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Practical and Efficient Suzuki−Miyaura Cross-Coupling of 2-Iodocycloenones with Arylboronic Acids Catalyzed by Recyclable Pd(0)/C[†]

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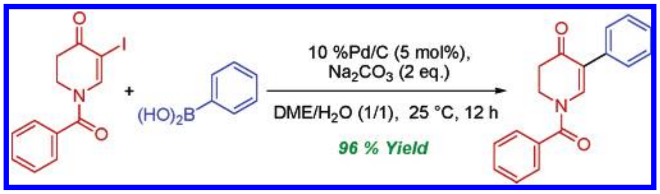

The first Suzuki−Miyaura cross-coupling of 2-iodocycloenones with arylboronic acids catalyzed by 10% Pd(0)/C is described as an interesting alternative to classical homogeneous conditions. Most of the substrate reacted under mild condition at 25 °C under air in aqueous DME. The conditions described tolerate a wide range of iodoenones and boronic acids. Notably, the procedure features inexpensive reagents and solvents with low toxicity rendering the method environmentally benign. Additionally 10% Pd(0)/C could be recovered and efficiently reused at least five times without significant alteration of the yields of the cross-coupled product.

The Suzuki−Miyaura reaction is probably one of the most important palladium-catalyzed processes for C−C bonds formation. Extensive studies have been made since the pioneering works from Suzuki and Miyaura.[1] The massive interest for the Suzuki reaction can be explained by the impressively wide range of substrates tolerated. Additionally, the relative stability of boronic acids to air and their low toxicity constitute a highly valuable practical advantage for both academic and industrial applications. Recently this process has reached a level of sophistication, and admirable results can be obtained with a homogeneous palladium catalyst ($Pd(OAc)_2$, $Pd_2(dba)_3$, ...) associated to a ligand.[2] However, the most popular tertiary phosphine ligands are often sensitive to air oxidation and therefore require careful and air-free handling. To circumvent this issue, the development of ligandless conditions using homogeneous palladium catalyst is of great interest.[3] However, several drawbacks remain to be solved: (1) the use of additives is often required in order to obtain high yields of cross-coupled products, and (2) the separation and recovery of palladium catalyst remain challenging if not impossible. In this context, heterogeneous catalysis using 10% Pd(0)/C as catalyst for Suzuki−Miyaura reactions appears as a suitable alternative to the "classical" homogeneous conditions.[4] Indeed, in this case ligands and additives are generally not required for efficient transformations, and catalyst removal is easily performed by simple filtration. Another important feature is the compatibility of 10% Pd(0)/C with water as solvent or cosolvent under air.[5] However, all studies using Pd/C as catalyst have been so far realized for the preparation of biaryl compounds. To the best of our knowledge there is no literature precedent for the Pd/C-mediated cross-coupling reaction of 2-halocycloenones with boronic acid partners. It should be noted that even under homogeneous Pd catalysis the cross-coupling of 2-haloenones with boronic acid has attracted much less attention compared to aryl-aryl coupling, in part because of the sensitive nature of 2-halocycloenones.[6] In an effort to develop "green" transformations during the course of a project requiring C−C bonds formation between enones and aryls for the preparation of biologically active compounds,[7] it was

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[†] This paper is dedicated with respect to my mentors Jacques Lebreton (Université de Nantes) and Robert S. Coleman (Ohio State University).

(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev*.**1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Miyaura, N. In *Topics in Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: Berlin, 2002; Vol. 219, p 11. (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695.

(2) For recent brilliant results, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.

(3) For some recent and representative examples see: (a) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034−5037. (b) Darses, S.; Jeffery, T.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1996**, *37*, 3857−3860. (c) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437−14450. (d) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170−7173. (e) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885−3890. (f) Chi, S. M.; Choi, J.-K.; Yum, E. K.; Chi, D. Y. *Tetrahedron Lett.* **2000**, *41*, 919−922. (g) Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199−8202. (h) Ma, D.; Wu, Q. *Tetrahedron Lett.* **2001**, *42*, 5279−5281. (i) Kabalka, G. W.; Namboodiri, V.; Wang, L. *Chem. Commun.* **2001**, 775. (j) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302−4314.

(4) (a) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277−3280. (b) Gala, D.; Stamford, A.; Jenkins, J.; Kugelman, M. *Org. Proc. Res. Dev.* **1997**, *1*, 163−164. (c) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405−3406. (d) Bykov, V.; Bumagin, N. *Russ. Chem. Bull.* **1997**, *46*, 1344−1345. (e) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Proc. Res. Dev.* **1999**, *3*, 248−252. (f) LeBlond, C. R.; Andrews, A. T.; Sun, Y.; Sowa, J. R., Jr. *Org. Lett.* **2001**, *3*, 1555−1557. (g) Dyer, U. C.; Shapland, P. D. Tiffin, P. D. *Tetrahedron Lett.* **2001**, *42*, 1765−1767. (h) McClure, M. S.; Roschangar, F.; Hodson, S. J.; Millar, A.; Osterhout, M. H. *Synthesis* **2001**, 1681−1685. (i) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721−2722. (j) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118−1122. (k) Organ, M. G.; Mayer, S. *J. Comb. Chem.* **2003**, *5*, 118−124. (l) Conlon, D. A.; Pipik, B.; Ferdinand, S.; LeBlond, C. R.; Sowa, J. R. Jr.; Izzo, B.; Collins, P.; Ho, G.-J.; Williams, J. M.; Shi, Y.-J.; Sun, Y. *Adv. Synth. Catal.* **2003**, *345*, 931−935. (m) Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, *68*, 9412−9415. (n) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080−4086. (o) Zhang, G. J. *Chem. Res.* **2004**, *9*, 593−595. (p) Cravotto, G.; Palmisano, G.; Tollari, S.; Nano, G. M.; Penoni, A. *Ultrason. Sonochem.* **2005**, *12*, 91−94. (q) Poláčková, V.; Hut'ka, M.; Toma, ×b3Š. *Ultrason. Sonochem.* **2005**, *12*, 99−102. (r) Cravotto, G.; Beggiato, M.; Penoni, A.; Palmisano, G.; Tollari, S.; Lévêque, J.-M.; Bonrath, W. *Tetrahedron Lett.* **2005**, *46*, 2267−2271. (s) Sajiki, H.; Kurita, T.; Kozaki, A.; Zhang, G.; Kitamura, Y.; Maegawa, T.; Hirota, K. *Synthesis* **2005**, 537−542. (t) Lu, G.; Franzén, R.; Zhang, Q.; Xu, Y. *Tetrahedron Lett.* **2005**, *46*, 4255−4259. (u) Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101−2104. (v) Lysén, M. Köhler, K. *Synlett* **2005**, 1671−1674.

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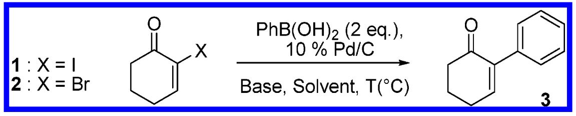
TABLE 1. Optimization of Reaction Conditions



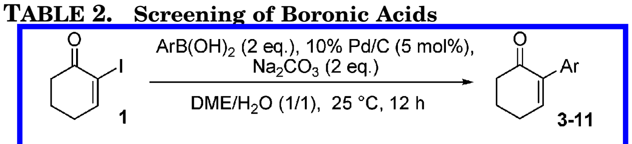
entry	sub-strate	Pd/C (mol%)	base	solvent	*T* (°C)	*t* (h)	yield[a] (%)
1	**1**	5	Na_2CO_3	$EtOH/H_2O$ (1/1)	25	12	82
2	**1**	5	Na_2CO_3	$EtOH/H_2O$ (1/1)	80	5	70
3	**1**	5	Na_2CO_3	DME/H_2O (95/5)	80	12	(75)
4	**1**	**5**	**Na_2CO_3**	**DME/H_2O (1/1)**	**25**	**12**	**86**
5	**1**	5	Na_2CO_3	DME/H_2O (1/1)	80	5	85
6	**1**	1	Na_2CO_3	DME/H_2O (1/1)	25	12	(33)
7	**1**	1	Na_2CO_3	DME/H_2O (1/1)	80	12	80
8	**1**	0.5	Na_2CO_3	DME/H_2O (1/1)	80	12	81
9	**1**	5	Et_3N	DME/H_2O (1/1)	25	12	5
10	**1**	5	NaOH	DME/H_2O (1/1)	25	12	64
11	**2**	5	Na_2CO_3	DME/H_2O (1/1)	25	12	0
12	**2**	5	Na_2CO_3	DME/H_2O (1/1)	80	12	0

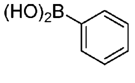
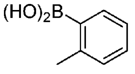
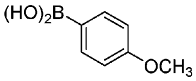
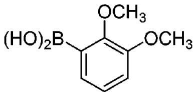
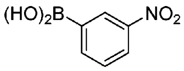
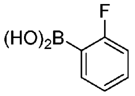
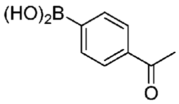
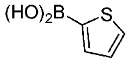
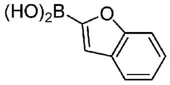
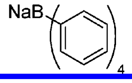
[a] Yields are for isolated products. Conversion in brackets

found that heterogeneous 10% Pd(0)/C is a valuable source of palladium for such a reaction. Herein, we present our studies concerning the first cross-coupling reaction of 2-iodocycloenones with boronic acids catalyzed by 10% Pd(0)/C.

Optimization of Reaction Conditions. For our first investigations on 10% Pd(0)/C-mediated Suzuki reaction we selected 2-iodo-2-cyclohexen-1-one **1** and phenyl boronic acid as model partners (Table 1). A number of parameters were evaluated. Under optimized conditions 2-iodo-2-cyclohexen-1-one **1** in a mixture of DME (1,2-dimethoxyethane) and H_2O (1/1) reacted with phenyl boronic acid in the presence of 10% Pd(0)/C (5 mol %) and Na_2CO_3 (2 equiv) at 25 °C to give the corresponding cross-coupled product **3** in 86% yield (entry 4). It is important to note that all our subsequent studies have been carried out *under air and with undistilled solvents*, rendering the method exceptionally practicable. Recent reports highlighted the beneficial effect of alcoholic solvent for the Pd/C-mediated cross-coupling of aryl bromide with aryl boronic acids.[4s] On the basis of these results, we first used EtOH and water as solvent system. Although the reaction rate was faster at 80 °C, the reaction conducted at 25 °C gave also good results (entries 1 and 2). However, we detected some impurities on TLC that proved to be difficult to separate by flash chromatography. Since alcoholic solvents could be oxidized by Pd/C under air atmosphere, EtOH was replaced by DME. We found that the DME/H_2O volumetric ratio was critical for the success of the cross-coupling reactions. Low water concentration had deleterious effects, resulting only in a partial conversion (entry 3). After considerable experimentation, we determined that the optimal volumetric ratio was 1/1. The reaction can be run at 25 or 80 °C without any significant changes for the yields (entries 4 and 5). Although the reaction rate was slower at 25 °C, subsequent studies were conducted at that temperature for the extremely mild conditions. Alternatively the reaction can be efficiently conducted at low catalyst loading (0.5 mol % of 10% Pd(0)/C) albeit at a higher temperature (entry 8). To our knowledge, this catalyst loading (0.5 mol %) is the lowest reported to date for such a transformation. This finding could be useful for large scale preparation; however, on a laboratory scale (1.5 mmol) 5 mol % of 10% Pd(0)/C proved to simplify handling procedure. We also screened other bases without relevant success. The use of an organic base such as Et_3N resulted in a dramatically low yield due to extensive decomposition of starting material (entry 9). On the other hand, the inorganic base NaOH proved to be less effective than Na_2CO_3 (entry 10). An important point to note is the complete inefficiency of 2-bromo-2-cyclohexen-1-one **2** under these conditions to undergo the Suzuki−Miyaura cross-coupling (entries 11 and 12). Only extensive decomposition of starting materials was observed whatever the temperature (25 or 80 °C).

TABLE 2. Screening of Boronic Acids



Entry	Ar-B(OH)$_2$	Product	Yield (%)[a]
1		**3**	86
2		**4**	80
3		**5**	87
4		**6**	90
5		**7**	80
6		**8**	80
7		**9**	98
8		**10**	81
9		**11**	94
10		**3**	78

[a] Yields are for isolated products.

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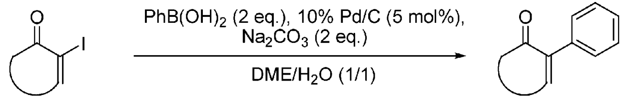
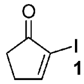
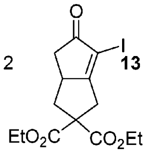
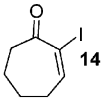
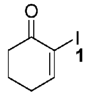
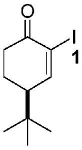
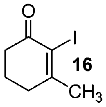
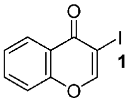
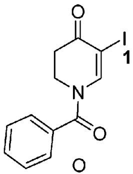
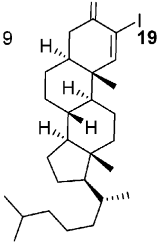
(6) For some relevant examples in total synthesis of natural products, see: (a) Yoshida, M.; Mori, K. *Eur. J. Org. Chem.* **2000**, 1313−1317. (b) Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4509−4511. (c) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, 127, 5342−5344.

(7) Felpin, F.-X. Unpublished results.

TABLE 3. Screening of 2-Iodocycloenones



Entry	Iodoenone	Conditions	Prod.	Yield (%)[a]
1	 **12**	25 °C, 12 h	**20**	81
2	 **13**	80 °C, 4 h	**21**	46
3	 **14**	25 °C, 12 h	**22**	71
4	 **1**	25 °C, 12 h	**3**	86
5	 **15**	25 °C, 12 h	**23**	85
6	 **16**	50 °C, 12 h	**24**	81
7	 **17**	25 °C, 12 h	**25**	95
8	 **18**	25 °C, 12 h	**26**	96
9	 **19**	80 °C, 6 h	**27**	91

[a] Yields are for isolated products.

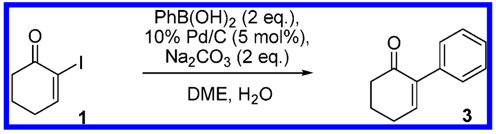
Screening of Boronic Acids. Encouraged by these promising results, we then explored the reaction of 2-iodocyclohexenone **1** with a variety of boronic acids. Table 2 summarizes the most significant experiments of this study. As already observed, the reaction took place under very mild conditions at room temperature in aqueous DME, affording excellent yields of expected products regardless of the nature of boronic acids. For instance, activated boronic acids (electron-rich) in *ortho*, *meta*, or *para* positions reacted well (entries 2−4). Most importantly, electron-poor boronic acids (entries 5−7) also gave excellent results, although these substrates are generally less reactive and sometime prone to homocoupling and protodeboronation in protic solvent. The reaction conditions are notably compatible with fluoro-, nitro-, and keto-aryls. We also examined the introduction of heteroaromatic substituents, which are of great importance in pharmaceutical drug discovery processes. For instance, thiophenyl and benzofuranyl boronic acids can be readily cross-coupled under our conditions (entries 8 and 9). Finally, we found that the inexpensive and very stable sodium tetraphenyl borate can advantageously be used as an efficient alternative to phenyl boronic acid (entry 10).

Screening of 2-Iodocycloenones. Having established a reasonable range of boronic acid partners, we next examined the scope of the reaction with various 2-iodocycloenones (Table 3). The process showed excellent tolerance toward the ring size of 2-iodocycloenones (5−7 carbons), and high yield of cross-coupled products were obtained. Next, we studied the influence of substitutions on various 2-iodocycloenones. Gratifyingly, all substrates tested during our studies gave cross-coupled products in high yields and most of the substitution patterns were tolerated at room temperature. However, for the 3-substituted cycloenone **16** and the hindered steroid **19** higher temperatures (50 and 80 °C, respectively) were required for complete conversion (entries 6 and 9). Finally, heterocycloenones could be envisaged as part of the backbone of naturally occurring biologically active compounds. Pleasingly, these substrates were found to be highly reactive under 10% Pd(0)/C catalysis as demonstrated in entries 7 and 8. The major limitation of this process results in the relative instability of some 2-iodocycloenones. As illustrated in entry 4, the modest yield obtained for **21** (46%) is due to competitive degradation of starting material **13**. Interestingly, the conversion was total at 25 °C after 12 h of stirring, but **21** was isolated with only 20% yield. The degradation of **13** was minored at 80 °C by enhancing the kinetic of the cross-coupling.

Since the catalyst could be easily separated from the reaction mixture by simple filtration, a particularly attractive feature would be its recyclability. We examined the cross-coupling of 2-iodo-2-cyclohexen-1-one **1** with phenyl boronic acid and recovered the catalyst to reuse it (Table 4). We were pleased to find that with the same batch of 10% Pd(0)/C it was possible to carry out at least five runs without affecting the yield. The progressive decrease of the activity can be efficiently balanced by increasing the temperature of the reaction.

In conclusion, we have reported that Pd(0)/C can efficiently catalyze the Suzuki−Miyaura cross-coupling

TABLE 4. Recycling Test



entry	run[a]	T (°C)	t (h)	yield (%)[b]
1	1	25	12	86
2	2	25	12	85
3	3	25	24	79
4	4	50	12	81
5	5	50	12	80

[a] Reaction products carried out with the same batch of Pd/C. [b] Yields are for isolated products.

of 2-iodocycloenones with arylboronic acids. We have shown that the reaction can be mostly conducted at 25 °C in aqueous DME under air, rendering the method very practicable. Additionally, the possibility to easily recycle the catalyst makes the process very cheap and highly valuable for environmental concerns.

Experimental Section

General Procedure for Suzuki Cross-Coupling Reaction. To a solution of iodoenone (1.5 mmol) in DME (4.5 mL) and H_2O (4.5 mL) were added Na_2CO_3 (318 mg, 3 mmol), Ar-B(OH) (3 mmol), and 10% Pd(0)/C (79.5 mg, 5 mol %). The mixture was stirred for the specified time and temperature. Pd(0)/C was filtered, and the filtrate was diluted with H_2O (4.5 mL) and extracted with Et_2O (3×). The collected organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

Eventually, the catalyst was washed twice with water and twice with Et_2O, dried under vacuum (4 h), and reused in a new run.

2-Phenylcyclohex-2-enone (3). Purification by flash chromatography (10% EtOAc−petroleum ether) gave **3** as a colorless solid (222 mg, 86%): Mp 93−94 °C [lit.[8] 92−93 °C]. IR (KBr) ν 1662, 2933, 3016 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.09−2.17 (m, 2H), 2.53−2.64 (m, 4H), 7.06 (app t, 1H, J = 4.1 Hz), 7.28−7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.9, 26.5, 39.0, 127.5, 127.9, 128.5, 136.5, 140.3, 147.9, 197.9. HRMS (EI) calcd for $C_{12}H_{12}O$ (M $^+$) 172.0888, found 172.0886.

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Supporting Information Available: Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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