Durch Konkurrenzexperimente wurden die relativen Reaktivitäten von substituierten Brombenzolen sowie von verschiedenen Arylzink-Reagenzien in [Pd(PPh$_3$)$_4$]-katalysierten Negishi-Kreuzkupplungsreaktionen bestimmt (THF, 25 °C). Die Kreuzkupplungsreaktionen werden durch Elektronenakzeptoren in den Brombenzolen beschleunigt, deren Effekt in der Reihe ortho <meta <para zunimmt. Andererseits verringern Elektronenakzeptoren in den Arylzinkhalogeniden die Reaktionsgeschwindigkeiten. Hammett-Beziehungen zeigen, dass sich Substituentenvariationen bei den Brombenzolen ($\rho = +2.5$) stärker auswirken als bei den Arylzinkhalogeniden ($\rho = -0.98$).*

$$\kappa = \frac{k_1}{k_2} = \frac{\log([\mathbf{R1}]_0/[\mathbf{R1}]_t)}{\log([\mathbf{R2}]_0/[\mathbf{R2}]_t)} \tag{1}$$

$$[\mathbf{R1}]_0 = [\mathbf{R1}]_t + [\mathbf{P1}]_t \tag{2}$$

$$[\mathbf{R2}]_0 = [\mathbf{R2}]_t + [\mathbf{P2}]_t \tag{3}$$

$$\kappa = \frac{\log(1 + [\mathbf{P1}]_t/[\mathbf{R1}]_t)}{\log(1 + [\mathbf{P2}]_t/[\mathbf{R2}]_t)} \tag{4}$$

The competition constants κ are independent of the concentrations of the reactants. Because the oxidative insertion is an irreversible step,[8] the competition constants κ reflect the relative reactivities of the bromoarenes towards the Pd^0 complexes. Each of the 18 aryl bromides listed in Figure 1 was subjected to competition experiments with several other bromobenzene derivatives to give the 28 competition constants κ listed in Figure 1. Solving the resulting overdetermined set of linear equations [Eq. (5)] by least squares minimization yielded the k_{rel} values listed in Figure 1.

$$\log k_1 - \log k_2 = \log \kappa \tag{5}$$

Figure 1 shows a reactivity range of 10^3, from 4-methoxybromobenzene, the least reactive compound, to 4-bromobenzonitrile, the most reactive compound of this series. In agreement with earlier studies on oxidative additions of palladium complexes into carbon–halide bonds,[9] electron acceptors in the aromatic ring accelerate the reaction while electron donors retard the cross-coupling reaction.

Figure 2 shows that the accelerating effects of strong electron acceptors CN, CO$_2$Et, and CF$_3$ decrease in the order *para*> *meta*> *ortho*, opposite the reactivity order in Br–Mg exchange reactions with *i*PrMgCl·LiCl (*ortho*> *meta*> *para*), which are dominated by inductive effects.[10]

As illustrated in Figure 3, *p*-bromobenzonitrile is 300–500 times more reactive than the parent bromobenzene towards the palladium complex as well as towards *i*PrMgCl·LiCl. Whereas this ratio decreases to 13 for the oxidative addition of [Pd(PPh$_3$)$_4$] into *o*-bromobenzonitrile, it increases to 10000 for the reaction of *i*PrMgCl·LiCl with the corresponding *ortho*-isomer.

The low reactivities of the *ortho*-substituted compounds in the oxidative additions of palladium complexes can be rationalized by steric effects and shall not be discussed in detail. Unlike the substituent effects in the Br–Mg exchange reactions,[10] the *p*- and *m*-substituent effects of the aryl bromides correlate with Hammett's substituent constants σ^- (Figure 4),[11,12] suggesting a three-centered transition state **1** resembling that of a nucleophilic aromatic substitution,[9e] while the transition state of the bromine–magnesium exchange reaction resembles the ate complex **2** (Figure 5).[10,13]

The Hammett reaction constant $\rho = +2.5$ is consistent with previously reported ρ values for the amination of aryl

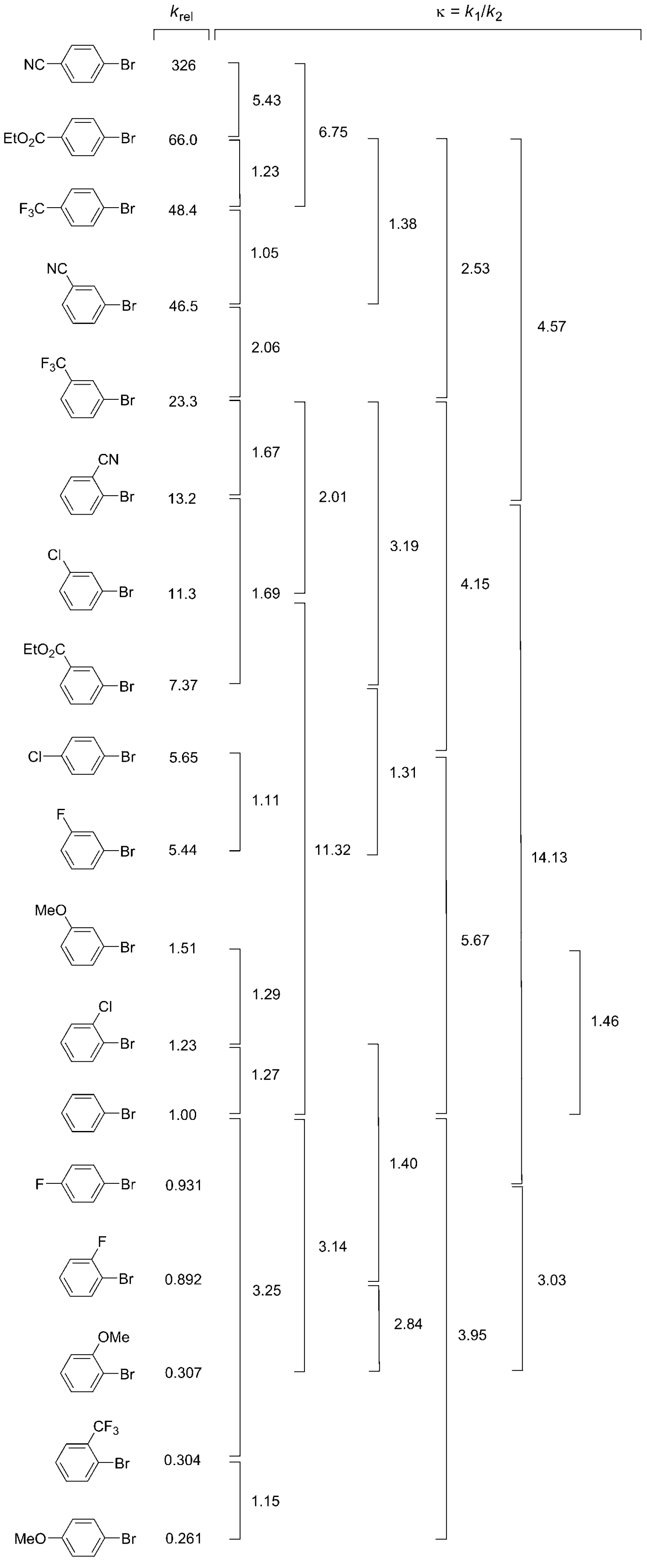


Figure 1. Relative reactivities of substituted bromobenzenes in $[Pd(PPh_3)_4]$-catalyzed cross-couplings with 4-tolylzinc iodide/lithium chloride in THF at 25 °C.

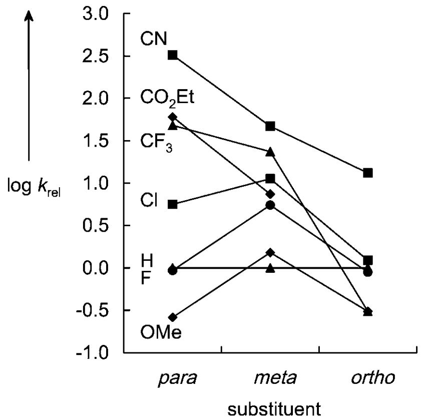


Figure 2. Substituent effects on the reactivities of aryl bromides in the Negishi reaction.

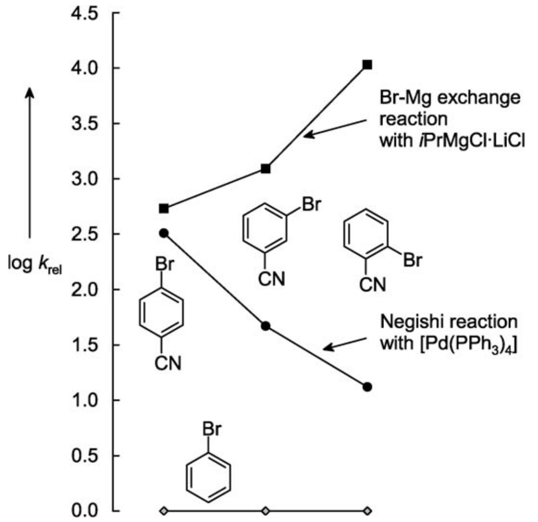


Figure 3. Substituent effects on the reactivities of CN-substituted bromobenzene in the Negishi reaction and the Br–Mg exchange reaction (log $k_{rel} = 0$ for bromobenzene).

chlorides, Heck and Suzuki reactions with aryl bromides, and the directly measured reaction of $[Pd(PPh_3)_4]$ with aryl halides (Table 1).

Relative reactivities of arylzinc iodides in the transmetalation step: Competition experiments analogous to those described above have been performed for determining the relative reactivities of different *p*-substituted phenylzinc iodides against 4-bromobenzonitrile/$[Pd(PPh_3)_4]$ (Scheme 3).

As shown in Figure 6, the relative reactivities increase moderately with increasing electron donating abilities of the *p*-substituents of the arylzinc iodide.

An even smaller substituent dependence has been observed in couplings with aryl bromides bearing weaker electron acceptor substituents, as illustrated for the selectivities k_{Me}/k_{COOEt} in Scheme 4. While the *p*-cyano substituted phe-

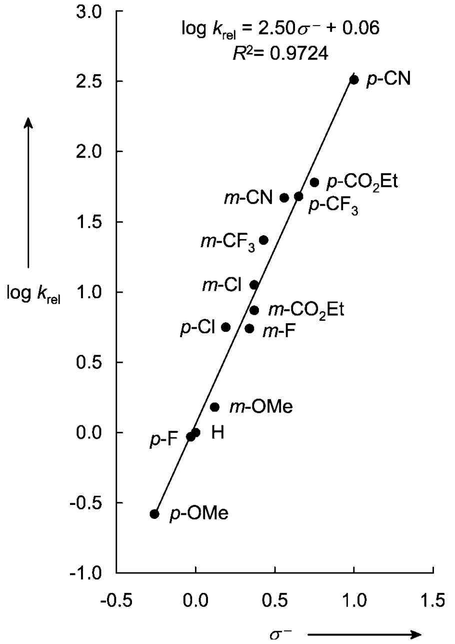
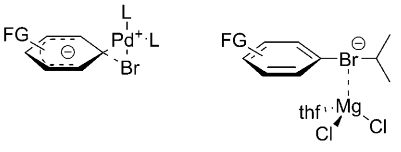


Figure 4. Hammett correlation for $[Pd(PPh_3)_4]$-catalyzed cross-coupling reactions of substituted bromobenzenes with 4-tolylzinc iodide/lithium chloride in THF at 25 °C.



1 **2**

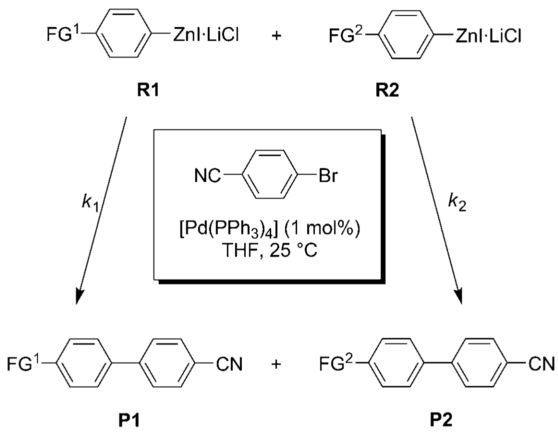
Figure 5. Comparison of the transition states of the oxidative addition of PdL_2 and of the Br–Mg exchange with *i*PrMgCl·LiCl.

Table 1. Hammett reaction constants ρ for the oxidative addition step in various palladium-catalyzed coupling reactions.

Ar–X	Substrate	Conditions	ρ	Ref.
Ar–Br	$[Pd(PPh_3)_4]$/*p*-tolyl-ZnI·LiCl	THF, 25 °C	+2.50	this work
Ar–Cl	$[Pd(dipp)_2]$[a]	dioxane, 58 °C	+2.4	[14]
Ar–Cl	XphosPd^0	toluene, 25 °C	+2.3	[15]
Ar–Br	$H_2C{=}CH\text{-}CO_2Bu/Pd^0$[b]	DMA, 150 °C	+(2.4–2.5)	[16]
Ar–I	$H_2C{=}CH\text{-}CO_2Bu/Pd^0$[b]	DMA, 80 °C	+(1.7–1.8)	[16]
Ar–Br	$PhB(OH)_2/Pd^0$[c]	DMF, 80 °C	+2.3	[17]
Ar–I	$PhB(OH)_2/Pd^0$[c]	DMF, 80 °C	+0.65	[17]
Ar–OTf	$[Pd(PPh_3)_4]$[d]	DMF, 20 °C	+2.55	[9a]
Ar–I	$[Pd(PPh_3)_4]$[e]	toluene, 25 °C	+2.3	[9d]
Ar–I	$[Pd(PPh_3)_4]$[e]	THF, 25 °C	+2	[9e]

[a] ^{31}P NMR spectroscopic monitoring of the oxidative addition. [b] Various five-membered palladacycles with N, P, and S ligands. [c] Five-membered S-palladacycle. [d] Conductimetric monitoring of the formation of the cationic arylpalladium complexes. [e] Electrochemical monitoring of the consumption of $[Pd(PPh_3)_4]$ in the oxidative addition.

nylpalladium(II) complex **3** reacts 4.1 times faster with the *p*-methyl-substituted phenylzinc iodide than with the *p*-ethoxycarbonyl-substituted phenylzinc reagent, this reactivi-



Scheme 3. Competition experiment for determing the relative reactivities of arylzinc iodides.

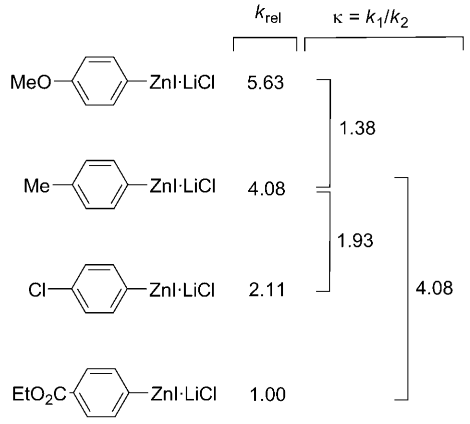
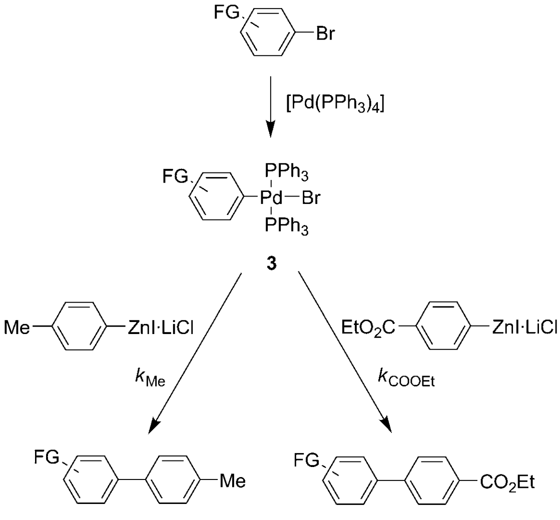


Figure 6. Relative reactivities of arylzinc iodides towards *p*-bromobenzonitrile/$[Pd(PPh_3)_4]$ in THF at 25 °C.



FG	p-Cl	m-CN	p-CN
k_{Me}/k_{COOEt}	2.3	3.5	4.1

Scheme 4. Relative reactivities of arylzinc iodides towards substituted aryl bromides and $[Pd(PPh_3)_4]$.

ty ratio decreases to 2.3 for the *p*-Cl-substituted phenylpalladium(II) complex **3**.

The Hammett plot shown in Figure 7 with a reaction constant $\rho = -0.98$ reveals that the transmetalation step depends much less on the electronic nature of the *para* substituents than the oxidative addition. The negative slope indicates an increased reactivity of arylzinc iodides, bearing electron-donating groups. Similar Hammett reaction constants have been determined for the transmetalation step in Stille and Suzuki reactions (Table 2). In contrast, $[NiCl_2(PCy_3)_2]$-catalyzed Suzuki cross-couplings of phenyl tosylate with arylboronic acids were reported to be accelerated by acceptor groups in the arylboronic acids ($\rho = +0.80$).[18]

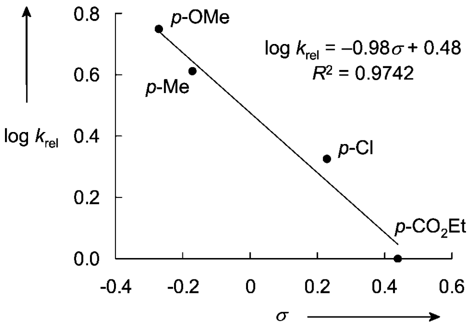


Figure 7. Hammett correlation of the reactivities of substituted arylzinc iodides towards *p*-bromobenzonitrile/$[Pd(PPh_3)_4]$.

Table 2. Hammett reaction constants ρ for the transmetalation step in various palladium-catalyzed coupling reactions.

Substrate	Reaction partner	Conditions	ρ	Ref.
ArZnX·LiCl	$4\text{-NCC}_6H_4Br/[Pd(PPh_3)_4]$	THF, 25°C	−0.98	this work
$ArB(OH)_2$	PhBr/Pd^0[a]	DMF, 80°C	−0.68	[17]
$ArB(OH)_2$	PhI/Pd^0[a]	DMF, 80°C	−0.68	[17]
$ArSnBu_3$	4-(*tert*-butyl)cyclohexenyl-triflate/$[Pd_2(dba)_3]/AsPh_3$	NMP, 25°C	−0.89	[19]

[a] Five-membered S-palladacycle.

Conclusions

As in other palladium-catalyzed cross coupling reactions, the oxidative addition of Pd^0 to bromoarenes is strongly accelerated by acceptor substituents. From the excellent correlation of the relative reactivities of the bromoarenes with Hammett's σ^- constants ($\rho = 2.5$) one can derive a transition state resembling that of nucleophilic aromatic substitutions (**1**, Figure 5), which significantly differs from that for bromine–magnesium exchange reactions (**2**, Figure 5). The transmetalation step is accelerated by electron-donor substituents in the arylzinc iodide, but the effect is relatively small ($\rho = -0.98$ for the reaction with $4\text{-NCC}_6H_4PdL_n$) and decreases with decreasing electrophilicity of the arylpalladium intermediate.

Experimental Section

Typical procedure for a competition experiment between two aryl bromides: A dry and N_2-flushed Schlenk flask was charged with **R1** (4-bromobenzonitrile, 364 mg, 2.00 mmol), **R2** (4-trifluoromethylbromobenzene, 450 mg, 2.00 mmol), $[Pd(PPh_3)_4]$ (23.1 mg, 0.02 mmol), *n*-hexadecane (70 mg, 0.31 mmol), and THF (2 mL). The flask was thermostated with a water bath (25°C). Then *p*-tolylzinc iodide/lithium chloride (4.0 mL, 0.50 M in THF, 2.00 mmol) was added in one portion and the reaction mixture was stirred at 25°C. After certain times (for example 20 min), about 0.1 mL of the mixture was taken out with a syringe and poured into saturated aqueous NH_4Cl solution (1 mL). The aqueous phase was extracted with diethyl ether (ca. 2–3 mL). The ethereal solutions were dried over Na_2SO_4 and analyzed by GC.

Typical procedure for a competition experiment between two arylzinc reagents: A dry and N_2-flushed Schlenk flask was charged with **R1** (*p*-tolylzinc iodide/lithium chloride, 4.0 mL, 0.50 M in THF, 2.00 mmol), **R2** (4-(ethoxycarbonyl)phenylzinc iodide/lithium chloride, 3.51 mL, 0.57 M in THF, 2.00 mmol) and *n*-hexadecane (70 mg, 0.31 mmol). The flask was thermostated with a water bath (25°C). Then a solution of 4-bromobenzonitrile (364 mg, 2.00 mmol) and $[Pd(PPh_3)_4]$ (23.1 mg, 0.02 mmol) in THF (2 mL) was added in one portion and the reaction mixture was stirred at 25°C. After certain times (for example 20 min), about 0.1 mL of the mixture was taken out with a syringe and poured into saturated aqueous NH_4Cl solution (1 mL). The aqueous phase was extracted with diethyl ether (ca. 2–3 mL). The ethereal solutions were dried over Na_2SO_4 and analyzed by GC.

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