

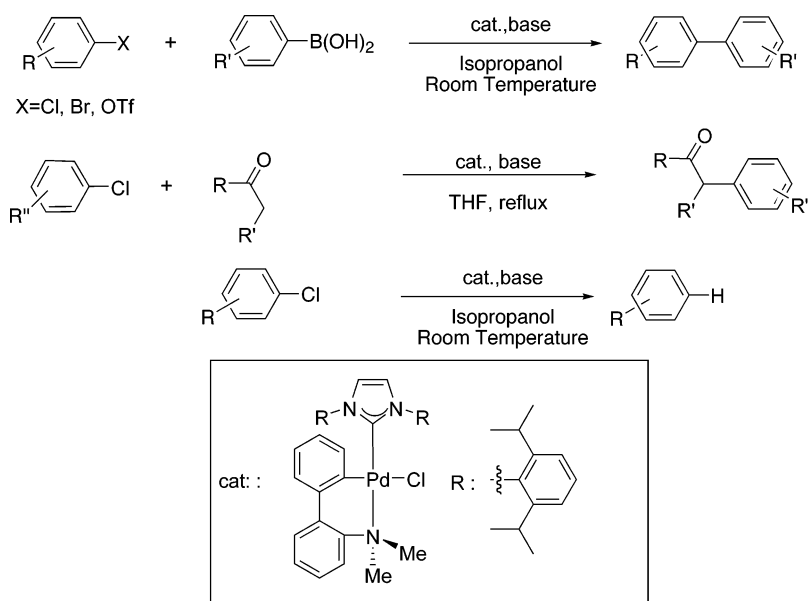
Suzuki–Miyaura, α -Ketone Arylation and Dehalogenation Reactions Catalyzed by a Versatile *N*-Heterocyclic Carbene–Palladacycle Complex

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The activity of the complex (IPr)PdCl(η^2 -*N*,*C*-C₁₂H₇NMe₂), **1** [IPr = (*N*,*N'*-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene)], in the Suzuki–Miyaura cross-coupling reaction involving unactivated aryl chlorides and triflates with arylboronic acids at room temperature in technical grade 2-propanol is described. These conditions allow for the synthesis of di- and tri-*ortho*-substituted biaryls in very short reaction times. This complex also displays very high activity for α -ketone arylation and dehalogenation reactions of activated and unactivated aryl chlorides.

Introduction

Cross-coupling reactions have become a powerful tool in the arsenal of methods available to chemists for the formation of new C^{sp2}–C^{sp2} or C^{sp2}–C^{sp3} bonds.¹ While from the late 1970s to the early 1990s research focused mainly on finding new coupling partners, especially organometallic partners, attention during the past 10 years has turned toward the development of more powerful catalysts that allow reactions to be conducted using milder reaction conditions and unprecedented substrate

activations. One particular interest has been the development of catalysts that can operate at very low metal loadings. To achieve this, catalytic species must be highly reactive while decomposition should be minimal. Palladacyclic complexes have

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played a significant role in this regard. Although the vast majority of palladacycles reported to date contain phosphines, especially bulky tertiary and secondary phosphines, as ancillary ligands to stabilize the palladium center,² the costly price usually associated with this phosphine type, along with phosphine ligand and ligand decomposition byproduct removal difficulties, have led to the use of *N*-heterocyclic carbenes (NHCs)³ as a very attractive ligand alternative.⁴ We have reported preliminary results on the very efficient performance of such palladacyclic complexes as precatalysts in aryl amination reactions and α -ketone arylation reactions of aryl chlorides and triflates.⁵ Later, we reported on the use of **1** in room temperature Suzuki–Miyaura reactions.⁶ Herein, we expand the substrate scope of **1** for the α -ketone arylation and the Suzuki–Miyaura reaction and also report on the use of this complex as an active precatalyst for the dehalogenation of aryl chlorides at room temperature.

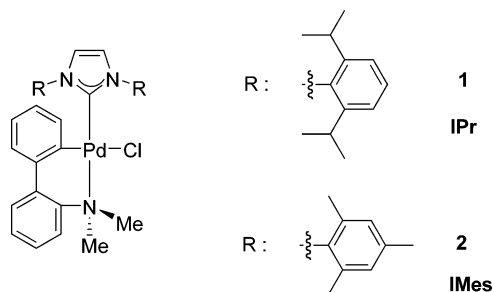


FIGURE 1. NHC-bearing palladacycles.

Results and Discussion

Suzuki–Miyaura Cross-Coupling Reactions. Since its discovery in 1979,⁷ the Suzuki–Miyaura reaction⁸ involving the coupling of organoboron reagents with organic halides has widened its scope, becoming arguably one of the most important transformations leading to the formation of a C–C bond. One major reason is that organoboron reagents show many advantages,⁹ for example, (1) ready availability of reagents by hydroboration and transmetalation, (2) inert to water and related solvents, as well as oxygen, (3) generally thermally stable, (4) tolerant toward various functional groups, and (5) low toxicity of starting materials and byproducts. A plethora of new catalysts,

reaction conditions, and organoboron reagents have been developed by a number of research groups. Nowadays, the method is routinely employed in retrosynthetic schemes, and a large number of drugs,¹⁰ polymers,¹¹ and natural products¹² make use of a Suzuki–Miyaura cross-coupling step in their assembly. Pioneering work in the use of palladacycles for the Suzuki–Miyaura reaction was performed by Herrmann and co-workers using a phosphine-bearing palladacycle in the coupling of activated chlorides with precatalyst loadings of 0.1 mol %.¹³ Good activity is not limited to phosphorus donor systems^{14,15} because *N*-donor,^{16,17} oxime-containing,¹⁸ and *S*-donor¹⁹ palladacycles have also been described with good results. Tertiary phosphine adducts of phosphorus-, imine-, and amine-based palladacycles^{20,21} show excellent activity at very low catalyst loadings when aryl chlorides, both activated and unactivated, are used as substrates. Our group reported on the activity of the NHC-bearing palladacycle **1** for the Suzuki–Miyaura cross-coupling of sterically hindered unactivated aryl chlorides with sterically hindered boronic acids, allowing for the synthesis in high yields of di- and tri-*ortho*-substituted biaryls at room

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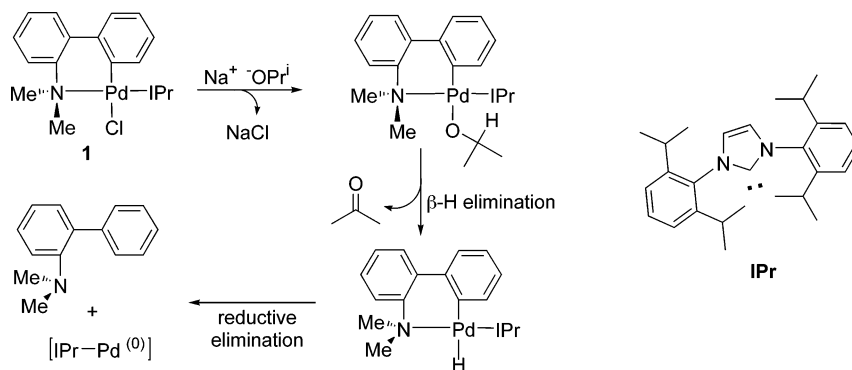
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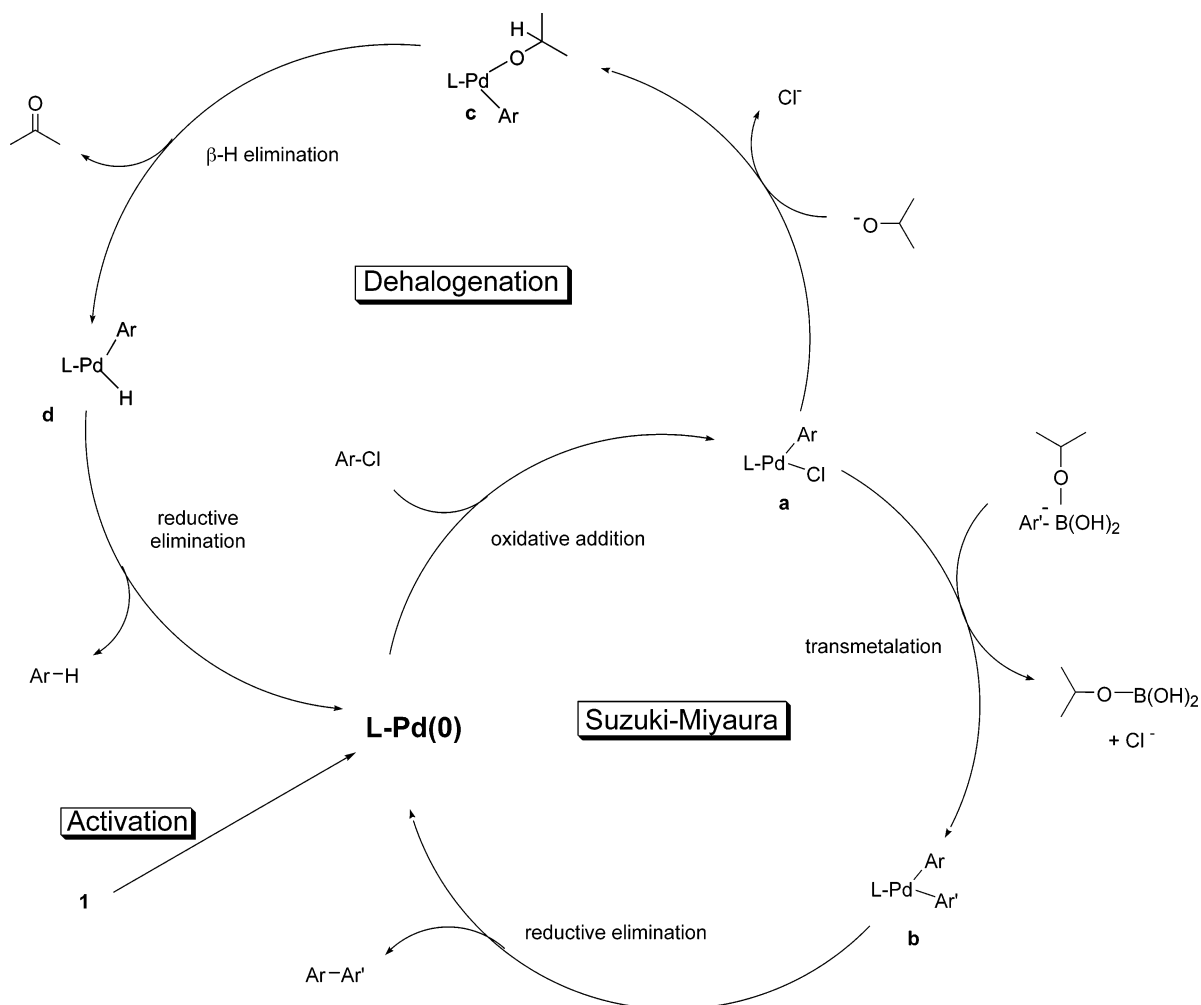
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SCHEME 1. Proposed Mechanism for the Activation of **1**

SCHEME 2. Proposed Catalytic Cycle



temperature and in very short reaction times. We proposed that the activity of the complex at room temperature was directly related to its particular activation mode, shown in Scheme 1, generating a catalytically very efficient Pd(0) species at room temperature.

In our initial experiments, we observed the formation to a large extent, 10–50% depending on the substrates, of the corresponding dehalogenated species as a side product. The coupling of either sterically demanding chlorides or boronic acids (or both) produced a larger amount of dehalogenated byproduct. Because we²² and others²³ have reported on the use of 2-propanol as a hydrogen source for palladium-catalyzed

dehalogenation of aryl halides, we propose that in the present system both processes, the Suzuki–Miyaura reaction and the catalytic dehalogenation, are intertwined, sharing the oxidative addition step (Scheme 2, intermediate **a**) and leading in both instances to the (IPr)–Pd(0) species after one turnover.²⁴ Sterically demanding substrates should lead to a decrease in the rate of transmetalation, favoring then the dehalogenation

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pathway. A proposal in line with our experimental observations is depicted in Scheme 2.

To minimize this undesirable side reaction, the aryl chlorides were initially required to be slowly added to the catalytic reaction mixture at an injection rate of 20 $\mu\text{L}/30\text{ s}$.²⁵ This procedure permitted the couplings to occur with less than 5% of the dehalogenation byproducts regardless of the substrates coupled. Although it might not seem to be a big difference in the process to account for the suppression of the dehalogenated byproduct, it is needed to explain that, for these reactions, *more than 75% of the desired product is produced in half of the reaction time*, as monitored by gas chromatography. Also, the dehalogenation byproduct is formed in the first minutes of the reaction and its amount does not increase with time. We will show later how the dehalogenation reactions we carried out at room temperature require shorter reaction times and, even more important, only half of the catalyst loading (1 mol %), which again suggests an extremely rapid oxidative addition process even for deactivated aryl chlorides (*vide infra*). In the initial stages of the reaction, once intermediate **a** has been formed, the possible lack of the in situ formed tetracoordinate boronate, together with the “large” concentration of aryl chloride and isopropoxide, might shift the equilibrium toward the dehalogenation process.

As we previously reported, activated and unactivated aryl chlorides couple smoothly with phenylboronic acid at room temperature in short reaction times (Table 1). Di- and tri-*ortho*-substituted biaryls can also be synthesized using the same conditions in high yields (Table 2). These results are obtained at room temperature in remarkably short reaction times! From a practical point of view, these conditions are very appealing, especially considering the use of an inexpensive and environmentally friendly solvent without predrying or purification. An experiment on the scale of 2.5 mmol of aryl chloride was carried out for the reaction depicted in entry 4 (Table 2) and afforded 428 mg (87%) of the desired product in 75 min.

Heterocyclic moieties are of great importance because they are ubiquitous in pharmaceutically active compounds.²⁶ Despite their importance, the cross-coupling reaction of heterohalides remains a challenge, especially at low temperatures. The use of **1** allows for the coupling of 2-chlorothiophene, 2-benzimidazole, and 2-chloropyridine with phenylboronic acid at room temperature within 1 h. The more deactivated substrates, 3-chlorothiophene and 3-chloropyridine, require a slightly higher temperature and longer reaction times (Table 3). To the best of our knowledge, the Suzuki–Miyaura cross-coupling reaction of chlorothiophenes at such low temperatures and in such yields has not been reported to date.

The present catalytic system also allows for the coupling of activated and unactivated aryl triflates under the same conditions in high yields (Table 4). From a synthetic point of view, aryl triflates are a very interesting type of substrate for the Suzuki–Miyaura reaction because they can be readily synthesized from the corresponding phenols in high yields.²⁷

(24) Another possibility would be that both catalytic cycles are connected at intermediate **c**, what has been described as a suitable intermediate for the Suzuki–Miyaura reaction, which can undergo direct transmetalation with the boronic acid (ref 7b). Studies aimed at elucidating the mechanism at play in this system are currently ongoing.

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TABLE 1. Suzuki–Miyaura Cross-Coupling Reactions with Aryl Chlorides

entry	aryl chloride	product	time(min)	%yield ^a
1			75	95
2			45	85
3			90	87
4			60	84
5			90	94
6			90	93
7			120	95
8			60	92 ^b

^a Isolated yields are the average of two runs. ^b Reaction at 45 °C.

α -Ketone Arylation Reactions. The coupling of enolizable ketones and aryl halides, despite its great synthetic importance, has been less explored.²⁸ Because this reaction requires the formation of an enolate that further binds to the palladium center, a possible side reaction is the condensation of two ketone molecules to form an α -hydroxyketone.²⁹ After optimization, we were able to successfully carry out the α -arylation of a series of aryl and alkyl ketones at 70 °C in dry THF in the presence of sodium *tert*-butoxide using a variety of aryl halides. It is noteworthy that we were able to perform every reaction with as low as 0.25 mol % of palladium precatalyst. Results with aryl chlorides are presented in Table 5. These substrates are of significant interest because they have in general lower costs and wide availability. Propiophenone can be efficiently coupled with neutral (entry 1), activated (entry 2), unactivated (entry 3), and sterically hindered (entry 4) aryl chlorides. We observed the same trend for acetophenone with slightly longer reaction times (entries 6–8). Satisfyingly, our catalytic system allows for the α -arylation of tetralone, even with an *ortho*-substituted substrate (entries 9 and 10). Dialkyl ketones are also suitable partners, as highlighted by the reaction of cyclohexanone and 3-pentanone with chlorobenzene (entries 11 and 12). In the latter case, the use of our standard reaction conditions always resulted in mixtures of mono- and diarylated products, even with a large excess of ketone. Then we decided to take advantage of this feature by synthesizing the diarylated ketone as the only product. This can be easily achieved in only 30 min when 2 equiv of

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TABLE 2. Synthesis of Di- and Tri-Ortho-Substituted Biaryls

entry	aryl chloride	boronic acid	product	time(min)	%yield ^a
1				50	77
2				60	85
3				75	88
4				75	79
5				75	87

^a Isolated yields are the average of two runs.

TABLE 3. Suzuki–Miyaura Cross-Coupling Reactions with Heteroaryl Chlorides

entry	substrate	product	time (min)	yield (%) ^a
1			60	75
2			300	78 ^b
3			60	94
4			90	83 ^b
5			90	91

^a Isolated yields are the average of two runs. ^b 45 °C.

aryl chloride are used (entry 12). When a nonsymmetrical dialkyl ketone was used, a mixture of monoarylated products was observed. Butanone reacted preferentially at the internal position

TABLE 4. Suzuki–Miyaura Cross-Coupling Reactions with Aryl Triflates

entry	aryl triflate	product	yield (%) ^a
1			90
2			95
3			90
4			84

^a Isolated yields are the average of two runs.

(entry 13); this can be explained by the greater stability of the internal enolate compared to that of the terminal one. Finally, regarding the significant role of the heterocyclic moiety in biologically active compounds, we attempted the coupling of 3-chloropyridine and propiophenone. Pleasantly, the corresponding heterocyclic ketone was obtained in good yield (entry 15). In addition, large-scale reactions (10 mmol of aryl chloride)

TABLE 5. α -Ketone Arylation Using Aryl Chlorides

entry	ketone	aryl chloride	product	time (h)	yield ^a (%)	entry	ketone	aryl chloride	product	time (h)	yield ^a (%)
1				1 2	99 92 ^b	9				5	85
2				1	86	10				3	88
3				3	85	11				1	72
4				2	94	12				0.5	90 ^c
5				3	98	13				2	90 4 : 1
6				2 3	93 90 ^b	14				2	95
7				4	92	15				4	76
8				3	85						

^a Isolated yields are the average of two runs. ^b Aryl chloride, 10 mmol; ketone, 10 mmol; NaOt-Bu, 11 mmol; THF, 30 mL. ^c A total of 1 mmol of ketone, 2.1 mmol of aryl chloride, and 2.2 mmol of NaOt-Bu were used.

were carried out for entries 1 and 6 with similar yields in slightly longer reaction times.

This coupling reaction was also tested using microwave heating with excellent results (Table 6). When the temperature is raised to 130 °C with this rapid heating mode, reactions could reach completion within 2 min with no decrease in the yields. Interestingly, we observed a higher selectivity in the arylation of butanone under microwave heating mode, presumably because of conditions favoring the more stable enolate. Decreasing the temperature might shift the regioselectivity toward the terminal arylated ketone, but all attempts to perform α -ketone arylation at room temperature were unsuccessful.

As expected, aryl bromides were suitable substrates for reactions under these conditions, and a variety of aryl and alkyl ketones could be easily arylated using unactivated and sterically demanding aryl bromides in very good yields and, in general, shorter reaction times than for the analogous chlorides (Table 7). Gratifyingly, the use of sterically hindered aryl bromides did not appear to be a limiting factor with our catalytic system. *Ortho*-substituted (entries 3, 4, and 7) and even di-*ortho*-substituted aryl bromides were coupled efficiently and in short reaction times. Following the same trend, α -tetralone reacted in high yields with 2-bromotoluene and 2-bromoanisole to afford the arylated products (entries 9 and 10).

Catalytic Dehalogenation Reactions. The dehalogenation of aryl halides, and more specifically aryl chlorides, represents an important chemical transformation in organic synthesis.³⁰ As a result of the high toxicity of polychlorinated arenes, it also has relevance to environmental remediation.³¹ A plethora of systems and conditions have been reported to perform this

transformation.³² In light of our findings in the Suzuki–Miyaura cross-coupling reaction, we carried out dehalogenation reactions using the same system but without the presence of a boronic acid. The ability of the (IPr)–Pd(0) species to activate the C–Cl bond at ambient temperatures translates into a very active system for the dehalogenation of aryl chlorides at rt. We observed that the use of the stronger base KOt-Bu permitted a catalyst loading reduction to 1 mol % using the same conditions (room temperature and technical grade 2-propanol). A variety of aryl chlorides (unactivated, activated, and heterocyclic) yielded the corresponding dehalogenated products in excellent yields and in short reaction times (Table 8). The catalytic performance is excellent considering these reactions are carried out at room temperature and require such short reaction times. Unfortunately, attempts to effectively dehalogenate polychlorinated substrates in these conditions led to incomplete reactions. Interestingly, electron-rich chlorides (entries 4–6) require shorter reaction times than electron-poor chlorides (entries 8–10). Because

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TABLE 6. Microwave-Assisted versus Conventionally Heated α -Ketone Arylation Using Aryl Chlorides

entry	ketone	aryl chloride	product	heating mode	T (°C)	time	GC conv. ^a (%)
1				conventional	70	1 h	99
				microwave	130	2 min	98
2				conventional	70	1 h	100
				microwave	130	2 min	99
3				conventional	70	2 h	89
				microwave	130	2 min	98
4			+	conventional	70	2 h	97 [4 : 1]
				microwave	130	2 min	100 [10 : 1]
5				conventional	70	2 h	100
				microwave	130	2 min	98

^a Average of two runs.TABLE 7. α -Ketone Arylation Using Aryl Bromides

entry	ketone	aryl bromide	product	time (h)	yield ^a (%)	entry	ketone	aryl bromide	product	time (h)	yield ^a (%)
1				1	88	7				1	90
2				2	91	8				4	90
3				1	93	9				4	92
4				2	96	10				4	97
5				2	85	11				0.5	68
6				2.5	89	12				1.5	91

^a Isolated yields are the average of two runs.

electron-poor chlorides are supposed to undergo oxidative addition easier than electron-rich chlorides, these results suggest that the rate-determining step in this process is not the oxidative addition but is either the replacement of the chloride by the

isopropoxide anion or the replacement of the chloride by the reductive elimination step, if we presume that neither steric nor electronic effects at the aryl moiety will have a large effect in the β -hydrogen elimination step (Scheme 2). In the case of entry

TABLE 8. Catalytic Dehalogenation of Aryl Chlorides at Room Temperature

entry	aryl chloride	product	time (min)	yield (%) ^a
1			60	100
2			60	100
3			60	100
4			30	100
5			30	100
6			30	100
7			60	100
8			30	100
9			120	90
10			60	100
11			60	100 ^b

^a GC yields. ^b Reaction at 60 °C.

8, the substituent at the *ortho* position should enhance the reductive elimination step, shortening the reaction time when compared with the *para*-substituted analogue (entry 9). Studies in this matter are currently ongoing.

Conclusions

In summary, we have examined the catalytic behavior of the NHC–palladacycle **1**. In particular, a general system involving the use of **1** and NaOt-Bu has proven suitable for the Suzuki–Miyaura cross-coupling of activated and unactivated aryl chlorides or triflates at room temperature, in technical grade 2-propanol, and requiring only short reaction times. In addition, the catalytic dehalogenation of aryl chlorides and the catalytic α -arylation of ketones with aryl bromides and chlorides were carried out using the same complex, highlighting the great versatility of the precatalyst. Further mechanistic and reactivity

studies of this and related complexes in various cross-coupling reactions are ongoing in our laboratories.

Experimental Section

Representative Procedure for the Suzuki–Miyaura Cross-Coupling Reaction: The Coupling of 2-Chloroanisole and Phenylboronic Acid. In a glovebox, **1** (2 mol %, 14.6 mg), sodium *tert*-butoxide (1.2 mmol, 115 mg), and phenylboronic acid (1.2 mmol, 146 mg) were added in turn to a vial equipped with a magnetic bar and sealed with a screw cap fitted with a septum. A parallel reaction was conducted at the same time in another vial. Outside the glovebox, technical grade 2-propanol (1.5 mL per vial) was injected into the vials, and the mixtures were stirred on a stirring plate at room temperature for 15 min. 2-Chloroanisole (1 mmol, 127 μ L) was then injected at a rate of 20 μ L/30 s into each vial. The reactions were monitored by gas chromatography. When the reactions reached completion, as gauged by GC analysis, both were combined in one vial, a small amount of silica gel was added, the solvent was evaporated in vacuo, and the product was isolated by flash chromatography (hexanes/ethyl acetate, 10:1), yielding 342 mg (93%) of the desired coupling product 2-methoxybiphenyl.

Representative Procedure for the α -Ketone Arylation: The α -Arylation of Propiophenone with 4-Chlorotoluene. In a glovebox, **1** (0.25 mol %, 1.8 mg), sodium *tert*-butoxide (1.1 mmol, 106 mg), and anhydrous THF (3 mL) were added in turn to a vial equipped with a magnetic bar and sealed with a screw cap fitted with a septum. A parallel reaction was conducted at the same time in another vial. Outside the glovebox, propiophenone (1.1 mmol, 134 μ L) and 4-chlorotoluene (1 mmol, 118 μ L) were injected in turn through the septum into each vial. The vials were then stirred on a stirring plate at 70 °C, unless otherwise indicated. The reactions were monitored by gas chromatography. When no further conversion could be observed, both mixtures were combined, water was added to the reaction mixture, the organic layer was extracted with diethyl ether and dried over magnesium sulfate, and the solvent was evaporated in vacuo. After flash chromatography on silica gel (hexane/EtOAc, 95:5), 442 mg (99%) of 2-(4-methylphenyl)-1-phenyl-1-propanone was isolated.

Representative Procedure for the Catalytic Dehalogenation of Aryl Chlorides: The Catalytic Dehalogenation of 4-Chlorotoluene. In a glovebox, **1** (1 mol %, 7.3 mg) and potassium *tert*-butoxide (1.2 mmol, 134.7 mg) were added in turn to a vial equipped with a magnetic bar and sealed with a screw cap fitted with a septum. A parallel reaction was conducted at the same time in another vial. Outside the glovebox, technical grade 2-propanol (2 mL per vial) was injected into the vial and the mixtures were stirred on a stirring plate at room temperature for 15 min. 2-Chloroanisole (1 mmol, 127 μ L) was then injected into each vial. The reactions were monitored by gas chromatography, and the product identity was compared with authentic samples.

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Supporting Information Available: Details for experimental procedures and product isolation are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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