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Pd(0)-Catalyzed Decarboxylative Coupling and Tandem C−H Arylation/Decarboxylation for the Synthesis of Heteroaromatic Biaryls

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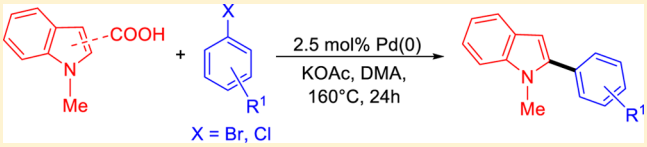
Supporting Information

ABSTRACT: An effective Pd(0) carbene complex was successfully employed in the decarboxylative coupling of the heteroaromatic carboxylic acids (imidazo[1,2-*a*]pyridine and isoxazole) with aryl halides. For carboxyindoles, either decarboxylative coupling or tandem C−H arylation and decarboxylation occurred, leading to the formation of C2-monoarylated indoles.



Heteroaromatic biaryls have attracted much attention because of their significant commercial value. Arylated indoles, for example, exhibit broad pharmacological properties in numerous therapeutic agents and natural products.[1,2] Metal-catalyzed Suzuki-type cross-coupling reactions have been widely used in preparing biaryls.[2] However, stoichiometric organometallic substrates are required which give rise to availability problems, metal waste, and the need for additional synthetic steps. Recently, C−H arylation[3−6] and decarboxylative coupling[7−9] have emerged as appealing approaches for the construction of biaryls. Successive advances in C−H arylation have allowed a broad range of heteroaromatic biaryls to be synthesized,[10−13] but poor regioselectively is a significant limitation of these procedures. Decarboxylative coupling is an equally interesting approach for preparing heteroaromatic biaryls because the carboxyl group can direct the regioselectivity and the only waste product from the reaction is CO_2. However, this approach is still largely unexplored,[14−23] and reports on simple monometallic Pd-based systems for the intermolecular coupling of heteroaromatic carboxylic acids with aryl halides are scarce.[14−17] Forgione pioneered the synthesis of several heteroaromatic biaryls via decarboxylative couplings with $Pd[P(t\text{-}Bu)_3]_2$ as the catalyst.[14,16] A number of different heteroaromatic biaryls can successfully be achieved with the use of aryl bromides. However, the reaction was found to be limited by the specificity of the position of the carboxyl group on the heterocyclic ring. While 2-fuoric acid can be regioselectively C2-monoarylated, the analogous conversion of 3-fuoric acid was not able to be observed. Miura's work on the 2,3-diarylation of carboxyindole derivatives employing $Pd(OAc)_2/PCy_3$ is a recent example of decarboxylative coupling involving indole derivatives.[15] However, monoarylated compound is not accessible by the method. Herein, we report the coupling reactions between heteroaromatic carboxylic acids and aryl bromides (and in certain cases, chlorides) to produce decarboxylated biaryls. In cases involving carboxylic acids of imidazo[1,2-*a*]pyridine and isoxazole, regioselective decarboxylative coupling cleanly occurred to afford the corresponding biaryls. In cases involving carboxyindoles, 3-carboxyindole can be utilized to produce C2-monoarylated indoles regioselectively.

The decarboxylative carbometalation is most often the key step in decarboxylative couplings.[8] However, the difficulty associated with this process is the general requirement of harsh conditions for metal carboxylates to extrude CO_2. The resulting organometallic species is therefore unlikely to undergo a C−C bond formation step but rather, fast protonation by the surrounding medium. Thus, we developed a new Pd(0) bis(carbene) complex **1** as a precatalyst for the decarboxylative coupling of heteroaromatic carboxylic acids with aryl halides (Chart 1). Facile bond activation via oxidative addition could be expected from the Pd(0) carbene complex. Another notable feature is the pendant amide arms of the carbene ligand. We reasoned that this "biomimetic" functionality may involve in the molecular recognition of carboxyl group and therefore facilitate its extrusion. The new complex can be prepared very readily following the procedure of relevant compounds reported by us.[24] The structure of **1** was established by X-ray crystallographic analysis (see the Supporting Information). A desirable characteristic for practical application of **1** is its high stability in air.

The initial investigation was aimed at revealing the effectiveness of **1** in the decarboxylation activity of a range of heteroaromatic carboxylic acids. As shown in Table 1, **1** was capable of mediating the decarboxylation of carboxylic acids of imidazo[1,2-*a*]pyridine and isoxazole smoothly at 160 °C with a modest 2.5 mol % of Pd loading (entries 1 and 2). In sharp contrast, the catalyst system was unable to convert both 2- and

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Chart 1. Synthesis of the Pd(0) Precatalyst

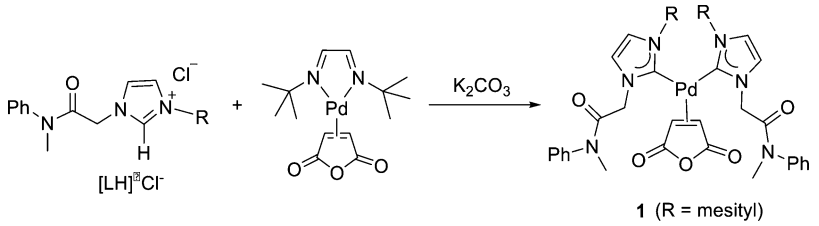
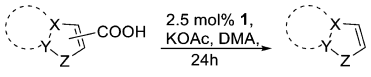
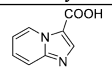
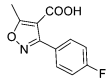
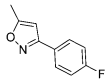
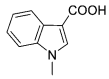
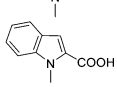
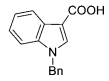


Table 1. Study of Decarboxylation Reaction for Various Heteroaromatic Systems[a]



entry	carboxylic acids		products		temp (°C)	yield (%)
1		2'		2	160	>99
2		3'		3	160	98
3		4'		4	160	trace
4		4"		4	160	trace
5		5'		5	160	trace
6					200	10

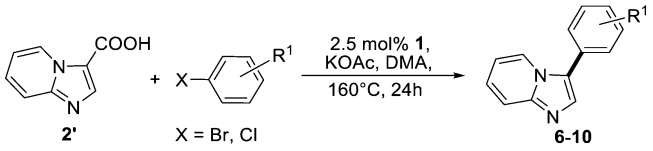
[a]Reaction conditions: 1 mmol of heteroaromatic carboxylic acid, 2 mmol of KOAc, 3 mL of dry DMA, 2.5 mol % of **1**, 24 h.

3-carboxyindoles into the corresponding decarboxylated products (entries 3−5). Even under the harsh condition of 200 °C, the decarboxylation of **5′** was still very sluggish affording only a 10% yield of the decarboxylative product (entry 6).

Since **1** can effectively mediate the decarboxylation of **2′** and **3′**, it is expected that the aryl Pd species involved should be able to cross-couple with aryl halides. Indeed, under similar decarboxylation conditions and in the presence of aryl halides, **1** successfully catalyzed the decarboxylative couplings of these substrates leading to the formation of the desirable biaryls. Using aryl bromides as coupling partners, imidazoles **6−10** were obtained with yields in the range of 73−88% (Table 2, entries 1, 3−6). Notably, the decarboxylative couplings were highly regioselective, with the C−C bonds formed only at the C5 position of the imidazole rings, following the same reactivity trend of C−H arylation when preparing similar imidazole compounds.[25] In addition to aryl bromides, the catalyst system was also able to utilize less reactive aryl chloride as substrates. Thus, **6** could also be obtained from 4-chloroacetophenone albeit in a slightly lower yield than that from the bromide analog (65% vs 74%; entries 1 and 2). Similarly, the isoxazole **3′** was also successfully applied in decarboxylative couplings with a range of aryl halides to afford various novel heteroaromatic biaryls in a range of 65−90% yields (Table 3). The X-ray structure of **6** was obtained (see the Supporting Information).

Interestingly, even though the catalyst system was unable to affect the decarboxylation of 2- or 3-carboxyindoles, these substrates could still be employed successfully in the coupling reactions with aryl halides to produce decarboxylated biaryls. In the case of 3-carboxyindoles, intriguingly, a tandem C−H

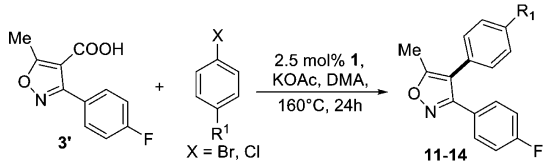
Table 2. Decarboxylative Arylation of Imidazo[1,2-*a*]pyridine-3-carboxylic Acid with Aryl Halides[a]



entry	X	R^1	product	yield (%)
1	Br	4-COMe	**6**	74
2	Cl	4-COMe	**6**	65
3	Br	4-CN	**7**	88
4	Br	H	**8**	73
5	Br	4-Me	**9**	74
6	Br	3-OMe	**10**	79

[a]Reaction conditions: 1.3 mmol of imdazol[1,2-*a*]pyridine-3-carboxylic acid, 1.3 mmol of ArX, 2.6 mmol of KOAc, 2 mL of dry DMA, 2.5 mol % of cat., 160 °C, 24 h.

Table 3. Decarboxylative Arylation of 3-(4-Fluorophenyl)-5-methylisoxazole-4-carboxylic Acid with Aryl Halides[a]



entry	X	R^1	product	yield (%)
1	Br	COMe	**11**	81
2	Cl	CN	**12**	65
3	Br	CN	**12**	90
4	Br	OMe	**13**	67
5	Br	H	**14**	71

[a]Reaction conditions: 0.5 mmol of **3′**, 0.5 mmol of ArX, 1.0 mmol of KOAc, 2 mL of dry DMA, 2.5 mol % of **1**, 160 °C, 24 h.

arylation/decarboxylation reaction occurred, leading to the exclusive formation of C2-arylated product despite the acid group at the C3 position (Table 4). The C3-arylated or 2,3-diarylated products were not observed, and only unreacted starting materials remained in the reaction mixture. Thus, C2-arylated products were obtained in decent yields (45−63%) from a range of aryl bromides having electron-donating or -withdrawing groups. In Miura' work, the same reaction between **4′** and PhBr did not yield the monoarylated product **19A** but a mixture of 1-methyl-2-phenyl-1*H*-indole-3-carboxylic acid and 2,3-diphenylated product.[15] In contrast, a decent 62% yield of **19A** was obtained in this work (entry 6). The X-ray structures of **17A**, **21A**, and **23A** were obtained (see the Supporting Information).

The analogous conversion of the C2 substrate (**4″**) was subsequently investigated in order to establish whether it was

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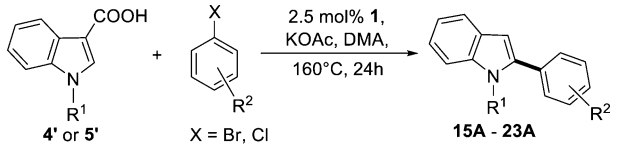
Table 4. Tandem C−H Arylation and Decarboxylation of 1-Alkylindole-3-carboxylic Acid and Aryl Halides[a]

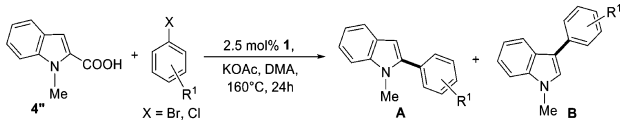


entry	R^1	X	R^2	product	yield (%)
1	Me (4′)	Br	4-COMe	**15A**	60
2	Bn (5′)	Br	4-COMe	**16A**	58
3	Me	Br	4-CN	**17A**	53
4	Me	Cl	4-CN	**17A**	35
5	Bn	Br	4-CN	**18A**	63
6	Me	Br	H	**19A**	62
7	Me	Br	3,4,5-OMe	**20A**	45
8	Me	Br	Ph	**21A**	50
9	Me	Br	3-OMe	**22A**	48
10	Me	Br	4-Me	**23A**	45

[a]Reaction conditions: 3.0 mmol of **4′** or **5′**, 3.0 mmol of aryl halide, 6.0 mmol of KOAc, 4 mL of dry DMA, 2.5 mol % of **1**, 160 °C, 24 h.

also possible. In this case, *ipso* decarboxylative coupling occurred more favorably, leading to the formation of C2-arylated indole as the major compound (Table 5). Similar to

Table 5. Decarboxylative Coupling of 1-Methylindole-2-carboxylic Acid with Aryl Halides[a]



entry	X	R^1	product	yield (%)	selectivity
1	Br	4-COMe	**15A,B**	58	3:1
2	Br	4-CN	**17A,B**	61	3:1
3	Cl	4-CN	**17A,B**	41	3:1
4	Br	H	**19A**	52	
5	Br	3-OMe	**22A**	46	

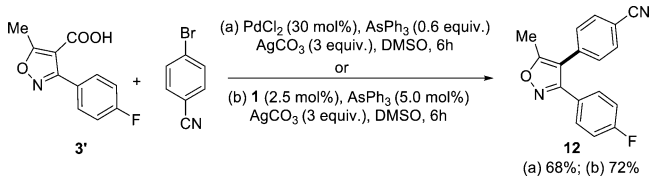
[a]Reaction conditions: 3.0 mmol of **4″**, 3.0 mmol of aryl halide, 6.0 mmol of KOAc, 4 mL of dry DMA, 2.5 mol % of cat., 160 °C, 24 h.

the C3 substrates, various aryl halides were successfully employed. Interestingly, a certain amount of C3-arylated products were also observed in several cases (entries 1−3). The structure of **17B** was also established by X-ray structural study (see the Supporting Information).

Since **1** is also capable of mediating the C−H arylation, it would be of interest to compare its effectiveness in catalyzing C−H arylation and decarboxylative transformation to obtain the monarylated indole. Following our previously established conditions of C−H arylation using a Pd(II) carbene complex,[26] the arylation reaction using **4** as substrate led to a mixture of C2- and C3-arylated compounds with 41 and 20% yields respectively (Scheme 1). In contrast, employing **4′** as substrate, **15A** can be obtained in 60% yield as a single product (Table 4, entry 1).

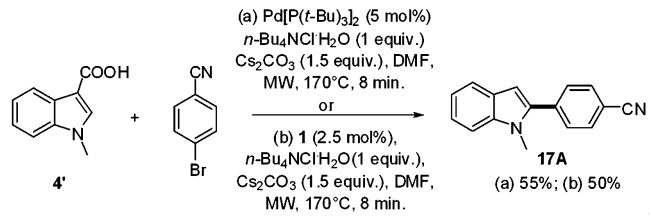
To evaluate the effectiveness of our monometallic Pd catalyst system, the same reaction between **3′** and 4-bromobenzonitrile was repeated with Becht's bimetallic Pd/Ag catalytic conditions.[27] The high Pd loading of 30 mol % afforded a yield of 68% (Scheme 2). The use of **1** (2.5 mol %) in Becht conditions

Scheme 2. Decarboxylative Coupling under Becht Conditions



gave a yield of 72%. In both cases, the yields were inferior to the 90% yield obtained by our conditions (see entry 3, Table 3). We also compared the efficiency of our catalyst system with that reported by Forgione,[16] the reaction between **4′** and 4-bromobenzonitrile was repeated under his conditions employing MW heating (Scheme 3). A 55% yield was obtained,

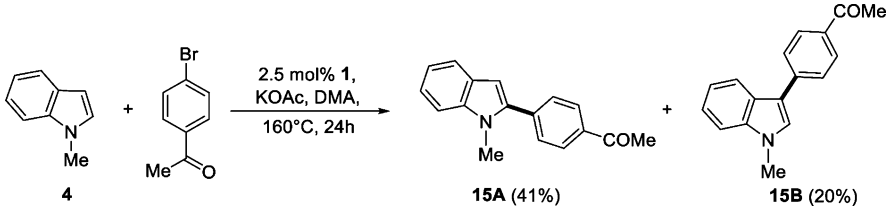
Scheme 3. Tandem C−H Arylation/Decarboxylation under Forgione Conditions



whereas the replacement of $Pd(P(t\text{-}Bu)_3)_2$ with **1** under Forgione conditions gave a yield of 50%. These yields were comparable to the 53% yield obtained by our conditions (see entry 4, Table 3). Finally, we compared the catalytic activities of **1** with other catalyst systems (see Table S3, Supporting Information). In general, the Pd(0) carbene catalyst outperformed those based on Pd/PR_3 in regard to both yield and the selectivity of the product.

The catalyst system based on **1** exhibits remarkable chemoselectivity. In the case of substrates **2′** and **3′**, decarboxylation was possible, but decarboxylative couplings occur preferentially leading to the desired biaryl products. For 3-carboxyindole (**4′** and **5′**), no decarboxylation was possible, whereas coupling reaction occurred leading to the 2-arylated

Scheme 1. C−H Arylation Catalyzed by 1



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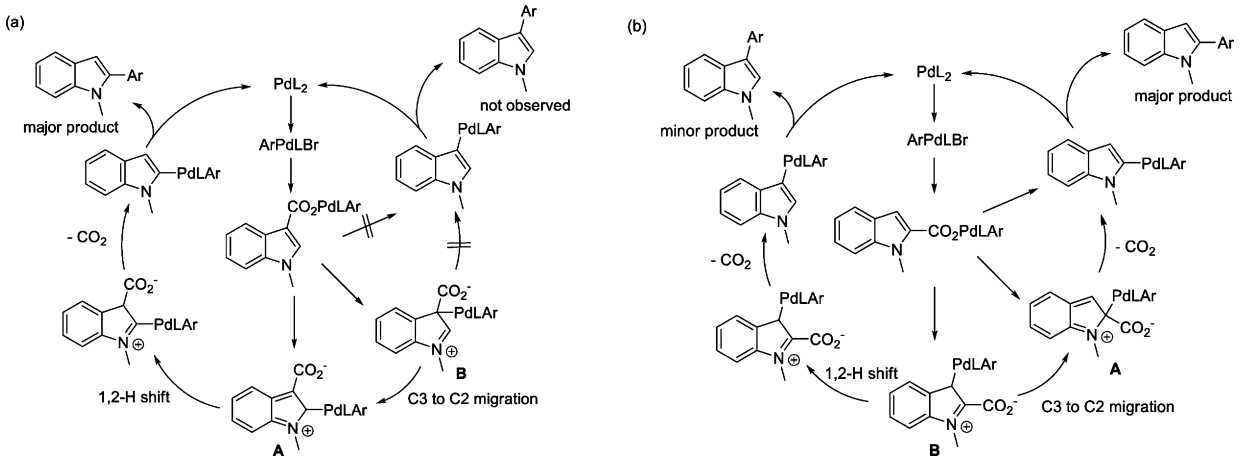
Scheme 4. Proposed Catalytic Cycles for the Coupling Reaction with (a) 3-Carboxyindole and (b) 2-Carboxyindole



indole. In the case of the 2-carboxyindole (**4″**), its decarboxylation was also not possible, and *ipso* decarboxylative coupling occurred favorably. For the decarboxylation reactions in Table 1, a Pd(0) species is probably involved in the oxidative addition of the O−H bonds. The decarboxylated product was obtained after the extrusion of CO_2 and reductive elimination (see Scheme S1, Supporting Information). The results in Table 1 also implied that the decarboxylative couplings with **2′** and **3′** (see Table 2 and 3) share a similar catalytic cycle, whereas the reactions with **4′**, **4″**, and **5′** involve alternative mechanisms (see Tables 4 and 5). Liu reported the monometallic Pd-catalyzed decarboxylative coupling of potassium polyfluorobenzoates with aryl halides and triflates and the computational analysis of the mechanism.[17] A similar mechanism could be constructed for the decarboxylative couplings with **2′** and **3′** (see Scheme S2, Supporting Information). For the coupling reactions with **4′**, **4″**, and **5′** as substrates, unlike the mechanistic pathways for **2′** and **3′**, electrophilic palladations as reported by Forgione were involved.[14,16] For 3-carboxyindoles, both C2 and C3 electrophilic palladations were possible, forming species **A** and **B**, respectively (Scheme 4a). The latter species can transform rapidly into the former species via facile C3 to C2 migration. The species **A** can then generate the C2-arylated product via 1,2-H shift and decarboxylation. For 2-carboxyindole as substrate (Scheme 4b), the species **B** from C3 palladation can also undergo facile C3 to C2 migration, leading subsequently to the same C2-arylated product. Notably, this species can also proceed via 1,2-H shift and then decarboxylation, leading to the eventual formation of the C3-arylated compound as the minor product.

In summary, we have identified a new, effective monometallic Pd catalyst for the regioselective syntheses of decarboxylated biaryls from heteroaromatic carboxylic acids. To our knowledge, this is the first example of preformed Pd(0) carbene complex employed in such reactions. The high chemoselectivity exhibited by **1** ensured the success of these processes. Such methodology for obtaining heteroaromatic biaryls is an attractive alternative complementary to the C−H arylations previously reported in the literature.

EXPERIMENTAL SECTION

All manipulations were performed under a dry nitrogen atmosphere using standard Schlenk techniques. Solvents were dried with standard procedures. Starting chemicals were purchased from commercial sources and used as received. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded at 300.13 and 75.48 MHz, respectively. ESI-MS was carried out on a sector field mass spectrometer.

Synthesis of $[LH]^+Cl^-$. To a 100 mL Schlenk flask were added 1-(2,4,6-trimethylphenyl)-1*H*-imidazole (2.87 g, 15.4 mmol), 2-chloro-*N*-methyl-*N*-phenylacetamide (1.94 g, 15.4 mmol), and dry DMF. The mixture was allowed to stir at 100 °C for 2 days. After the mixture was cooled to room temperature, the solvent was removed completely under vacuum. The residue was washed thoroughly with THF. The white solid formed was then filtered on a frit and dried under vacuum. Yield: 3.98 g, 70%. Mp = 237.4−238.7 °C dec. ^1H NMR ($CDCl_3$): δ 2.03 (s, 6H), 2.29 (s, 3H), 3.29 (s, 3H), 5.53 (s, 2H), 6.95 (s, 2H), 7.05−7.56 (m, 7H), 10.49 (s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 17.4, 17.4, 21.0, 37.8, 51.7, 122.1, 124.5, 127.6, 128.8, 129.6, 130.3, 130.7, 134.3, 134.3, 139.8, 140.8, 141.0, 164.3. Anal. Calcd for $C_{21}H_{24}ClN_3O$: C, 68.19; H, 6.54; N, 11.36. Found: C, 68.33; H, 6.61; N, 11.36.

Synthesis of 1. To a 50 mL Schlenk flask containing the Pd(0) precursor[28] (0.41 g, 1.10 mmol), $[LH]^+Cl^-$ (0.81 g, 2.20 mmol), and K_2CO_3 (0.31 g, 2.20 mmol) was added dry DMF (10 mL). The mixture was allowed to stir for 5 h at ambient temperature. The solvent was completely removed under vacuum. The residue was dissolved in CH_2Cl_2. The organic layer was then washed twice with water. After drying with anhydrous $MgSO_4$, the solvent was completely removed under vacuum. The residue was washed with diethyl ether. The pale yellow solid was then filtered on a frit and dried under vacuum. Crystals suitable for X-ray diffraction studies were obtained by vapor diffusion of Et_2O into a CH_2Cl_2 solution containing **1**. Yield: 0.62 g, 65%. Mp = 231.2−232.9 °C dec. ^1H NMR ($CDCl_3$): δ 1.43 (s, 3H), 1.67 (s, 3H), 1.77 (s, 3H), 2.03 (s, 3H), 2.07 (s, 3H), 2.23 (s, 3H), 2.33 (s, 1H), 3.02 (d, $^2J_{HH}$ = 18 Hz, 1H), 3.20 (s, 3H), 3.25 (s, 1H), 3.31 (s, 3H), 4.06 (d, $^2J_{HH}$ = 18 Hz, 1H), 4.40 (d, $^2J_{HH}$ = 18 Hz, 1H), 5.15 (d, $^2J_{HH}$ = 18 Hz, 1H), 6.08 (s, 1H), 6.56 (s, 1H), 6.61 (s, 2H), 6.71 (s, 1H), 6.88 (s, 2H), 6.97 (s, 1H), 7.26−7.29 (m, 4H), 7.41−7.57 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 17.3, 17.4, 18.0, 18.5, 21.1, 21.2, 37.2, 38.7, 38.9, 39.3, 51.2, 53.3, 122.0, 122.3, 122.6, 123.2, 127.0, 127.9, 128.1, 128.7, 128.9, 129.0, 129.9, 130.5, 134.5, 135.2, 135.8, 136.8, 137.0, 137.8, 138.0, 138.1, 141.7, 142.6, 166.2, 166.5, 173.9, 174.1, 188.7, 193.1. Anal. Calcd for $C_{46}H_{48}N_6O_5Pd$: C, 63.40; H, 5.55; N, 9.64. Found: C, 62.97; H, 5.70; N, 9.43.

Typical Procedure for Decarboxylation Reaction. To a 50 mL flask fitted with a magnetic stirrer were added imidazo[1,2-*a*]pyridine-3-carboxylic acid (0.162 g, 1.00 mmol), KOAc (0.196 g, 2.00 mmol), and **1** (0.022 g, 0.025 mmol) (2.5 mol %) under N_2. Dry DMA (2 mL) was added to it. The reaction mixture was stirred at 160 °C for 24 h and then was allowed to cool at room temperature. After dilution with distilled water (15 mL), the solution was extracted with EtOAc (3 × 15 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Removal of the solvent resulted in a brownish gummy mass which was subjected to column chromatography over silica gel using *n*-hexane and an increasing proportion of EtOAc as eluent.

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Imidazo[1,2-*a*]pyridine (2).[29] Brownish liquid. Yield: 0.08 g, 99%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (td, J = 6.9 Hz, J = 1.2 Hz, 1H), 6.88 (ddd, J = 9.3 Hz, J = 6.7 Hz, J = 1.2 Hz, 1H), 7.33−7.41 (m, 3H), 7.87 (dt, J = 6.9 Hz, J = 1.2 Hz, 1H).

3-(4-Fluorophenyl)-5-methylisoxazole (3).[30] Colorless viscous compound. Yield: 0.078 g, 98%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 6.22 (s, 1H), 7.10 (t, J = 9.0 Hz, 2H), 7.71−7.76 (m, 2H).

1-Benzylindole (5).[31] Yellowish liquid. Yield: 0.01 g, 10% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32 (s, 2H), 6.55 (d, J = 1.5 Hz, 1H), 7.09−7.31 (m, 9H), 7.65 (d, J = 3.8 Hz, 1H).

Typical Procedure for Decarboxylative Coupling of Imidazo-[1,2-*a*]pyridine-3-carboxylic Acid with Aryl Halides. To a 50 mL flask fitted with magnetic stirrer were added imidazo[1,2-*a*]pyridine-3-carboxylic (0.211 g, 1.30 mmol), 4-bromobenzonitrile (0.236 g, 1.30 mmol), KOAc (0.255 g, 2.60 mmol), and **1** (0.028 g, 0.032 mmol) (2.5 mol %) under nitrogen. Dry DMA (3 mL) was added to it. The reaction mixture was stirred at 160 °C for 24 h and then was allowed to cool at room temperature. After dilution with distilled water (15 mL), the solution was extracted with EtOAc (3 × 15 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Removal of the solvent resulted in a brownish gummy mass which was subjected to column chromatography over silica gel using *n*-hexane and an increasing proportion of EtOAc as eluent.

4-Imidazo[1,2-*a*]pyridin-3-ylacetophenone (6).[25] Yellow solid. Yield: 0.23 g, 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H), 6.84 (t, J = 6.9 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.64−7.76 (m, 3H), 7.77 (s, 1H), 8.07 (d, J = 7.8 Hz, 2H), 8.37 (d, J = 6.9 Hz, 1H).

4-Imidazo[1,2-*a*]pyridin-3-ylbenzonitrile (7).[25] Orange solid. Yield: 0.25 g, 88%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (td, J = 6.9 Hz, J = 1.2 Hz, 1H), 7.22 (ddd, J = 9.0 Hz, J = 6.9 Hz, J = 1.2 Hz, 1H), 7.62−7.75 (m, 6H), 8.32 (dt, J = 6.9 Hz, J = 0.9 Hz, 1H).

3-Phenylimidazo[1,2-*a*]pyridine (8).[32] Brownish liquid. Yield: 0.18 g, 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (td, J = 6.9 Hz, J = 1.2 Hz, 1H), 7.06 (ddd, J = 9.0 Hz, J = 6.6 Hz, J = 1.2 Hz, 1H), 7.25−7.59 (m, 7H), 8.19 (dt, J = 6.9 Hz, J = 1.2 Hz, 1H).

3-(4-Methylphenyl)imidazo[1,2-*a*]pyridine (9).[33] Brownish liquid. Yield: 0.21 g, 75%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 6.64 (td, J = 6.9 Hz, J = 1.2 Hz, 1H), 7.03 (ddd, J = 9.0 Hz, J = 6.6 Hz, J = 1.2 Hz, 1H), 7.16−7.31 (m, 4H), 7.54−7.57 (m, 2H), 8.16 (dt, J = 6.9 Hz, J = 1.2 Hz, 1H).

3-(3-Methoxyphenyl)imidazo[1,2-*a*]pyridine (10).[33] Brown solid. Yield: 0.23 g, 79%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H), 6.63 (td, J = 6.9 Hz, J = 0.9 Hz, 1H), 6.78−6.82 (m, 1H), 6.94−7.05 (m, 3H), 7.27 (t, J = 8.1 Hz, 1H), 7.53 (d, J = 9.0 Hz, 1H), 7.58 (s, 1H), 8.20 (d, J = 6.9 Hz, 1H).

Typical Procedure for Decarboxylative Coupling of 3-(4-Fluorophenyl)-5-methylisoxazole-4-carboxylic Acid with Aryl Halides. To a 50 mL flask fitted with magnetic stirrer were added 3-(4-fluorophenyl)-5-methylisoxazole-4-carboxylic acid (0.110 g, 0.50 mmol), 4-bromobenzonitrile (0.091 g, 0.50 mmol), KOAc (0.098 g, 1.00 mmol), and **1** (0.011 g, 0.0125 mmol) (2.5 mol %) under nitrogen. Dry DMA (2 mL) was added to it. The reaction mixture was stirred at 160 °C for 24 h and then was allowed to cool at room temperature. After dilution with distilled water (15 mL), the solution was extracted with EtOAc (3 × 15 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Removal of the solvent resulted in a brownish gummy mass which was subjected to column chromatography over silica gel using *n*-hexane and an increasing proportion of EtOAc as eluent.

1-[4-[3-(4-Fluorophenyl)-5-methyl-1,2-oxazol-4-yl]phenyl]-ethanone (11). Yellow solid. Yield: 0.12 g, 81%. Mp = 99.3−99.8 °C. HRMS (EI): calcd $C_{18}H_{14}FNO_2$ 295.1009, found 295.0999. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 2.58 (s, 3H), 6.98 (t, J = 8.7 Hz, 2H), 7.25 (d, J = 1.8 Hz, 2H), 7.33−7.38 (m, 2H), 7.94 (d, J = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 11.8, 26.7, 114.9, 115.8 (d, J = 21.9 Hz), 124.8, 127.5, 128.8, 129.9, 130.5 (d, J = 7.5 Hz), 135.2, 136.3, 160.2, 163.5 (d, J = 249.1 Hz), 167.3, 197.6.

4-[3-(4-Fluorophenyl)-5-methyl-4-isoxazolyl]benzonitrile (12). Orange-red solid. Yield: 0.13 g, 90%. Mp = 129.8−130.2 °C. HRMS (EI): calcd $C_{17}H_{11}FN_2O$ 278.0855, found 278.0848. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 6.98 (t, J = 8.7 Hz, 2H), 7.23−7.33 (m, 4H), 7.63 (d, J = 8.1 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 11.8, 111.7, 114.4, 116.0 (d, J_{CF} = 22.6 Hz), 118.4, 124.5 (d, J_{CF} = 3.0 Hz), 128.0, 130.3, 130.4 (d, J_{CF} = 9.1 Hz), 132.6, 132.9, 135.2, 163.6 (d, J_{CF} = 249.1 Hz), 167.5.

3-(4-Fuorophenyl)-4-(4-methoxyphenyl)-5-methyl-1,2-oxazole (13). Yellow solid. Yield: 0.095 g, 67%. Mp = 92.3−92.7 °C. HRMS (EI): calcd $C_{17}H_{14}FNO_2$ 283.1005, found 283.1002. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.68 (s, 3H), 6.76 (d, J = 9.0 Hz, 2H), 6.85 (t, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 7.25−7.30 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 29.7, 55.3, 114.3, 115.3, 115.6 (d, J_{CF} = 21.9 Hz), 122.2, 125.4, 130.3 (d, J_{CF} = 8.3 Hz), 131.0, 159.2, 160.3, 163.4 (d, J_{CF} = 249.1 Hz), 166.6.

3-(4-Fluorophenyl)-5-methyl-4-phenylisoxazole (14).[34] Yellow solid. Yield: 0.090 g, 71%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 3H), 6.98 (t, J = 8.7 Hz, 2H), 7.13−7.16 (m, 2H), 7.33−7.43 (m, 5H).

Preparation of 12 under Becht Conditions. A degassed DMSO solution (6 mL) containing a mixture of 4-bromobenzonitrile (0.090 g, 0.50 mmol, 1.0 equiv), **3′** (0.115 g, 0.50 mmol, 1.0 equiv), Ag_2CO_3 (0.414 g, 1.5 mmol, 3.0 equiv), $AsPh_3$ (0.092 g, 0.30 mmol, 0.6 equiv), and $PdCl_2$ (0.027 g 0.15 mmol, 30 mol %) or **1** (0.011 g, 2.5 mol %) was heated under N_2 at 150 °C for 6 h. The workup procedure was that reported in the literature.[27] Yields: 0.095 g, 68% from $PdCl_2$; 0.10 g, 72% from **1**.

Typical Procedure for Coupling Reactions of Carboxyindoles with Aryl Halides. To a 50 mL flask fitted with magnetic stirrer were added *N*-methylindole-3-carboxylic acid (0.526 g, 3.00 mmol), 4-bromobenzonitrile (0.596 g, 3.00 mmol), KOAc (0.588 g, 6.00 mmol), and **1** (0.065 g, 0.075 mmol) (2.5 mol %) under N_2. Dry DMA (4 mL) was added to it. The reaction mixture was stirred at 160 °C for 24 h and then was allowed to cool at room temperature. After dilution with distilled water (15 mL), the solution was extracted with EtOAc (3 × 15 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Removal of the solvent resulted in a brownish gummy mass which was subjected to column chromatography over silica gel using *n*-hexane and an increasing proportion of EtOAc as eluent.

2-(*p*-Acetylphenyl)-1-methylindole (15A).[35] Yellow solid. Yield: 0.45 g, 60%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H), 3.77 (s, 3H), 6.65 (s, 1H), 7.16 (t, J = 6.9 Hz, 1H), 7.24−7.30 (m, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.62 (t, J = 6.9 Hz, 3H), 8.04 (d, J = 6.6 Hz, 2H).

3-(*p*-Acetylphenyl)-1-methylindole (15B).[36] Yellow solid. Yield: 0.11 g, 15%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (s, 3H), 4.09 (s, 3H), 7.13−7.18 (m, 1H), 7.34−7.39 (m, 2H), 7.46 (s, 1H), 7.68−7.72 (m, 3H), 8.04 (d, J = 7.8 Hz, 2H).

1,1′-[(1-Methyl-1*H*-indole-2,3-diyl)dibenzene-4,1-diyl]-diethanone (15C). Yellow solid. Yield: 0.16 g, 15%. Mp = 189.7−190.2 °C. HRMS (EI): calcd $C_{25}H_{21}NO_2$ 367.1572, found 367.1579. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.57 (s, 3H), 2.63 (s, 3H), 3.70 (s, 3H), 7.22−7.25 (m, 1H), 7.32−7.45 (m, 6H), 7.78 (d, J = 6.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.98 (d, J = 9.0 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 26.6, 26.7, 31.2, 110.0, 115.1, 119.6, 121.0, 123.1, 128.6, 129.7, 131.3, 134.5, 136.4, 136.6, 137.8, 140.3, 197.6, 197.7.

1-[4-(1-Methyl-1*H*-indol-2-yl)phenyl]ethanone (16A). Yellow solid. Yield: 0.56 g, 58%. Mp = 129.8−130.2 °C. HRMS (EI): calcd $C_{23}H_{19}NO$ 325.1467, found 325.1468. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (s, 3H), 5.38 (s, 2H), 6.75 (s, 1H), 7.04 (d, J = 8.1 Hz, 2H), 7.17−7.32 (m, 6H), 7.53 (dd, J = 6.6 Hz, J = 1.8 Hz, 2H), 7.68−7.71 (m, 1H), 7.96 (d, J = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 29.7, 47.9, 103.7, 110.7, 120.5, 120.9, 122.6, 125.8, 127.3, 128.2, 128.6, 128.9, 129.0, 136.2, 137.3, 137.9, 138.6, 140.4, 197.6.

1-Methyl-2-(4′-cyanophenyl)indole (17A).[37] Orange-red solid. Yield: 0.37 g, 53%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (s, 3H), 6.65 (s, 1H), 7.17 (td, J = 6.9 Hz, J = 0.9 Hz, 1H), 7.29 (td, J = 6.9 Hz, J = 1.2 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.60−7.66 (m, 3H), 7.74 (d, J = 9.0 Hz, 2H).

1-Methyl-3-(4′-cyanophenyl)indole (17B). Orange-red solid. Yield: 0.11 g, 16%. Mp: = 136.5−137.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 7.20−7.40 (m, 4H), 7.65−7.76 (m, 4H), 7.91

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(d, J = 6.0 Hz, 1H). HRMS (EI): calcd $C_{16}H_{12}N_2$ 232.1000, found 232.1006. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 32.7, 108.0, 109.5, 114.5, 119.0, 119.1, 120.3, 122.1, 125.1, 126.6, 127.4, 132.2, 137.2, 140.2.

4-(1-Benzyl-1*H*-indol-2-yl)benzonitrile (18A). Brown solid. Yield: 0.58 g, 63% yield. Mp = 183.2−183.8 °C. HRMS (EI): calcd $C_{22}H_{16}N_2$ 308.1313, found 308.1317. ^1H NMR (300 MHz, $CDCl_3$): δ 5.35 (s, 2H), 6.74 (s, 1H), 7.00 (d, J = 7.2 Hz, 2H), 7.15−7.29 (m, 6H), 7.51(d, J = 8.1 Hz, 2H), 7.63−7.70 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 48.0, 104.2, 110.7, 111.4, 118.7, 120.7, 121.1, 123.0, 125.8, 127.5, 128.0, 129.0, 129.4, 132.4, 137.2, 137.6, 138.8, 139.6.

2-Phenyl-1-methylindole (19A).[38] White solid. Yield: 0.38 g, 62%. ^1H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, CH_3), 6.56 (s, 1H), 7.14 (t, J = 9.0 Hz, 1H), 7.24 (td, J = 7.2 Hz, J = 0.9 Hz, 1H), 7.35−7.53 (m, 6H), 7.64 (d, J = 9.0 Hz, 1H).

1-Methyl-2-(3,4,5-trimethoxyphenyl)-1*H*-indole (20A). Orange solid. Yield: 0.40 g, 45%. Mp = 101.6−102.1 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H), 3.89 (s, 9H), 6.53 (s, 1H), 6.70 (s, 2H), 7.13 (td, J = 6.9 Hz, J = 0.9 Hz, 1H), 7.21−7.26 (m, 2H), 7.35 (d, J = 7.8 Hz, 1H), 7.62 (dd, J = 8.1 Hz, J = 0.9 Hz, 1H). HRMS (EI): calcd $C_{18}H_{19}NO_3$ 297.1365, found 297.1376. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 31.2, 56.3, 61.0, 101.4, 106.7, 109.6, 120.0, 120.4, 121.8, 127.8, 128.4, 138.3, 141.6, 153.2.

2-(Naphthalene-1-yl)-*N*-methylindole (21A).[39] Yellow solid. Yield: 0.38 g, 50%. ^1H NMR (300 MHz, $CDCl_3$): δ 3.51 (s, 3H), 6.66 (s, 1H), 7.24 (td, J = 5.4 Hz, J = 0.9 Hz, 1H), 7.32 (t, J = 6.0 Hz, 1H), 7.42−7.61 (m, 5H), 7.73 (d, J = 6.0 Hz, 2H), 7.93−7.98 (m, 2H).

2-(3-Methoxyphenyl)-1-methyl-1*H*-indole (22A).[40] Orange solid. Yield: 0.34 g, 48%. ^1H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 3.87 (s, 3H), 6.59 (s, 1H), 6.97 (dd, J = 8.1 Hz, J = 2.4 Hz, 1H), 7.07−7.19 (m, 3H), 7.27 (td, J = 8.1 Hz, J = 1.2 Hz, 1H), 7.40 (t, J = 9.0 Hz, 2H), 7.66 (d, J = 9.0 Hz, 1H).

4-Methylphenyl 1-Methylindol-2-yl Ketone (23A).[38] Orange solid. Yield: 0.30 g, 45%. ^1H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.74 (s, 3H), 6.53 (s, 1H), 7.13 (t, J = 9.0 Hz, 1H), 7.21−7.42 (m, 6H), 7.62 (d, J = 7.8 Hz, 1H).

Preparation of 17A under Forgione Conditions. In a microwave vial were added a DMF solution (4 mL) of 4-bromobenzonitrile (0.546 g, 3.0 mmol, 1.0 equiv), **4′** (0.525 g, 3.0 mmol, 1 equiv), n-$Bu_4NCl{\cdot}H_2O$ (0.887 g, 3.0 mmol, 1.0 equiv), Cs_2CO_3 (1.46 g, 4.5 mmol, 1.5 equiv), and $Pd[P(t\text{-}Bu)_3]_2$ (0.076 g, 5 mol %) or **1** (0.065 g, 2.5 mol %). The heating and workup procedures were those reported in the literature.[16] Yields: 0.380 g, 55% from $Pd[P(t\text{-}Bu)_3]_2$; 0.350 g, 50% from **1**.

Direct Arylation of 1-Methylindole with 4-Bromoacetophenone. To a 50 mL flask fitted with a magnetic stirrer were added 1-methylindole (0.394 g, 3.00 mmol), 4-bromoacetophenone (0.599 g, 3.00 mmol), KOAc (0.588 g, 6.00 mmol), and **1** (0.065 g, 0.075 mmol) (2.5 mol %) under N_2. Dry DMA (4 mL) was added to the solution. The reaction mixture was allowed to stir at 140 °C for 16 h. After cooling and dilution with 15 mL of distilled water, the solution was extracted with EtOAc (3 × 15 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Removal of the solvent resulted in a brownish gummy mass which was subjected to column chromatography over silica gel using n-hexane and an increasing proportion of EtOAc as eluent. Yield: 0.306 g, 41% (**15A**) and 0.150 g, 20% (**15B**).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional catalytic table, schemes, NMR spectra for all products, and crystallographic data of **1**, **6**, **17A**, **17B**, **21A**, and **23A**. This material is available free of cost via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179.
(2) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.
(3) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.
(4) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253.
(5) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.
(6) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447.
(7) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373.
(8) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030.
(9) Cornella, J.; Larrosa, I. *Synthesis* **2012**, *44*, 653.
(10) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.
(11) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.
(12) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20.
(13) Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, *2006*, 3283.
(14) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350.
(15) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674.
(16) Bilodeau, F.; Brochu, M.-C.; Guimond, N.; Thesen, K. H.; Forgione, P. *J. Org. Chem.* **2010**, *75*, 1550.
(17) Shang, R.; Xu, Q.; Jiang, Y.-Y.; Wang, Y.; Liu, L. *Org. Lett.* **2010**, *12*, 1000.
(18) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824.
(19) Gooßen, L. J.; Rodríguez, N.; Lange, P. P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111.
(20) Zhang, F.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 4745.
(21) Gooßen, L. J.; Lange, P. P.; Rodríguez, N.; Linder, C. *Chem.—Eur. J.* **2010**, *16*, 3906.
(22) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350.
(23) Arroyave, F. A.; Reynolds, J. R. *Org. Lett.* **2010**, *12*, 1328.
(24) Lee, J.-Y.; Cheng, P.-Y.; Tsai, Y.-H.; Lin, G.-R.; Liu, S.-P.; Sie, M.-H.; Lee, H. M. *Organometallics* **2010**, *29*, 3901.
(25) Fu, H. Y.; Chen, L.; Doucet, H. *J. Org. Chem.* **2012**, *77*, 4473.
(26) Kumar, P. V.; Lin, W.-S.; Shen, J.-S.; Nandi, D.; Lee, H. M. *Organometallics* **2011**, *30*, 5160.
(27) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.
(28) Cavell, K. J.; Stufkens, D. J.; Vrieze, K. *Inorg. Chim. Acta* **1981**, *47*, 67.
(29) Lombardino, J. G. *J. Org. Chem.* **1965**, *30*, 2403.
(30) Xu, W. M.; Tang, E.; Huang, X. *Tetrahedron* **2005**, *61*, 501.
(31) Kamata, K.; Kasai, J.; Yamaguchi, K.; Mizuno, N. *Org. Lett.* **2004**, *6*, 3577.
(32) Enguehard, C.; Renou, J.-L.; Collot, V.; Hervet, M.; Rault, S.; Gueiffier, A. *J. Org. Chem.* **2000**, *65*, 6572.
(33) Wu, Z.; Pan, Y.; Zhou, X. *Synthesis* **2011**, *43*, 2255.
(34) Kumar, J. S. D.; Ho, M. M.; Leung, J. M.; Toyokuni, T. *Adv. Synth. Catal.* **2002**, *344*, 1146.
(35) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897.
(36) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748.
(37) Labadie, S. S.; Teng, E. *J. Org. Chem.* **1994**, *59*, 4250.
(38) Ishikura, M.; Terashima, M. *J. Org. Chem.* **1994**, *59*, 2634.
(39) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.

(40) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473.