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Palladium–imidazolium-catalyzed carbonylative coupling of aryl diazonium ions and aryl boronic acids

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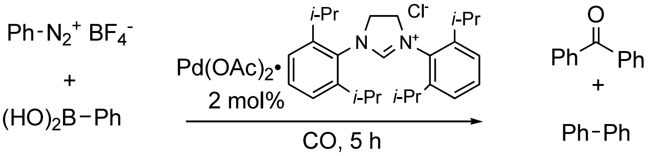
Abstract—Palladium(II) acetate and *N*,*N*-bis-(2,6-diisopropylphenyl)dihydroimidazolium chloride (2 mol%) were used to catalyze the carbonylative coupling of aryl diazonium tetrafluoroborate salts and aryl boronic acids to form aryl ketones. Optimal conditions include carbon monoxide (1 atm) in 1,4-dioxane at 100°C for 5 h. Yields for unsymmetrical aryl ketones ranged from 76 to 90% for isolated materials with only minor amounts of biaryl coupling product observed (2–12%). © 2002 Elsevier Science Ltd. All rights reserved.

Palladium-catalyzed carbonylative cross coupling is an attractive approach to the formation of unsymmetrically substituted biaryl ketones.[1] Aryl halides with various coupling partners have found success including stannanes,[2] magnesium,[3] aluminum,[4] silanes,[5] and boronic acids.[6] Draw backs to this approach often involve significant amounts of biaryl coupled product, the result of coupling without carbon monoxide insertion, and poor reactivity with electron-deficient aryl halides. The form of the palladium catalyst, ligands, base, additives, solvent, and temperature have been shown to have an effect on the amount of ketone versus biaryl formed. We now report the use of palladium(II) acetate with *N*,*N*-bis-(2,6-diisopropylphenyl)dihydroimidazolium chloride as ligand (2 mol%) for carbonylative cross-coupling reactions. Aryl diazonium tetrafluoroborate salts and arylboronic acids are used in 1,4-dioxane to form aryl ketones with minimal biaryl formation. Previously this palladium-ligand combination has been show to efficiently catalyze both Suzuki and Heck coupling reactions at room temperature without added base.[7] The nature of the palladium–imidazolium catalyst was investigated showing acetate to function as base to generate the active palladium–imidazolium carbene-type complex under these conditions. Palladium-carbenes have also been used recently for various coupling-type reactions.[8]

The reactivity of the process was explored using phenyldiazonium tetrafluoroborate and phenylboronic acid at 1:1 stoichiometry (Table 1). Reactions were performed in various solvents, at different temperatures, and pressures of carbon monoxide together with palladium(II) acetate and *N*,*N*-bis-(2,6-diisopropylphenyl)-dihydroimidazolium chloride both used at 2 mol%.

Table 1. Palladium-catalyzed carbonylation



Solvent	CO, atm	temp., °C	ketone % yield	bi-Ph % yield
Dioxane	1	100	71	6
Dioxane	1	100	72	3[a]
Dioxane	1	100	Trace	31[b]
Dioxane	1	23	71	12
Dioxane	2	23	84	5
Dioxane	5	23	88	Trace
Dioxane	10	23	90	0
Toluene	1	110	68	11
Toluene	1	23	61	13
THF	1	65	58	37
THF	1	23	41	50
THF	1	0	32	61

[a] Reaction was performed using dihydroimidazolium chloride (2 mol%) as ligand.
[b] Reaction was performed in the absence of ligand.

Keywords: palladium; imidazolium; catalysis; carbonylative; ketone; aryldiazonium; arylboronic acid.

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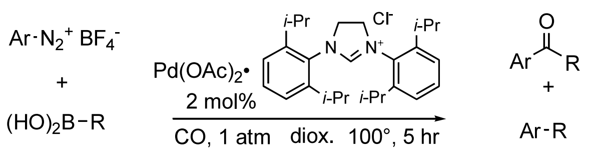
The reactions times were held constant at 5 h for comparison purposes. 1,4-Dioxane proved to be the superior solvent giving higher yields of ketone product together with less biphenyl formation. At 100°C, ketone was produced in 71% yield with only 6% biphenyl by-product. The two products were easily separated using silica gel chromatography. The analogous aromatic ligand, *N*,*N*-bis-(2,6-diisopropylphenyl)imidazolium chloride ligand also gave ketone with only a small amount of biphenyl. When the imidazolium ligand was omitted from the reaction mixture, the amount of ketone formed was hardly detectable, yet a significant amount of biaryl formation, 31%, was obtained after 5 h. At room temperature, more of the non-carbonylative process producing biphenyl was observed, 12%. Higher pressures of carbon monoxide, in accord with the studies of Miyaura and Suzuki,[6b] increased the yield of ketone and lowered the amount of biphenyl formation.[9] At 10 atm CO, biphenyl was not found and ketone was obtained in 90% yield. The conditions of Miyaura and co-workers included aryliodides and boronic acids reacted with $PdCl_2(dppf)_2$ as catalyst with excess K_2CO_3 and KI in anisole to give ketones with minimal biaryl formation.[6b] Toluene, used as solvent under the palladium–imidazolium conditions at reflux temperature with 1 atm CO, gave benzophenone in 68% isolated yield together with 11% biphenyl formation. At room temperature, ketone was produced in a reduced 61% yield and biphenyl increased to 13%. THF as solvent gave mixtures of products. At room temperature and at 0°C with 1 atm CO, biphenyl became the major product.

Table 2. Electron-rich aryl diazonium coupling



entry	Ar-	-R	ketone %yield	bi-Ph %yield
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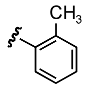
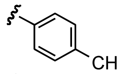
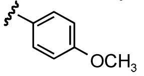
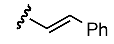
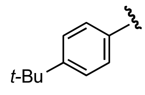
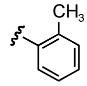
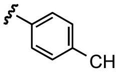
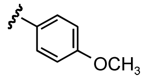
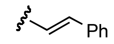
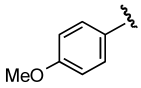
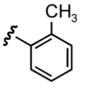
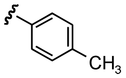
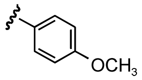
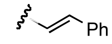
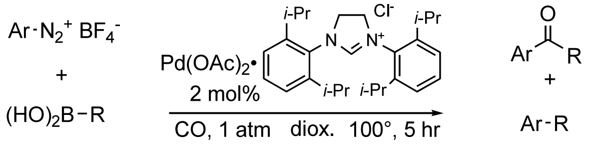
2			52	12
3			68	4
4			50	23
5			49	9
6		-Ph	75	6
7			68	9
8			78	4
9			71	7
10			71	6
11		-Ph	78	3
12			69	7
13			82	6
14			74	3
15			80	5

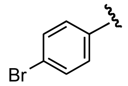
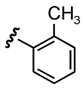
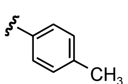
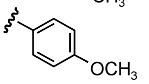
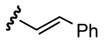
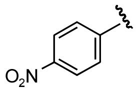
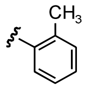
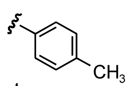
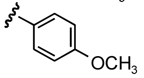
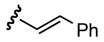
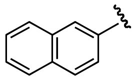
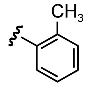
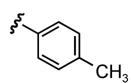
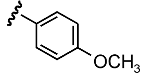
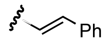
The palladium–imidazolium conditions were explored with various aryldiazonium tetrafluoroborates.[10] Aryl and vinylboronic acids under 1 atm CO and 2 mol% palladium(II) acetate–imidazolium catalyst were coupled.[11] Electron-rich diazonium ion substrates were the initial substrates (Table 2). *o*-Toluylboronic acid (entry 2) gave a reduced yield of 52% with increased production of biaryl product 12%. 4-Methoxyphenylboronic acid (entry 4) was also problematic with a 50% yield of ketone along with 23% biaryl formation using the phenyldiazonium ion. The more electron-rich substrates *p*-*tert*-butylphenyl and *p*-methoxydiazonium ions coupled with improved selectivity and yield. Vinylboronic acid (entries 10 and 15) also gave ketone products in good yield (71 and 80%) with only small amounts of biaryl products. 4-Methoxyphenylboronic acid also performed well with these ions giving improved selectivities and yields (entries 9 and 14) compared to the unsubstituted phenyldiazonium ion (entry 4).

Electron-deficient *p*-bromo, nitro, and naphthyl diazonium ions were also explored using this catalyst system (Table 3). Electron-deficient halides typically have given higher amounts of non-carbonylative biaryl product formation previously.[2,6] All boronic acids reacted with *p*-bromophenyldiazoium tetrafluoroborate (entries 1–5) to give ketones in very good 76–88% isolated yields. Only with the *p*-methoxy and styryl boronic acid were significant amounts of non-carbonylative aryl coupling products obtained. Surprisingly, *p*-nitrophenyl was even better forming ketones in excellent yields (81–90%) with less biaryl by-product formed. 2-Naphthyldiazonium salt also proved to be an effective substrate giving ketones in the excellent range. In these cases, both the *ortho*-toluyl and the *para*-substituted boronic acids, substrates that proved to be problematic with the electron-rich diazonium ions, gave ketone products with excellent selectivity and high isolated yield.

In summary, both electron-rich and -deficient aryldiazonium ions couple with boronic acids under palladium–imidazolium catalysis at a convenient 1 atm pressure of CO to give aryl ketones in good to excellent

Table 3. *p*-Bromo, nitro, and 2-naphthyl coupling



entry	Ar-	-R	ketone %yield	bi-Ph %yield
1		-Ph	87	5
2			81	6
3			88	4
4			76	12
5			78	10
6		-Ph	90	2
7			81	4
8			89	7
9			86	5
10			83	2
11		-Ph	81	6
12			87	5
13			88	5
14			81	6
15			89	4

isolated yields. In many cases only very small amounts of non-carbonylative biaryl coupling was observed. Electron-deficient diazonium ions are particularly efficient. The versatility of the conditions will be further developed and applied to more complex targets.

Acknowledgements

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9. An autoclave with a pressure gauge was used.
10. Aryl diazonium ions were formed using the procedure of: Doyle, M. P.; Siegfreid, B.; Elliot, R. C.; Dellaria, J. F. *J. Org. Chem.* **1977**, *42*, 2431.
11. *General procedure*: Aryldiazonium tetrafluoroborate (0.250 mmol), arylboronic acid (0.250 mmol), $Pd(OAc)_2$ (0.91 mg, 0.002 mmol, 2 mol%) and *N*,*N*-bis-(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (1.70 mg, 0.002 mmol, 2 mol%) were mixed under nitrogen in a round bottom flask. Anhydrous dioxane (2 mL) was added and the flask was charged with CO (1 atm). The resulting suspension was stirred at reflux temperature for 5 h. The reaction mixture was cooled and methylene chloride (10 mL) was added. The solution was washed three times with aqueous brine and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the mixture was purified by silica gel chromatography. Adequate characterization (^1H NMR, MS) for the ketone products, all of which are known, was obtained. Representative examples and data follows:
    Benzophenone: Yield: 71%, R_f: 0.55 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$): δ 7.33–7.68 (m, 10H); MS (EI) *m*/*z* 180.
    Chalcone: Yield: 49%, R_f: 0.45 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$): δ 7.08–7.69 (m, 11H), 6.81 (d, 1H, $J=6.8$); MS (EI) *m*/*z* 208.
    4-*t*-Butylbenzophenone: Yield: 75%, R_f: 0.40 (10% EtOAc/hexanes); ^1H NMR ($CDCl_3$): δ 7.30–7.67 (m, 9H), 1.32 (s, 9H); MS (EI) *m*/*z* 238.

4-*t*-Butyl-4′-methylbenzophenone: Yield: 78%, R_f: 0.40 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.27–7.71 (m, 8H), 2.40 (s, 3H), 1.30 (s, 9H); MS (EI) *m*/*z* 252.

4-Methoxylchalcone: Yield: 80%, R_f: 0.40 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.13–7.69 (m, 9H), 6.91 (d, 1H, $J=6.8$), 3.78 (s, 3H); MS (EI) *m*/*z* 238.

4-Bromobenzophenone: Yield: 87%, R_f: 0.50 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.01–7.71 (m, 9H); MS (EI) *m*/*z* 260, 262.

4-Bromo-4′-methylbenzophenone: Yield: 88%, R_f: 0.50 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.08–7.69 (m, 8H), 2.37 (s, 3H); MS (EI) *m*/*z* 274, 276.

4-Bromochalcone: Yield: 89%, R_f: 0.45 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.07–7.72 (m, 10H), 6.83 (d, 1H, $J=6.8$); MS (EI) *m*/*z* 287, 289.

4-Nitrobenzophenone: Yield: 90%, R_f: 0.35 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 6.94–7.62 (m, 9H); MS (EI) *m*/*z* 253.

4-Nitro-4′-methylbenzophenone: Yield: 89%, R_f: 0.35 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 6.96–7.71 (m, 8H), 2.32 (s, 3H); MS (EI) *m*/*z* 241.

4-Nitro-4′-methoxylbenzophenone: Yield: 86%, R_f: 0.30 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 6.86–7.69 (m, 8H), 3.82 (s, 3H); MS (EI) *m*/*z* 257.

4-Nitrochalcone: Yield: 83%, R_f: 0.35 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.12–7.76 (m, 10H), 6.88 (d, 1H, $J=6.8$), MS (EI) *m*/*z* 253.

2-(2′-Methybenzoyl)naphthalene: Yield: 87%, R_f: 0.45 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.25–7.62 (m, 11H), 2.38 (s, 3H); MS (EI) *m*/*z* 246.

2-(4′-Methybenzoyl)naphthalene: Yield: 88%, R_f: 0.45 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.26–7.62 (m, 11H), 2.38 (s, 3H); MS (EI) *m*/*z* 246.

3-Phenyl-1-(2-naphthyl)prop-2-en-1-one: Yield: 89%, R_f: 0.40 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): δ 7.21–7.77 (m, 13H), 6.79 (d, 1H, $J=6.8$); MS (EI) *m*/*z* 258.