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Exhaustive Suzuki-Miyaura Reactions of Polyhalogenated Heteroarenes with Alkyl Boronic Pinacol Esters

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Abstract

A novel Suzuki-Miyaura protocol is described that enables the exhaustive alkylation of polychlorinated pyridines. This method enables a formal synthesis of normuscopyridine and the rapid assembly of a dumbbell shaped portion of a [2]rotaxane.

The 2-alkylpyridine scaffold is critical to bioactive small molecules, to molecular machines, and within ligands for metal catalyzed transformations (Figure 1).[1] Several powerful approaches have been developed to install alkyl substituents on pre-formed pyridyl cores.[2] In terms of traditional cross-coupling approaches, 2-pyridyl organometallic reagents have been advanced, but suffer from air instability[3] and reaction-specific limitations, including requirements for high catalyst loadings or a narrow range of cross-coupling partners.[4] A complementary approach involves the direct functionalization of affordable, readily accessible, and chemically stable heteroaryl chlorides by way of a cross-coupling reaction.[5] The Suzuki–Miyaura reaction relies on commercially available reagents that offer reduced toxicity.[6,7] Only a few conditions can couple alkyl organoboron reagents with 2-halopyridines.[8] To complement our disclosed selective and serial Suzuki-Miyaura reactions of polychlorinated pyridines with alkyl pinacol boronic esters (Scheme 1, eq 1, 2),[9] we now describe an exhaustive Suzuki-Miyaura reaction of haloarenes, including 2-pyridylchlorides (Scheme 1, eq 3).

The challenges in this transformation derive from (1) the ability of the Lewis basic pyridine nitrogen to bind the metal and inhibit further reactivity,[10] and (2) the relatively slow transmetallation of alkyl organoboron species. Slow transmetallation renders decomposition pathways more competitive, including protodehalogenation of aryl halides, protodeborylation[11] of the alkyl boronic esters, and β-hydride elimination processes of palladium-alkyl intermediates.

Initially, we chose to interrogate the Suzuki-Miyaura reaction of 2,6-dichloropyridine (**3a**) with heptyl pinacol boronic ester to generate 2,6-dialkylpyridine **5a** (Table 1). The targeted bond-forming reactions do not proceed efficiently using many cutting-edge protocols to

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Electronic Supplementary Information (ESI) available: Full experimental details, copies of NMR spectra (PDF).

couple aryl halides with alkyl boron compounds.[12] We anticipated that this reaction would be promoted by sterically encumbered alkyl phosphine ligands. Such ligands favor formation of mono-coordinated palladium-phosphine complexes, which undergo accelerated oxidative addition,[13] transmetallation, and reductive elimination processes.[14] Moreover, sterically encumbered ligands can help to mitigate β-hydride elimination following transmetallation of the organoboron species. We found that di(1-adamantyl)-*n*-butylphosphine provided the highest levels of dialkylpyridine **5a** (entries 1–3).

The optimal conditions vary slightly from those disclosed recently to affect the Suzuki-Miyaura reaction of halopyridines with boronic acids (entry 4),[15] but the differences have a dramatic impact on the reaction. Empirical studies with different palladium sources and solvents revealed a beneficial effect derived from the use of a $Pd(OAc)_2$ pre-catalyst and solvation with 4:1 dioxane:water (entries 4–8). Presumably, water mediates pinacol boronic ester speciation.

Pinacol boronic ester speciation also depends on reaction pH. Reaction conversion increases with increasing basicity (entries 9–12; pK_a of corresponding conjugate acids in water: HF, 3.2; HCO_3^-, 10.2; HPO_4^{2-}, 12.7; HO*t*Bu, 16.5).[16] Interestingly, the identity of the counter cation resulted in significant differences in conversion to the exhaustively coupled product, presumably due to differences in nucleophilicity (entries 13–14).[17] Lithium alkoxides were the only bases screened that favoured exhaustive coupling over selective coupling (entries 1, 15). Under the optimal conditions, the reaction of 2,6-dichloropyridine with heptyl boronic pinacol ester (2.3 equiv) proceeded in a 4:1 mixture of dioxane:H_2O at 100 °C with LiO*t*Bu, 1 mol% $Pd(OAc)_2$ and 3 mol% Ad_2P^nBu to afford 2,6-diheptylpyridine (**5a**) in excellent selectivity and 94% isolated yield (entry 1). In general, LiO*t*Bu is not included as a base during empirical screens of Suzuki-Miyaura reaction conditions.[12,18] These results suggest that it could be of broad relevance to base-tolerant substrates.

With 2,6-dichloropyridine, exhaustively coupled product **5a** is predominately formed only with an excess of boronic ester **6a**. Conversely, when **6a** is employed as the limiting reagent, selectively coupled **4a** is the major product (entry 16). By contrast, 2,6-dibromopyridine generates nearly exclusively exhaustively coupled **5a** when **6a** is used as the limiting substrate (entry 17). We hypothesize that during the transformation, the palladium catalyst remains ligated to the 2-bromo-6-alkylpyridine intermediate, but can dissociate from 2-chloro-6-alkylpyridine species prior to the second transmetallation event. This differential reactivity could be a consequence of the higher barrier to oxidative addition to aryl chlorides relative to bromides.

Under the optimized conditions, 2,6-dibromo- and 2,6-dichloropyridine react with similar efficiency (entries 1, 18). Consequently, we have chosen to investigate the reaction scope with chloroaromatic electrophiles, which are thought to be more challenging cross-coupling partners, and are often more readily available and less expensive. An array of aryl chlorides couple smoothly with pinacol boronic ester **6b** (Table 2). Mono-, di-, and trichloropyridines are converted to mono-, di-, and trialkylpyridines, respectively (entries 1–3). This protocol tolerates electron-donating substituents on pyridine, which were not effectively transformed under our previously reported selective conditions (entry 4–5),[9] as well as electron-deficient

aryl chlorides (entry 6). This protocol affects reaction of other 2-chloroheteroaryl compounds, such as isoquinolines (entry 7). In most cases, the starting aryl chloride and the reported product account for the mass balance of the reaction. An exception is 2,6-dichloro-4-trifluoromethyl pyridine, which is known to be unstable at elevated temperatures (entry 8).

These conditions do not productively transform more acidic substrates, such as 6-chloroindole and 6-chloropyridin-2-one, both of which would be expected to be deprotonated under the reaction conditions. Even *p*-chloroacetophenone does not undergo efficient cross-coupling, possibly due to competitive deprotonation (Table 2, entry 10). Relative to HO^{t}Bu, *p*-chloroacetophenone is more acidic in DMSO (pK_a 23.78 vs 32.2), and slightly more basic in water (pK_a 18.1 vs. 16.5.[16b, 19] Many base-originated limitations can be surmounted through use of a weaker base or by substrate design. For example, substrate redesign permits access to 6-alkylpyridin-2-ones from 2-alkoxy-6-chloropyridines (entry 11). Therefore, this protocol may be used as a launching point for optimization of Suzuki-Miyaura reactions of 2-halopyridines with alkyl boronic esters displaying increased base sensitivity.

Pyridyl chlorides react effectively with alkyl pinacol boronic esters that incorporate distal unsaturation, acetals, or ethers (Table 3, entries 1–8). The clean formation of unsaturated products is notable, as similar selectivity would be difficult to achieve via Heck olefination reactions or Suzuki-Miyaura reactions involving transmetallation of *in situ*-generated organoboranes. Additionally, these unsaturated compounds can be valuable intermediates: the reaction of 2,6-dichloropyridine to form 2,6-dihexenylpyridine constitutes a formal synthesis of the fragrance molecule normuscopyridine, which can be accessed upon ring-closing metathesis and reduction (entry 2).[20] As might be expected, these conditions can also be applied to access biaryl compounds (entry 8).

One feature of this exhaustive protocol is that base-sensitive substrates may undergo multiple base-mediated transformations in a single operation. Notably, application of the standard conditions to cross-couple a silyl ether with an activated 2-pyridyl chloride proceeds with desilylation to furnish alcohol **5s** (entry 9). As an alternative, the base labile silyl ether coupling partner is amenable to slightly modified conditions to deliver the intact silylated product (entry 10).

To push the limits of this protocol, we focused on allyl pinacol boronic ester, which is known to be highly reactive and easily protodeborylated (entry 11). While our optimized reaction protocol involving LiO^{t}Bu does not generate the desired product; anhydrous conditions can be applied with a more organic soluble base to promote productive cross-coupling. To the best of our knowledge, this represents the first example of direct Suzuki-Miyaura catalyzed allylation of an aryl chloride, previous reports being limited to the use of more reactive aryl iodides and bromides.

The utility of the disclosed reaction has been demonstrated in the synthesis of a dumbbell shaped molecule for a rotaxane (i.e., **1**). Pyridine **1** has been previously accessed in a longest linear sequence of five steps, or in three steps and 54% yield from common intermediate **9**

via palladium-catalyzed Sonagashira cross-coupling and hydrogenation reactions.[1d] This new protocol furnishes **1** in in two steps and 64% yield from common intermediate **9**. This protocol could assist in the development of new molecular machines, as, in principle, the alkyl boronic ester substrate can be easily modified to access threads of varying length or to generate differentially substituted dumbbell shaped molecules if deployed in sequence with the previously disclosed selective method.[9]

In conclusion, these optimized Suzuki-Miyaura reaction conditions enable the controlled alkylation of series of 2,6-dichloropyridines in presence of unsaturation, etherial linkages, or acetals. The use of bulky Ad_2P^nBu in combination with LiO^tBu facilitates oxidative addition onto 2-chloro-6-alkylpyridines, thereby forming exhaustively alkylated products. Importantly, these reaction conditions minimize β-hydride elimination processes as well as protodehalogenation of the starting materials. These conditions have been applied to gain efficient access to a known [2]rotaxane component.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Notes and references

1. (a) Schinz H, Ruzicka L, Geyer U, Prelog V. Helv Chim Acta. 1946; 29:1524.(b) Fürstner A, Leitner A. Angew Chem Int Ed. 2003; 42:308.(c) Davis JM, Truong A, Hamilton AD. Org Lett. 2005; 7:5405. [PubMed: 16288517] (d) Goldup SM, Leigh DA, Lusby PJ, McBurney RT, Slawin AMZ. Angew Chem Int Ed. 2008; 47:6999.(e) Zhang YH, Shi BF, Yu JQ. J Am Chem Soc. 2009; 131:5072. [PubMed: 19296661] (f) Goetz AE, Garg NK. Nature Chemistry. 2013; 5:54.
2. For select C–H activation processes, see:(a) Lewis JC, Bergman RG, Ellman JA. J Am Chem Soc. 2007; 129:5332. [PubMed: 17411050] (b) Nakao Y, Yamada Y, Kashihara N, Hiyama T. J Am Chem Soc. 2010; 132:13666. [PubMed: 20822182] For select examples that involve distinct bond-forming and deprotonation steps, see:(c) Jeffrey JL, Sarpong R. Org Lett. 2012; 14:5400. [PubMed: 23061536] (d) Chen Q, León T, Knochel P. Angew Chem Int Ed. 2014; 53:8746.(e) Hyodo I, Tobisu M, Chatani N. Chem Asian J. 2012; 7:1357. [PubMed: 22442050] For select Minisci type-pathways, see:(f) Jin J, MacMillan DWC. Nature. 2015; 525:87. [PubMed: 26308895] (g) Gianatassio R, Kawamura S, Eprile CL, Foo K, Ge J, Burns AC, Collins MR, Baran PS. Angew Chem Int Ed. 2014; 53:9851.(h) O'Hara F, Blackmond DG, Baran PS. J Am Chem Soc. 2013; 135:12122. [PubMed: 23859263]
3. For select 2-pyridyl zinc reagents, see:(a) Cornella J, Edwards JT, Qin T, Kawamura S, Wang J, Pan CM, Gianatassio R, Schmidt M, Eastgate MD, Baran PS. J Am Chem Soc. 2016; 138:2174. [PubMed: 26835704] (b) Colombe JR, Bernhardt S, Stathakis C, Buchwald SL, Knochel P. Org Lett. 2013; 15:5754. [PubMed: 24156393] (c) Luzung MR, Patel JS, Yin J. J Org Chem. 2010;

75:8330. [PubMed: 21047088] For select 2-pyridyl boron reagents, see:(d) Dick GR, Woerly EM, Burke MD. Angew Chem Int Ed. 2012; 51:2667.(e) Sakashita S, Takisawa M, Sugai J, Ito H, Yamamoto Y. Org Lett. 2013; 15:4308. [PubMed: 23952320] (f) Billingsley KL, Buchwald SL. Angew Chem Int Ed. 2008; 47:4695.For 2-pyridyl tin reagents, see:(g) Littke AF, Schawarz L, Fu GC. J Am Chem Soc. 2002; 124:6343. [PubMed: 12033863] (h) Bailey TR. Tetrahedron Lett. 1986; 27:4407.For 2-pyridyl aluminum reagents, see:(i) Chen X, Zhou L, Li Y, Xie T, Zhou S. J Org Chem. 2014; 79:230. [PubMed: 24308858]

4. For a select coupling reaction, see:Llaveria J, Leonori D, Aggarwal VK. J Am Chem Soc. 2015; 137:10958. [PubMed: 26292943]
5. For select Negishi and Kumada reactions, see:(a) Malhotra S, Seng PS, Koenig SG, Deese AJ, Ford KA. Org Lett. 2013; 15:3698. [PubMed: 23829418] (b) Fürstner A, Leitner A. Angew Chem Int Ed. 2003; 42:308.(c) Getmanenko YA, Tweig RJ. J Org Chem. 2008; 73:830. [PubMed: 18179227] For cross-electrophile reactions, see:(d) Everson DA, Buonomo JA, Weix DJ. Synlett. 2014; 25:233. [PubMed: 24795502]
6. Tyrrell E, Brookes P. Synthesis. 2003; 4:469.
7. (a) Han FS. Chem Soc Rev. 2013; 42:5270. [PubMed: 23460083] (b) Miyaura N, Suzuki A. Chem Rev. 1995; 95:2457.
8. (a) Martin R, Buchwald SL. Acc Chem Res. 2008; 41:1461. [PubMed: 18620434] (b) Billingsley K, Anderson KW, Buchwald SL. Angew Chem Int Ed. 2006; 45:3484.(c) Li L, Zhao S, Joshi-Pangu A, Diane M, Biscoe MR. J Am Chem Soc. 2014; 136:14027. [PubMed: 25226092] (d) Jouffroy M, Primer DN, Molander GA. J Am Chem Soc. 2016; 138:475. [PubMed: 26704168]
9. Laulhé S, Blackburn JM, Roizen JL. Org Lett. 2016; 18:4440. [PubMed: 27537216]
10. (a) Itoh T, Mase T. Tetrahedron Lett. 2005:3573.(b) Slagt VF, de Vries AHM, de Vries JG, Kellogg RM. Org Process Res Dev. 2009; 14:30.
11. Dreher SD, Dormer PG, Sandrock DL, Molander GA. J Am Chem Soc. 2008; 130:9257. [PubMed: 18582050]
12. (a) Yang CT, Zhang ZQ, Tajuddin H, Wu CC, Liang J, Liu JH, Fu Y, Czyzewska M, Steel PG, Marder TB, Liu L. Angew Chem Int Ed. 2012; 51:528.(b) Li Q, Liskey CW, Hartwig JF. J Am Chem Soc. 2014; 136:8755–8765. [PubMed: 24836159] (c) Fleury-Brégeot N, Presset M, Beaumard F, Colombel V, Oehlrich D, Rombouts F, Molander GA. J Org Chem. 2012; 77:10399. [PubMed: 23131122]
13. (a) Paul F, Pratt J, Hartwig JF. J Am Chem Soc. 1994; 116:5969.(b) Hartwig JF, Paul F. J Am Chem Soc. 1995; 117:5373.(c) Hartwig JF. Angew Chem Int Ed. 1998; 37:2046.
14. (a) Hartwig JF, Richards S, Barañano D, Paul F. J Am Chem Soc. 1996; 118:3626.(b) Hartwig JF. Inorg Chem. 2007; 46:1936. [PubMed: 17348724]
15. Reimann S, Ehlers P, Parpart S, Surkus A, Spannenberg A, Langer P. Tetrahedron. 2015; 71:5371.
16. (a) Haynes, WM., editor. CRC Handbook of Chemistry and Physics. 97th. CRC Press/Taylor & Francis; Boca Raton, FL: 2017. Internet Version(b) Reeve W, Erikson CM, Aluotto PF. Can J Chem. 1979; 57:2747.
17. Amatore C, Jutland A, Le Duc G. Chem Eur J. 2012; 18:6616. [PubMed: 22511514]
18. Yang CT, Zhang ZQ, Liu YC, Liu L. Chem Commun. 2011; 50:3904.
19. (a) Bordwell FG, Cornforth FJ. J Org Chem. 1978; 43:1763.(b) Olmstead WN, Margolin Z, Bordwell FG. J Org Chem. 1980; 45:3295.(c) Guthrie PJ, Cossar J, Klym A. Can J Chem. 1987; 65:2154.
20. Kotha S, Waghule GT, Shirbhate ME. Eur J Org Chem. 2014:984.

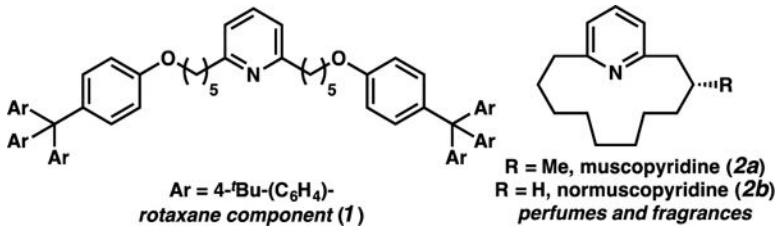
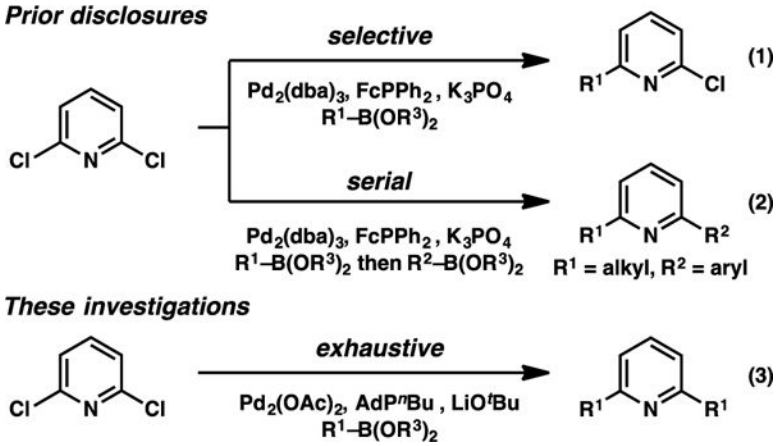
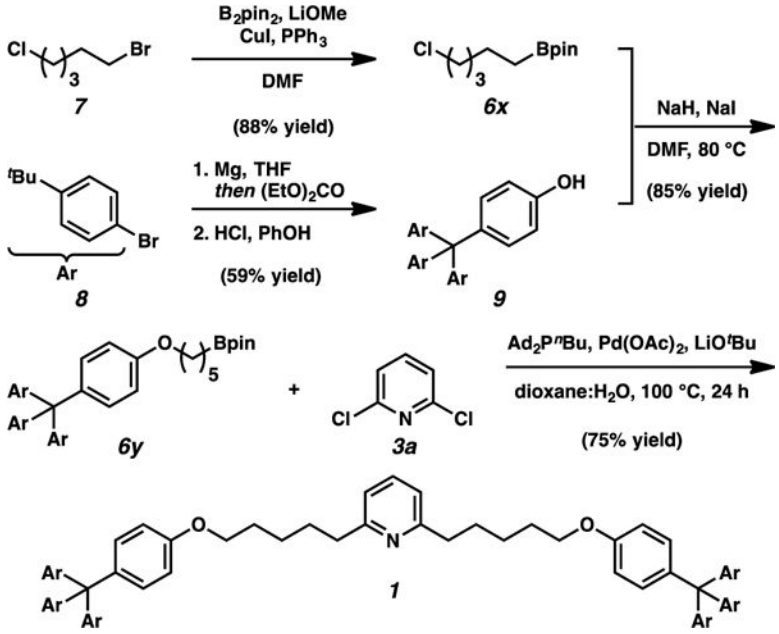


Figure 1.
Utility of the 2-alkylpyridines[1b,d]



Scheme 1.
Prior disclosures and these investigations

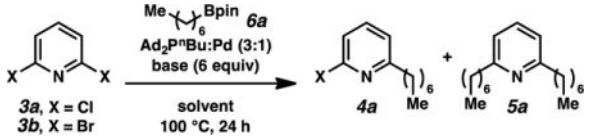


Scheme 2.

Application to the synthesis of a dumbbell shaped molecule for a rotaxane

Table 1

Influence of base, ligand, and palladium source on reaction outcome



entry	Pd source	X	equiv 6a	solvent	base	4a (%)[a]	5a (%)[a]
1	**$Pd(OAc)_2$**	**Cl**	**2.3**	**dioxane/H_2O**	**LiO^{t}Bu**	**nd[b]**	**94[c]**
2[d]	$Pd(OAc)_2$	Cl	2.3	dioxane/H_2O	LiO^{t}Bu	25%	5%
3[e]	$Pd(OAc)_2$	Cl	2.3	dioxane/H_2O	LiO^{t}Bu	52%	6%
4	$Pd_2(dba)_3$	Cl	2.3	PhMe	K_3PO_4	5	nd[b]
5	$Pd_2(dba)_3$	Cl	2.3	dioxane/H_2O	LiO^{t}Bu	5	90
6	$Pd(OAc)_2$	Cl	2.3	dioxane	LiO^{t}Bu	<5	nd[b]
7	$Pd(OAc)_2$	Cl	2.3	PhMe/H_2O	LiO^{t}Bu	40	<5
8	$Pd(OAc)_2$	Cl	2.3	PhMe	LiO^{t}Bu	<5	nd[b]
9	$Pd(OAc)_2$	Cl	2.3	dioxane/H_2O	CsF	29	<5
10	$Pd(OAc)_2$	Cl	2.3	dioxane	CsF	5	nd[b]
11	$Pd(OAc)_2$	Cl	2.3	dioxane/H_2O	Cs_2CO_3	72	7
12	$Pd(OAc)_2$	Cl	2.3	dioxane/H_2O	K_3PO_4	73	13
13	$Pd(OAc)_2$	Cl	2.3	dioxane/H_2O	NaO^{t}Bu	68	8
14	$Pd(OAc)_2$	Cl	2.3	dioxane/H_2O	KO^{t}Bu	39	31
15	$Pd(OAc)_2$	Cl	2.3	dioxane/H_2O	LiOMe	33	66
16	$Pd(OAc)_2$	Cl	1.0	dioxane/H_2O	LiO^{t}Bu	56	20
17	$Pd(OAc)_2$	Br	1.0	dioxane/H_2O	LiO^{t}Bu	nd[b]	48
18	$Pd(OAc)_2$	Br	2.3	dioxane/H_2O	LiO^{t}Bu	nd[b]	94

[a] Determined by ^{1}H NMR.

[b] nd = Not detected.

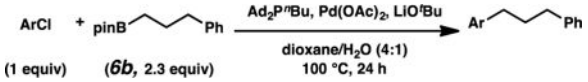
[c] Isolated yield.

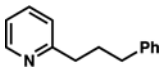
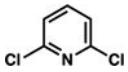
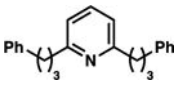
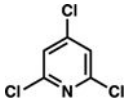
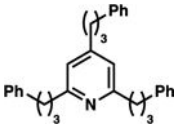
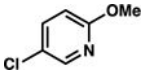
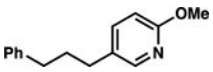
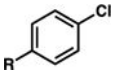
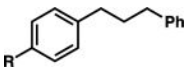
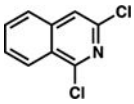
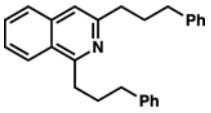
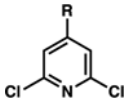
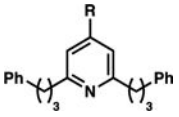
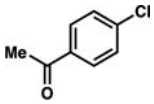
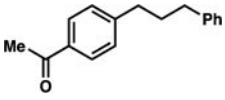
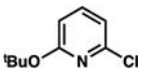
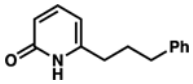
[d] $FcPPh_2$ used in place of Ad_2P^nBu.

[e] Tricyclohexylphosphine used in place of Ad_2P^nBu.

Table 2

A general procedure for Suzuki-Miyaura reactions of aryl chlorides



entry[a]	ArCl	product	yield (%)[b]
1[c]			***5b***, 81
2			***5c***, 95
3[d]			***5d***, 82
4[c,e]			***5e***, 98
5[e,f] 6[e,f]			***5f***, 90 ***5g***, 90
7[g]			***5h***, 84
8 9			***5i***, 52 ***5j***, 96
10[c,d]			***5k***, 18
11[e,h]			***5l***, 99

[a]General reaction conditions: 1.0 equiv aryl chloride, 0.105 M dioxane/H_2O (4:1), 2.3 equiv R^2Bpin, 1 mol % $Pd(OAc)_2$, 3 mol % Ad_2P^nBu, 6.0 equiv LiO^tBu, 24 h, 100 °C.

[b]Isolated yield.

[c]2 mol % $Pd(OAc)_2$, 6 mol % AdP^nBu.

[d]3.5 equiv R^2Bpin, 9.0 equiv LiO^tBu.

[e] 1.5 equiv R^2Bpin, 3.0 equiv LiO^{t}Bu.

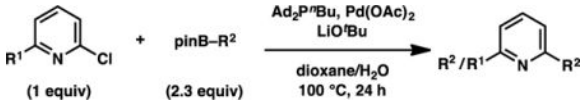
[f] 20 h.

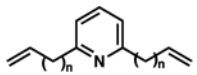
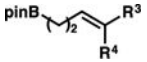
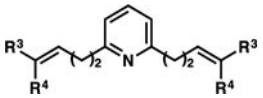
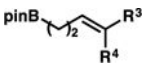
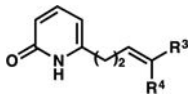
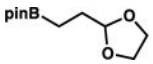
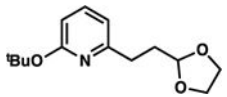
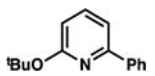
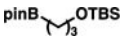
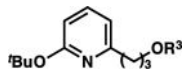
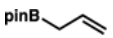
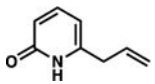
[g] 16 h.

[h] Isolated after reaction with trifluoroacetic acid.

Table 3

Functional group tolerance in disclosed Suzuki-Miyaura reactions



entry[a]	R[1]	organoboron		product	yield (%)[b]
1 2	Cl Cl				***5m***, 90 ***5n***, 85
3[c] 4[d]	Cl Cl				***5o***, 44 ***5p***, 45
5[c,e,f] 6[d,e,f]	*t*BuO *t*BuO				***5q***, 85 ***5r***, 84
7[f]	*t*BuO				***5s***, 90
8[g]	*t*BuO				***5t***, 99
9[f] 10[g]	*t*BuO *t*BuO				***5u***, 84 ***5v***, 89
11[e,i]	*t*BuO				***5w***, 47

[a] General reaction conditions: 1.0 equiv aryl chloride, 0.105 M dioxane/H_2O (4:1), 2.3 equiv R^2Bpin, 1 mol % $Pd(OAc)_2$, 3 mol % Ad_2P^nBu, 6.0 equiv LiO^tBu, 24 h, 100 °C.

[b] Isolated yield.

[c] Pinacol boronic ester and product have isomeric ratios of >19:1 *E*:*Z*.

[d] Pinacol boronic ester and product have isomeric ratios of >19:1 *Z*:*E*.

[e] Isolated after reaction with trifluoroacetic acid.

[f] 1.5 equiv R^2Bpin, 3.0 equiv LiO^tBu.

[g] 1.5 equiv R^1Bpin, 3.0 equiv K_3PO_4, no LiO^tBu.

[h] 1.5 equiv PhB(OH)2, no R^2Bpin, 3.0 equiv LiO^tBu, 18 h.

[i] 4.0 equiv CsF, no LiO^tBu.