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From High-Throughput Catalyst Screening to Reaction Optimization: Detailed Investigation of Regioselective Suzuki Coupling of 1,6-Naphthyridone Dichloride

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Abstract:

Efficient catalyst systems and reaction protocols were discovered for the regioselective Suzuki coupling of 1,6-naphthyridone dichloride through high-throughput experimentation. With $Pd_2(dba)_3 \cdot CHCl_3$ as the precatalyst, either $(2\text{-MeO-Ph})_3P$ or IMes·HCl afforded greater than 95% conversion to the coupling products with up to 92% desired regioselectivity. DMF/K_3PO_4 was found to be the most effective combination of solvent and base. The concentration profiles of reactants and products indicated that, with the regioselective catalyst, the first coupling step at one of the two competitive reactive centers was 10 times faster than the second coupling step at the other reactive center, resulting in high regioselectivity of the desired monoadduct.

Introduction

Carbon−carbon bond formation via the Suzuki cross-coupling reaction has been widely employed in the preparation of active pharmaceutical ingredients due to the broad scope of reaction, accessibility of the substrates, and environmentally benign waste treatment.[1] Recent advances in this field have resulted in catalysts with greatly enhanced reactivity, increasing the range of less reactive substrates that can participate in this transformation. In contrast, far less effort has been exerted towards developing catalytic conditions that can offer regioselectivity as well as reactivity.[2] Successful development of this type of technology would expand the scope of the Suzuki reaction to include inexpensive or readily prepared polyhalogenated aromatic compounds which could be used for the preparation of more complex molecular structures.

A recent review on various types of metal-catalyzed cross-coupling reactions by Schröter et al. includes a broad coverage on multiple halogenated aromatic heterocycles containing heteroatoms, such as nitrogen, oxygen, and sulfur.[3] Three major factors contribute to the regioselectivity of a cross-coupling reaction on a dihalogenated heterocycle: first, coupling at the most electrophilic position is favored if the oxidative addition is the rate-determining step; second, coupling at a position will be favored if there exists a neighboring heteroatom, such as N or O, which can facilitate the oxidative addition step by coordinating to Pd(0); third, a less hindered position is usually favored due to the more favorable steric environment around the metal in both the oxidative addition and transmetallation steps. That being established, process chemists are often still faced with the challenge of distinguishing between multiple sites in a polyhaloaromatic substrate with little obvious chemical difference between the reactive centers.

Regioselective cross-couplings of multisubstituted aryl chlorides with boronic acids can provide an efficient route to prepare disubstituted aryl compounds if the monocoupling step is highly selective and a second functional group can be introduced at a later stage. However, very often the chemical environments of two or more competitive reactive centers are not differentiated enough, and it is difficult to find reaction conditions that will afford the monoadduct exclusively. As an alternative solution, most selective monocoupling reactions involve in the preparations of chemically differentiated substrates, for example, chloro substrates with an I or Br in the desired reactive center that will be coupled first. Friesen et al. reported that 7-chloro-4-iodoquinoline undergoes cross-coupling reactions with various aryl boronic acids to give almost exclusively monoadducts.[4] But the preparation of differentiated substrates adds complexity to the synthesis and is often not feasible with some substrates. One would prefer to use the catalyst and reaction conditions as the source of selectivity, rather than the substrate. With the large armory of ligands currently available, discovering catalysts and conditions for highly selective cross-coupling of minimally differentiated substrates appears feasible. In order to do so, one must be able to explore a large volume of reaction space. Therefore, we utilize high-throughput

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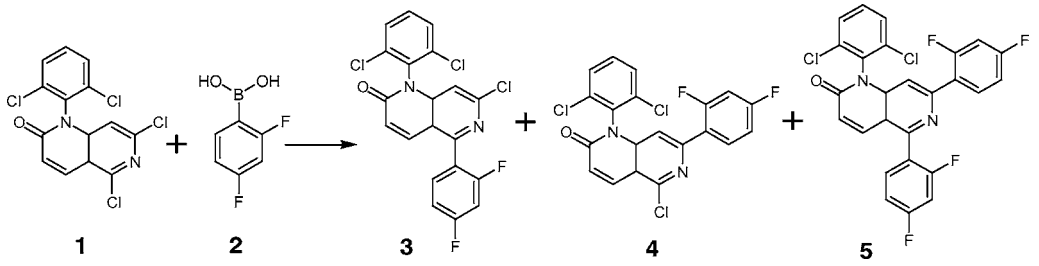
Scheme 1. **Suzuki Cross-Coupling Reaction between 1,6-Naphthyridone Dichloride (1) and 2,4-Difluorophenylboronic Acid (2)**



experimentation technologies to screen catalysts and conditions. Recently, we disclosed an efficient and cost-effective synthesis route for the synthesis of trisubstituted 1,6-naphthyridones through a highly regioselective Suzuki cross-coupling step.[5] Herein we report our further improvement and detailed investigation of the regioselective cross-coupling between 1,6-naphthyridone dichloride (**1**) and 2,4-difluorophenylboronic acid (**2**) (Scheme 1).

As a class, 1,6-naphthyridones have been prevalent in many anti-infective agents and kinase inhibitors. The 1,6-naphthyridone (**3**) is a key intermediate en route to a p38 mitogen-activated protein (MAP) kinase inhibitor.[5] Accordingly, an efficient means of preparing **3** from **1** and **2** was desired.

Results and Discussion

Screening of Catalyst and Reaction Parameters. The dichloride **1** was prepared by a recently disclosed method.[5] Our objective was to obtain monoadduct **3** in a yield as high as possible so that a simple isolation step, such as recrystallization, could be used in a manufacture process without resorting to chromatography separation. Our initial attempt was employing $Pd(OAc)_2/Ph_3P$ as the catalyst. Subjecting a 1:1.2 mixture of **1** and **2**, respectively, to classic reaction conditions (K_3PO_4, IPA, 100 °C for 3 h) yielded a 2:1 mixture of monoadduct **3** and bis-adduct **5** at 93% conversion. Further optimization on reaction conditions for this catalyst system was not able to improve the conversion and monoadduct selectivity simultaneously.

However, the initial result was encouraging. With the hope that some ligands with fine-tuned geometric and/or electronic properties may selectively afford the desired monoadduct, a broad catalyst screening was conducted. Approximately 80 commercially available ligands were carefully selected, including N-heterocyclic carbenes (NHCs), Buchwald's type biphenyl phosphines, Degussa's cataCXium phosphines, triaryl or -alkyl monodentate phosphines, ferrocenyl phosphines, and some achiral bidentate phosphines. Each type of ligand includes analogues with subtly changed geometric and/or electronic properties. Some of the ligand structures are depicted in Figure 1. Since the Pd-catalyzed reactions have many variables, besides the ligands, important variables that may interact with each other include solvent, base, precatalyst, ligand-to-palladium (L/Pd) ratio, Pd loading, and stoichiometry of **1**:**2**, as well as reaction temperature. To explore the combinations of all these possible interactions, the number of reactions to run is huge, and a substantial amount of starting material is required. However, for a complicated pharmaceutical intermediate, such as compound **1**, at its early development stage, the initial amount available for catalyst screening is limited. Therefore, as our high-throughput catalyst screening protocol, we screened each ligand in combination with four solvents (DMF, toluene, THF, dioxane, or IPA) and four bases (KF, K_3PO_4, K_2CO_3, Cs_2CO_3) under typical literature conditions. After the initial screens, the lead ligands were identified and optimized with further reaction parameters.

Starting with a 1:1.3 mixture of **1** and **2**, respectively, the reaction was carried out in two temperature stages: first at 50 °C for 6 h and then at 75 °C for an additional 8 h. HPLC samples were taken for analyses after each stage of reaction. The screening results for some representative ligands are summarized in Table 1. At 50 °C, >90% of the desired monoadduct selectivity was observed for several ligands, such as IMes·HCl, $(2\text{-MeO-Ph})_3P$, $(3\text{-MeO-Ph})_3P$, and $(4\text{-MeO-Ph})_3P$ (entries 1, 6−8); however, only $(2\text{-MeO-Ph})_3P$ afforded a reasonable conversion of 79%. At 75 °C, improved conversions were observed for all ligands; however, much worse monoadduct selectivities were observed for most ligands. For example, for X-Phos and S-Phos,

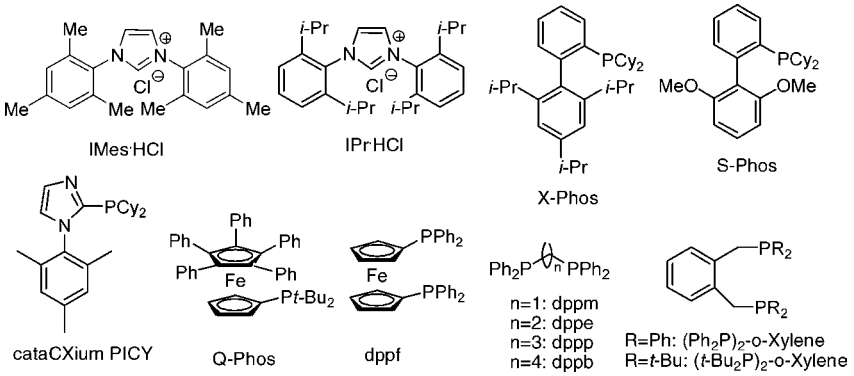


Figure 1. **Structures of some ligands with abbreviations.**

Table 1. **Ligand Effects**[a]

entry	ligand	results after temp profile A[b] conv %[d]	results after temp profile A[b] product ratio (**3:4:5**)[e]	results after temp profile B[c] conv %	results after temp profile B[c] product ratio (**3:4:5**)
1	IMes·HCl	20	100:0:0	78	95:3:2
2	IPr·HCl	42	82:3:15	88	72:0:28
3	S-Phos	73	51:0:49	78	36:0:64
4	X-Phos	22	58:0:42	65	31:0:69
5	cataCXium PICY	n/a	n/a	87	39:0:61
6	(2-MeO-Ph)$_3$P	79	91:5:4	98	77:0:23
7	(3-MeO-Ph)$_3$P	28	93:7:0	72	72:17:11
8	(4-MeO-Ph)$_3$P	17	95:5:0	54	81:14:5
9	(2,4,6-(MeO)$_3$-Ph) $_3$P	6	100:0:0	13	92:8:0
10	(3,5-Me$_2$-Ph)$_3$P	16	92:8:0	66	83:10:7
11	(4-MeO-3,5-Me$_2$-Ph)$_3$P	38	91:9:0	89	78:8:13
12	(2-furyl)$_3$P	56	88:12:0	58	87:13:0
13	(mesityl)$_3$P	5	88:12:0	8	86:14:0
14	Ph$_3$P	40	86:14:0	89	67:14:19
15	(4-F-Ph)$_3$P	25	84:16:0	65	55:32:13
16	PhP(PhSO$_3$K)$_2$·2H$_2$O	36	86:14:0	86	64:11:25
17	*n*-BuP(1-adamantyl)$_2$	82	85:8:7	98	75:0:25
18	(*t*-Bu)$_3$P·HBF$_4$	86	81:6:13	96	74:0:26
19	Cy$_3$P·HBF$_4$	6	73:27:0	18	65:35:0
20	Q-Phos	77	78:13:9	98	69:0:31
21	dppf	5	100:0:0	69	79:0:21
22	(Cy$_2$P)$_2$Me	n/a	n/a	80	82:4:14
23	1,2-(Cy$_2$P)$_2$Et	n/a	n/a	69	80:11:9
24	1,3-(Cy$_2$P)$_2$Pr	n/a	n/a	67	75:16:9
25	dppm	n/a	n/a	32	81:15:4
26	dppe	n/a	n/a	52	84:11:5
27[f]	dppp	n/a	n/a	4	77:23:0
28	dppb	n/a	n/a	56	84:8:8
29	1,2-(Ph$_2$P)$_2$benzene	n/a	n/a	34	87:4:9
30	(Ph$_2$P)$_2$-*o*-xylene	n/a	n/a	58	81:12:7
31	(*t*-Bu$_2$P)$_2$-*o*-xylene	n/a	n/a	26	85:10:5
32	no ligand	<1	100:0:0	<1	100:0:0

[a] Conditions: dichloride **1** (3.6 mg, 10 μmol), 2.0 mol % Pd$_2$(dba)$_3$·CHCl$_3$, 4,4′-dimethylbiphenyl (5 μmol) were added as the internal standard for HPLC assay; entries 1−20, boronic acid **2** (1.3 equiv), monodentate ligands, L/Pd = 2.0, K$_3$PO$_4$ (2.0 equiv), 500 μL of DMF; entries 21−31, boronic acid **2** (1.1 equiv), bidentate ligands, L/Pd = 1.1, Cs$_2$CO$_3$ (2.0 equiv), 200 μL of toluene. [b]Temp profile A: 50 °C 6 h. [c]Temp profile B: 50 °C 6 h and 75 °C 8 h. [d]Conv % defined as (**3**+**4**+**5**)/(**1**+**3**+**4**+**5**), average of two runs, determined by HPLC. (A rigid definition of conv % should be (**3**+**4**+**5**)/$\mathbf{1}_{t=0}$. The average material balance from the total amounts of **1**, **3**, **4**, and **5** is 12.0 ± 1.0 μmol for 48 reactions with 24 ligands and 2 repeats. Since we were not able to quantify every impurity for such micromole-scale reactions for each catalyst, we used the normalized definition as an approximation. This normalized definition was applied throughout this paper unless otherwise footnoted. For the ligands (2-MeO-Ph)$_3$P and IMes·HCl, no noticeable side reactions related to **1** were observed.) [e]Product ratio defined as **3:4:5**, in molar ratio, average of two runs, determined by HPLC. [f]Two more repeated runs with a freshly purchased ligand bottle.

approximately 1:2 mixtures of monoadduct **3** and bis-adduct **5** were observed (entries 3 and 4). Some ligands such as *n*-BuP(1-Adamantyl)$_2$, (*t*-Bu)$_3$P·HBF$_4$, and Q-Phos are very catalytically active for the coupling reaction, giving 96−98% conversions to the coupling products but with poor regioselectivities (entries 17−18, 20). However, IMes·HCl was an exception in that the conversion to the coupling products was improved to 78%, while the selectivity to the desired monoadduct **3** was still up to 95% at 75 °C (entry 1). It is worth noting that for (2-MeO-Ph)$_3$P, (3-MeO-Ph)$_3$P, and (4-MeO-Ph)$_3$P, despite that they afford similar regioselectivity, (2-MeO-Ph)$_3$P is a more catalytically active ligand than (3-MeO-Ph)$_3$P and (4-MeO-Ph)$_3$P (compare entry 6 to entries 7 and 8). On the other hand, for IMes·HCl and IPr·HCl, despite that they have similar catalytic activities, IMes·HCl is a much more regioselective ligand than IPr·HCl for monoadduct **3** (compare entry 1 to entry 2). These examples demonstrate that even a very minor variation in a ligand structure can unfavorably change either the reactivity or the regioselectivity of a catalyst. The results of some achiral bidentate ligands are also listed in Table 1. Bidentate phosphines could form chelating complexes with a Pd precursor, and the resulting different bite angles could provide additional selectivity which could not be offered by monodentate phosphines. It turned out that, indeed, most bidentate phosphine ligands provided 75% to 87% monoadduct selectivity (entries 21−31). However, compared to monodentate phosphines, in general, lower conversions were obtained under the same reaction conditions, indicating that these were not very active catalyst systems.

Table 2. **Solvent and Base Effects on Conversion**[a]

entry	solvent	percentage conversion by type of base: KF	Cs_2CO_3	K_3PO_4	K_2CO_3
1	toluene	48	79	76	57
2	dioxane	49	66	81	68
3	DMF	42	69	95	79
4	THF	62	96	96	93

[a] Conditions: dichloride **1** (3.6 mg), boronic acid **2** (1.1 equiv), 2.0 mol % Pd$_2$(dba)$_3$·CHCl$_3$, 8.0 mol % (2-MeO-Ph)$_3$P, 200 μL of solvent, 60 °C 20 h.

Table 3. **Solvent and Base Effects on Regioselectivity**

entry	solvent	product ratio (**3:4:5**) by type of base: KF	Cs_2CO_3	K_3PO_4	K_2CO_3
1	toluene	82:15:3	81:12:7	80:13:7	81:15:4
2	dioxane	84:13:3	84:12:5	81:10:9	82:12:6
3	DMF	90:10:0	83:17:0	87:4:9	89:5:6
4	THF	85:11:4	82:5:13	79:4:17	81:8:11

[a] Conditions: dichloride **1** (3.6 mg), boronic acid **2** (1.1 equiv), 2.0 mol % Pd$_2$(dba)$_3$·CHCl$_3$, 8.0 mol % (2-MeO-Ph)$_3$P, 200 μL of solvent, 60 °C 20 h.

As previously pointed out, there are many interacting factors for the Pd-catalyzed cross-coupling reactions. For example, for the Pd$_2$(dba)$_3$·CHCl$_3$/(2-MeO-Ph)$_3$P catalyst system, the solvent and base effects on the conversion and regioselectivity are summarized in Tables 2 and 3, respectively. The choice of solvent can greatly affect the extent of conversion; for example, conversions ranging from 57% to 93% were observed when the solvent was varied, K_2CO_3 was used as the base, and other reaction conditions were kept the same (Table 2, K_2CO_3 series). THF proved to be the most effective solvent, affording the highest conversion in each category of base tested (Table 2, entry 4). The solvent effect on the regioselectivity was not pronounced, and less than 8% variation was observed within each category of base (Table 3). The base effect on the reaction was highly dependent on the choice of solvent. For example, with DMF as the solvent, using K_3PO_4 as the base resulted in 95% conversion compared to 42% conversion when KF was used as the base (Table 2, entry 3). Several other combinations of solvent and base, such as THF/K_3PO_4, THF/K_2CO_3, THF/Cs_2CO_3, dioxane/K_3PO_4, and toluene/Cs_2CO_3, proved to be

Table 4. **Solvent and Base Effects for $Pd_2(dba)_3$·$CHCl_3$/IMes·HCl Catalyst**[a]

entry	solvent/base	conv %	product ratio (**3:4:5**)
1	DMF/K_3PO_4	88	90:10:0
2	DMF/K_2CO_3	96	92:4:4
3	DMF/Cs_2CO_3	44	100:0:0
4	toluene/ Cs_2CO_3	22	87:13:0
5	toluene/ K_3PO_4	41	86:14:0
6	THF/K_3PO_4	93	73:16:11

[a] Conditions: dichloride **1** (3.6 mg), boronic acid **2** (1.1 equiv), 2.0 mol % $Pd_2(dba)_3$·$CHCl_3$, 8.0 mol % IMes·HCl, 200 μL of solvent, 80 °C 20 h.

Table 5. **Precatalyst Effects on Conversion and Regioselectivity**[a]

entry	precatalyst	ligand	conv %	product ratio (**3:4:5**)
1	$Pd(OAc)_2$	(2-MeO-Ph)$_3$P	49	90:4:6
2	[Pd(allyl)Cl]$_2$	(2-MeO-Ph)$_3$P	91	88:5:7
3	$PdCl_2$	(2-MeO-Ph)$_3$P	94	90:2:8
4	$Pd_2(dba)_3$·$CHCl_3$	(2-MeO-Ph)$_3$P	94	88:3:9
5[b]	$Pd(OAc)_2$	IMes·HCl	71	96:2:2
6[b]	[Pd(allyl)Cl]$_2$	IMes·HCl	84	96:2:2
7[b]	$PdCl_2$	IMes·HCl	48	98:1:1
8[b]	$Pd_2(dba)_3$·$CHCl_3$	IMes·HCl	96	97:0:3
9[c]	$Pd(OAc)_2$	IMes·HCl	95	96:2:2

[a] Conditions: dichloride **1** (72 mg), boronic acid **2** (1.1 equiv), 4.0 mol % Pd, L/P = 2.0, K_3PO_4 (2.0 equiv), 3 mL of DMF, 50 °C 16 h for (2-MeO-Ph)$_3$P, 75 °C 12 h for IMes·HCl. [b]1.3 equiv of boronic acid **2**. [c]1.6 equiv of boronic acid **2**; isolated yield, 94%.

effective for the reaction. However, DMF/K_3PO_4 was found to be the most effective pair, affording a 95% conversion to the coupling products with a product ratio (**3**:**4**:**5**) of 87:4:9, respectively. Certainly, the choice of solvent and base was dependent on the catalyst. For the $Pd_2(dba)_3$·$CHCl_3$/IMes·HCl system, the best combinations were DMF/K_3PO_4 and DMF/K_2CO_3 (Table 4, entries 1 and 2), and all other combinations of solvent (DMF, toluene, THF, dioxane) and base (KF, K_2CO_3, K_3PO_4, Cs_2CO_3) resulted in lower conversion and/or poorer regioselectivity. Although we find that, for this specific reaction, DMF is a better solvent for many monodentate phosphines, and toluene is a better solvent for many bidentate phosphines, in general we are not able to observe a trend for the choice of solvent with respect to all ligands we screened.

Next, for the lead ligands, (2-MeO-Ph)$_3$P and IMes·HCl, several precatalysts were tested for their effectiveness. The results are summarized in Table 5. $Pd_2(dba)_3$·$CHCl_3$, $PdCl_2$, and [Pd(allyl)Cl]$_2$ were found to be equally effective when (2-MeO-Ph)$_3$P was used as the ligand (Table 5, entries 2−4), while $Pd_2(dba)_3$·$CHCl_3$ was found to be the most effective Pd source when IMes·HCl was used as the ligand (entry 8). In this case, a 96% conversion to the coupling products with 97% monoadduct selectivity was obtained. $Pd(OAc)_2$ was found to be less effective than $Pd_2(dba)_3$·$CHCl_3$ in terms of both reaction rate and conversion (compare entries 1−4, 5−8). An excess of boronic acid **2** was required to achieve a higher conversion of dichloride **1** because of the degradation of boronic acid **2** to 1,3-difluorobenzene as a side reaction (entry 9).

Table 6. **L/Pd Ratio Effects on Conversion and Regioselectivity**[a]

entry	ligand	L/Pd ratio	conv %	product ratio (**3:4:5**)
1	(2-MeO-Ph)$_3$P	0.5	89	92:3:5
2	(2-MeO-Ph)$_3$P	1.0	96	90:2:8
3	(2-MeO-Ph)$_3$P	1.5	94	89:3:8
4	(2-MeO-Ph)$_3$P	2.0	94	88:3:9
5	(2-MeO-Ph)$_3$P	2.5	93	87:4:9
6	(2-MeO-Ph)$_3$P	3.0	92	89:5:6
7[b]	IMes·HCl	1.0	96	97:0:3
8[b]	IMes·HCl	2.0	96	97:0:3
9[b]	IMes·HCl	3.0	95	97:1:2

[a] Conditions: dichloride **1** (72 mg), boronic acid **2** (1.1 equiv), 2.0 mol % $Pd_2(dba)_3$·$CHCl_3$, K_3PO_4 (2.0 equiv), 3 mL of DMF, 50 °C 16 h for (2-MeO-Ph)$_3$P, 75 °C 12 h for IMes·HCl. [b]1.3 equiv of boronic acid **2**.

For monodentate ligands, it is generally assumed that lower L/Pd ratios favor higher reactivity via coordinatively unsaturated metal species, while higher L/Pd ratios favor catalyst stability by inhibition of palladium black formation. Additionally, when using $Pd_2(dba)_3$·$CHCl_3$ as a precursor, the dibenzylidene ligands are known to participate in complex equilibria with added monodentate phosphines, which can also have an effect on both catalyst activity and stability. Accordingly, for the top two ligands, (2-MeO-Ph)$_3$P and IMes·HCl, L/Pd ratios ranging from 1.0 to 3.0 were examined and the results are listed in Table 6. It appeared that there was no significant impact of L/Pd ratio on both catalytic activity and regioselectivity for the (2-MeO-Ph)$_3$P/$Pd_2(dba)_3$·$CHCl_3$ catalyst over the L/Pd ratio range from 1.0 to 3.0 (entries 1−6). A slightly better result was obtained with L/Pd = 1.0 (entry 2, 96% conversion with 90% monoadduct selectivity). A similar trend was also observed for IMes·HCl. Up to 96% conversions and monoadduct selectivities were obtained at an L/Pd ratio between 1.0 and 3.0 (entries 7−9).

DOE Optimization. After identifying the lead ligands and studying the effects of discrete reaction parameters, such as solvent, base, precatalyst, and L/Pd ratio, we decided to further optimize the reaction with the (2-MeO-Ph)$_3$P/$Pd_2(dba)_3$·$CHCl_3$ catalyst. Although the IMes·HCl/$Pd_2(dba)_3$·$CHCl_3$ catalyst gives slightly better monoadduct selectivity, we have several other considerations: first, (2-MeO-Ph)$_3$P is a cheaper ligand compared to IMes·HCl and is easily available in bulk quantity; second, (2-MeO-Ph)$_3$P gives a higher catalyst turnover number than IMes·HCl, and the reaction can be operated at milder conditions; third, we find that, for the IMes·HCl/$Pd_2(dba)_3$·$CHCl_3$ catalyst, it requires a greater excess amount of boronic acid **2** to fully convert dichloride **1** to coupling products. The degradation of boronic acid **2** to 1,3-difluorobenzene is a major side reaction, and prolonged reaction time is not desirable. We will discuss this further in the next section Reaction Kinetic Profile.

In the next phase of reaction optimization, continuous reaction variables, such as catalyst loading, substrate concentration, stoichiometry of reactants, and reaction temperature, were investigated. These continuous variables are mathematically amenable to the design of experiment

Table 7. **Catalyst Loading and Substrate Concentration Effects**[a]

entry	mol % of $Pd_2(dba)_3{\cdot}CHCl_3$	concn (mol/L)	conv %	product ratio (**3:4:5**)
1[b]	0.5	0.1	86	91:3:6
2	1	0.1	98	89:2:9
3	2	0.1	97	88:3:9
4[c]	2	0.02	79	91:5:4

[a] Conditions: dichloride **1** (36 mg), boronic acid **2** (1.1 equiv), K_3PO_4 (2.0 equiv), 1 mL of DMF, 50 °C 15 h. [b]50 °C 20 h. [c]5 mL of DMF, 50 °C 20 h.

methodology (DOE) for interacting factors. A quick examination of $Pd_2(dba)_3{\cdot}CHCl_3$ loading reveals that the catalyst loading can be reduced to 0.5 mol %, and it has only a very slight effect on the regioselectivity (Table 7, entries 1−3). Also, the effect of substrate concentration is primarily on the reaction conversion with only a very slight impact on regioselectivity (entries 3 and 4). Based on this knowledge, we only selected two important factors for our DOE study: (1) stoichiometry of dichloride **1** and boronic acid **2** and (2) reaction temperature.

On the basis of our previous screens, the stochiometry of dichloride **1** and boronic acid **2** is defined by the equivalents of **2:1**, in the range from 0.8 to 1.4, and the reaction temperature ranges from 35 to 65 °C. In our study, the Central Composite Uniform Precision quadratic model was applied with 2 factors, 3 responses (conversion, regioselectivity, and yield), and a total of 13 experiments. Our target is to maximize both conversion and regioselectivity simultaneously so that the final yield of monoadduct **3** is maximized. The resulting response surface models for conversion and monoadduct **3** selectivity were plotted in Figures 2 and 3, respectively. The statistical significance of each model is validated by its large F-statistic, very small *p*-value, and good R^2 value (see footnotes in Figures 2 and 3). As expected, the conversion and regioselectivity are closely related to the reaction temperature and stoichiometry of reactants. At a low temperature, lower conversion was obtained concomitant with higher regioselectivity, while, at a high temperature, higher conversion was obtained with lower regioselectivity. A similar trend was observed for the effect of reactant stoichiometry: with less equivalents of boronic acid **2**, higher regioselectivity was obtained. These trends are clearly presented by the opposite response surface directions in Figures 2 and 3. In the contour projection of conversion response model in Figure 2, from front to back, with color code changing from orange to red, the contour lines indicate that the conversion of dichloride **1** reaches above 90%, 95%, and 100%, respectively. Based on this model, if the reaction is operated at 40 °C, 1.03 equiv of boronic acid **2** are required for a 95% conversion of dichloride **1** and 1.18 equiv are required for a full conversion. An excess amount of boronic acid **2** is required due to its degradation to 1,3-difluorobenzene, and this will be discussed further in the next section. Similarly, in the contour projection of monoadduct **3** selectivity response model in Figure 3, from back to front, with color code changing from green to orange-red, the contour lines indicate that the regioselectivity is

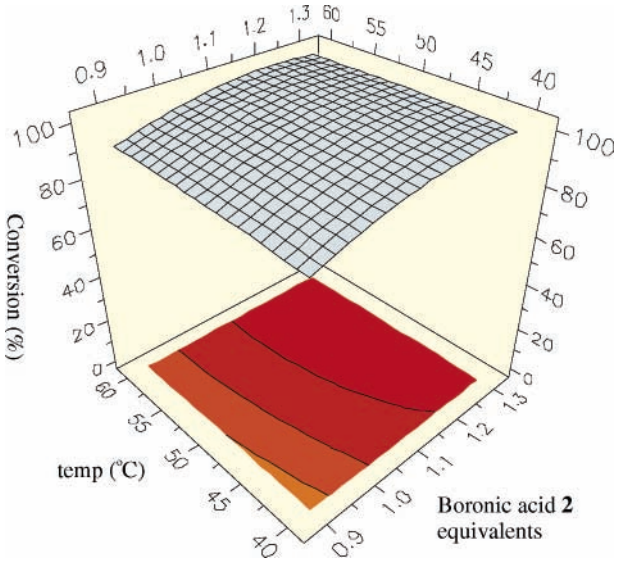


Figure 2. **Response surface model of dichloride 1 conversion with contour projection. From front to back, color code from orange to red, contour lines indicate crossing 90%, 95%, and 100% conversion. F-statistic, 75.4; *p*-value, 6.23 $\times 10^{-6}$; R^2, 0.982. Conditions: dichloride 1 (36 mg, 0.1 mmol), boronic acid 2 (0.8−1.4 equiv), 1.0 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, L = (2-MeO-Ph)$_3$P, L/Pd = 1.0, K_3PO_4 (2.0 equiv), 1 mL of DMF, 50 °C 14 h.**

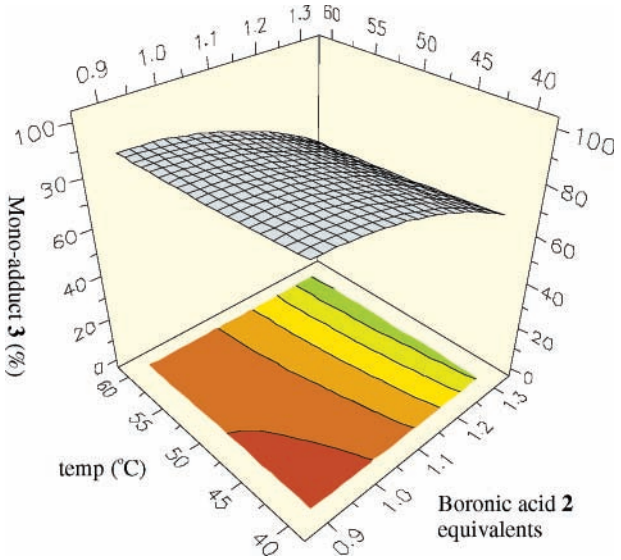


Figure 3. **Response surface model of monoadduct 3 selectivity with contour projection. From back to front, color code from green to orange-red, contour lines indicate crossing 70%, 75%, 80%, 85% to 90% regioselectivity. F-statistic, 47.3; *p*-value, 3.03 $\times 10^{-5}$; R^2, 0.971. Conditions: dichloride 1 (36 mg, 0.1 mmol), boronic acid 2 (0.8−1.4 equiv), 1.0 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, L = (2-MeO-Ph)$_3$P, L/Pd = 1.0, K_3PO_4 (2.0 equiv), 1 mL DMF, 50 °C 14 h.**

above 70%, 75%, 80%, 85%, and 90%, respectively. In order to achieve more than 90% regioselectivity, the reaction temperature needs to be controlled below 49 °C and the boronic acid needs to be below 1.04 equiv. Presented in Figure 4 is the response surface model of monoadduct **3** yield which is derived by multiplying conversion and regioselectivity. In its contour projection, the orange-red region is the operating region which could afford a >85% yield of

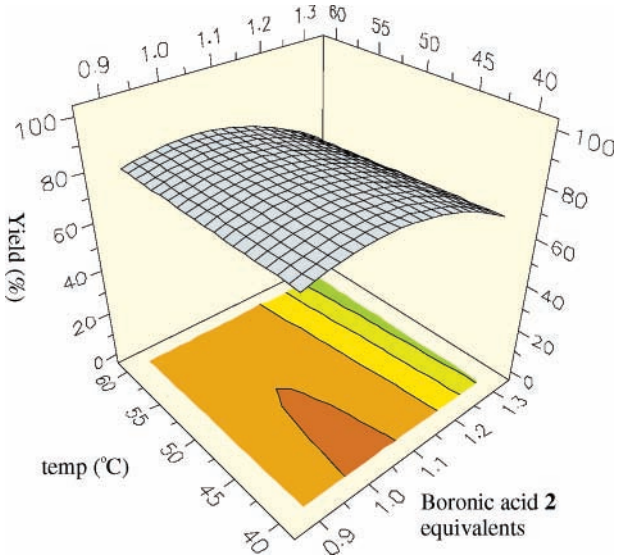


Figure 4. **Response surface model of monoadduct 3 yield with contour projection. From back to front, color code from green to orange-red, contour lines indicate reaching 70%, 75%, 80%, and 85% yield. F-statistic, 40.8; *p*-value, 4.97 $\times 10^{-5}$; R^2, 0.967. Conditions: dichloride 1 (36 mg, 0.1 mmol), boronic acid 2 (0.8−1.4 equiv), 1.0 mol % $Pd_2(dba)_3 \cdot CHCl_3$, L = (2-MeO-Ph)$_3$P, L/Pd = 1.0, K_3PO_4 (2.0 equiv), 1 mL of DMF, 50 °C 14 h.**

monoadduct **3**. The variables defined by this region are boronic acid equivalents from 0.98 to 1.08 and reaction temperatures from 40 to 48 °C. An optimal condition given by this model is to employ 1.04 equiv of boronic acid **2** and to carry out the reaction at 40 °C. Further demonstration runs under this improved conditions (0.1 M dichloride **1**, 1.04 equiv of boron acid **2**, 1 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 2 mol % (2-MeO-Ph)$_3$P, 2.0 equiv of K_3PO_4, 40 °C, 14 h) afforded an average of 98% conversion with a product ratio (**3:4:5)** of 92:3:5, respectively.

Reaction Kinetic Profile. In order to gain a better understanding of the competing reaction processes, we have investigated the concentration changes of dichloride **1**, monoadducts **3** and **4**, bis-adduct **5**, and 1,3-difluorobenzene over the course of the reaction. With our state-of-the-art liquid handling equipment, the reaction mixture could be sampled and quenched at specified time intervals using fully automated robot arms. Starting with a 1:1.3 mixture of dichloride **1** and boronic acid **2**, respectively, the results of our kinetic profiling experiment are plotted in Figure 5. The concentration profiles of **1**, **3**, **4**, and **5** show that the first step of the coupling reaction between **1** and **2** to form desired monoadduct **3** was very fast, with an average rate of 40 mM/h in the first hour, while the second step coupling to form bis-adduct **5** was relatively slow (average rate of 4 mM/h in the first hour). The rate to form undesired monoadduct isomer **4** was also slow, with an average rate of 2 mM/h in the first hour. However, isomer **4** was rapidly converted to bis-adduct **5** after its formation, and its accumulation was observed only in the first 2 h with a maximum of less than 5%. The fast generation and slow consumption of monoadduct **3** led to its accumulation in the first 2 h, and as a result, a maximum concentration of **3** was observed between the first and second hour. At a reaction time of 1 h, a 95% conversion of **1** was obtained with a **3:4:5** product ratio of approximately 86:5:9, respectively. Dichloride **1** was completely converted to either monoadduct **3** or bis-adduct **5** within 2 h, while the slow conversion of **3** to **5** continued for another ~10 h. At which point, the concentration of bis-adduct **5** leveled off, yielding a 1.6:1 ratio of **3** and **5**, respectively (Figure 5, arrow A). These observations indicate that careful control of reaction progress is important to achieve maximum conversion and regioselectivity. The extent to which one needs to control this will depend upon the rate of the second oxidative addition step.

After 12 h, assays of the reaction mixture indicated boronic acid **2** was still present, indicating that the reaction had stopped due to gradual catalyst degradation, not for lack of reagent. Up to this point, and for several hours thereafter, no evidence of 1,3-difluorobenzene was detected. However, approximately 6 h after conversion to **5** had stopped, the appearance of 1,3-difluorobenzene in the reaction mixture began to become evident (Figure 5, arrow B). In parallel to this kinetic profile experiment, we had conducted a control experiment containing all reagents except the palladium catalyst (Figure 6). In this profile, we observed a similar trend with regard to boronic acid degradation. The amount of 1,3-difluorobenzene did not become significant until approximately 6 h into the aging time (Figure 6, arrow C). Furthermore, the rate of 1,3-difluorobenzene formation appears to follow an exponential trend. Thus, it appears that the degradation of boronic acid **2** *does not require palladium catalysis* and appears to be an autocatalytic process with a long induction period. These results indicate that the degradation of boronic acid **2** can occur as a side reaction that is completely independent of the cross-coupling pathway. However, after comparing the profiles in Figures 5 and 6, it appears that the induction period does not begin until after the cross-coupling reaction has stopped.

Conclusion

In summary, efficient catalyst systems were discovered for the regioselective Suzuki cross-coupling of a poorly differentiated dichloroarene through high-throughput catalyst screening and reaction optimization. Two ligands, (2-MeO-Ph)$_3$P and IMes·HCl, were found to provide higher conversion and regioselectivity. While the IMes·HCl/$Pd_2(dba)_3 \cdot CHCl_3$ catalyst afforded 97% conversion to coupling products with up to 97% regioselectivity, the (2-MeO-Ph)$_3$P/$Pd_2(dba)_3 \cdot CHCl_3$ catalyst is a more robust and cost-effective system, which afforded >99% conversion to coupling products with up to 92% regioselectivity. The necessity to screen a broad range of discrete reaction parameters, such as ligands, solvents, and bases, and the DOE optimization of continuous reaction variables allowed for the discovery of catalysts and reaction conditions that require not only sufficient catalytic activity but also satisfying regioselectivity. With the (2-MeO-Ph)$_3$P/$Pd_2(dba)_3 \cdot CHCl_3$ catalyst, the concentration profiles of reactants and products showed that the first coupling step

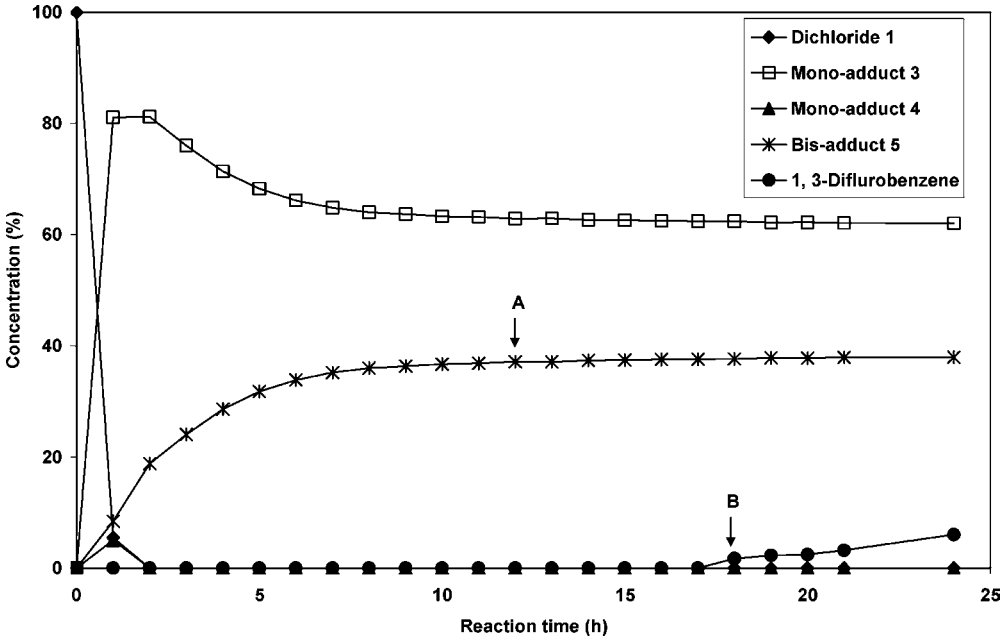


Figure 5. **Concentration changes of dichloride 1, monoadducts 3 and 4, bis-adduct 5 and 1,3-difluorobenzene vs reaction time. Conditions: dichloride 1 (72 mg, 200 μmol), boronic acid 2 (1.3 equiv), 2.0 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, L = $(2\text{-MeO-Ph})_3P$, L/Pd = 2.0, K_3PO_4 (2.0 equiv), 4 mL of DMF, 50 °C, 4,4′-dimethylbiphenyl (9 mg) as internal standard. Percentage of concentration [C] defined as $[C]_{t=t}/[1]_{t=0}$ for 1, 3, 4, and 5 and $[C]_{t=t}/[2]_{t=0}$ for 1,3-difluorobenzene.**

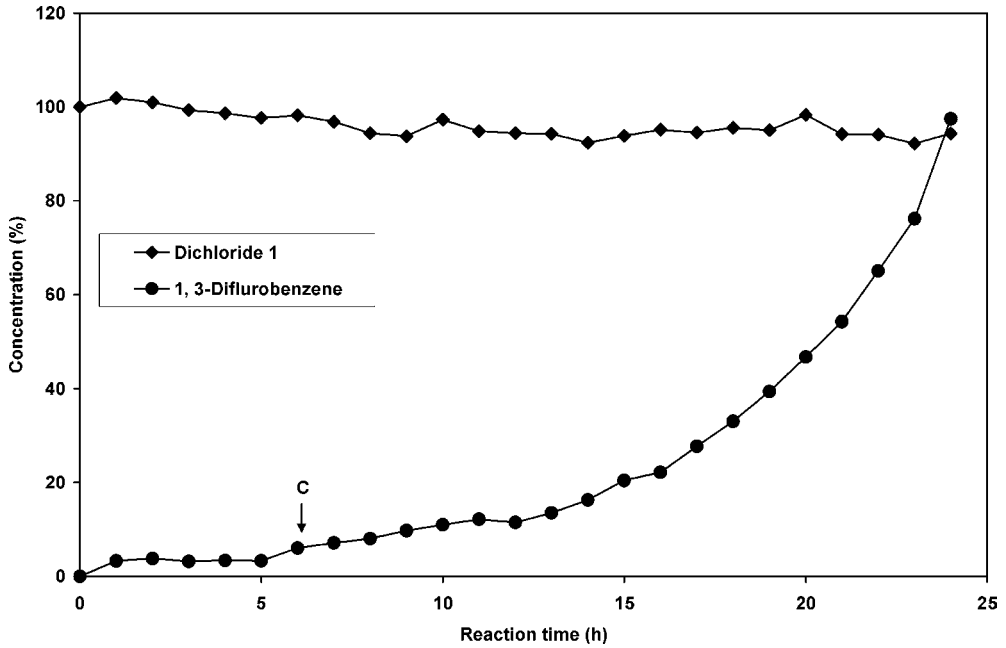


Figure 6. **Concentration changes of dichloride 1 and 1,3-difluorobenzene vs reaction time when no catalyst is present. Conditions: dichloride 1 (58 mg, 160 μmol), boronic acid 2 (1.3 equiv), K_3PO_4 (2.0 equiv), 4 mL of DMF, 50 °C, 4,4′-dimethylbiphenyl (9 mg) as internal standard. Percentage of concentration [C] defined as $[C]_{t=t}/[C]_{t=0 \text{ or } t=\infty}$.**

at one of the two competitive reactive centers was 10 times faster than the second coupling step at the other reactive center. The first step of the coupling reaction completed within 2 h under mild conditions, resulting in high regioselectivity of the desired monoadduct.

Experimental Section

All reactions were carried out under a N_2 atmosphere. All chemicals except dichloride **1** were obtained from commercial sources and used without further purification. Anhydrous solvents were used as purchased without further distillation throughout the entire experiment. All reactions were analyzed by reversed phase HPLC, conducted on an Agilent 1100 Series instrument with DAD using a 96-well plate auto sampler. The screening and scale-up procedures were carried out on the Cavro liquid handling robot deck with magnetic stirring and heating capabilities. Symyx Technology's software and hardware were used to conduct the entire screening experiments from library design, liquid and solid dispense, reaction heating and stirring, to HPLC

analysis for a 96-well reactor block.[6] Most pipetting jobs were conducted by the Cavro robot. An organic substance was usually charged as a stock solution, and an inorganic base was dispensed as slurry, usually in a dichloroethane suspension. Solid dispense by Powdernium robot was also used but was not as convenient as solution or slurry dispense.

In a typical screening procedure, a reactor block containing 96 disposable glass reaction vials (40 mm height × 8 mm diam) was dispensed with the ligands and precatalysts to be screened (4 mol % Pd loading relative to dichloride **1**) and aged at room temperature for 30 min to 1 h. A ligand-to-palladium ratio of 1.1 was employed for bidentate ligands, and that of 2.0, for monodentate ligands. The ligand and precatalyst were usually dissolved in a 2:1 toluene/dichloroethane mixture (DMF or MeOH was used instead of toluene to dissolve some ligands in salt forms). Dichloride **1** (3.6 mg, 10 μmol), 2,4-difluorophenylboronic acid (1 to 2 equiv), and base (2.0 equiv relative to boronic acid **2**) were then dispensed. The reaction mixture was concentrated down in a vacuum to remove all solvents from stock solutions or slurries. The solvents (200∼500 μL, THF, dioxane, toluene, or DMF) to be screened were added subsequently. The reaction block was then cap sealed and heated at the desired temperature for certain hours. The reaction was magnetically stirred at 600 rpm during the entire reaction period. At the end or in the middle of reaction, a small aliquot of the reaction mixture, usually 20 μL, was sampled by robot and quenched to 0.5 to 1 mL of acetonitrile to make HPLC samples. The scale-up procedure was similar to the screening procedure except the reaction was conducted in an 8 mL scintillation glass vial, and the chemicals were weighed and charged manually without the preparation of stock solutions or slurries. In the reaction profile studies, an aliquot of 20 μL of the reaction mixture was periodically sampled by the robot and quenched to 600 μL of acetonitrile to make HPLC samples. An internal standard (4,4′-dimethylbiphenyl) was added to the reaction mixture for the calculations of amounts of substances from HPLC analyses. Our DOE design and data analysis were carried out using the Intellichem Synthesis 3.65 software package.

The isolation, purification, and NMR spectra of mono-adduct **3**, isomer **4**, and bis-adduct **5** were previously reported.[5] The samples of reaction mixtures were analyzed by reversed phase HPLC (Agilent Zorbax Extend C-18 column, 3.5 μm, 4.6 mm × 75 mm) with a gradient method: 60% ACN/40% water to 95% ACN/5% water (0.1% H_3PO_4 buffer) in 5 min, held for 1.5 min, 2 min of post time. Flow rate: 1.5 mL/min, column temperature: 25 °C. Typical retention times are the following: 1.3 min (1,3-difluorobenzene); 2.1 min (dichloride **1**); 2.5 min (mono-adduct **3**); 3.6 min (isomer **4**); 3.7 min (bis-adduct **5**); 4.0 min (4,4′-dimethylbiphenyl).

(6) Bei, X.; Hagemeyer, A.; Volpe, A.; Saxton, R.; Turner, H.; Guram, A. S. *J. Org. Chem.* **2004**, *69*, 8628.

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