PAPER

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Synthesis of 3-aryl-2-phosphinoimidazo[1,2-*a*] pyridine ligands for use in palladium-catalyzed cross-coupling reactions†

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3-Aryl-2-phosphinoimidazo[1,2-*a*]pyridine ligands were synthesized from 2-aminopyridine *via* two complementary routes. The first synthetic route involves the copper-catalyzed iodine-mediated cyclizations of 2-aminopyridine with arylacetylenes followed by palladium-catalyzed cross-coupling reactions with phosphines. The second synthetic route requires the preparation of 2,3-diiodoimidazo [1,2-*a*]pyridine or 2-iodo-3-bromoimidazo[1,2-*a*]pyridine from 2-aminopyridine followed by palladium-catalyzed Suzuki/phosphination or a phosphination/Suzuki cross-coupling reactions sequence, respectively. Preliminary model studies on the Suzuki synthesis of sterically-hindered biaryl and Buchwald–Hartwig amination compounds are presented with these ligands.

Palladium-catalyzed cross-coupling reactions have revolutionized the formation of C–C and C–X bond formation in the academic and industrial synthetic organic chemistry sectors.[1,2] Applications such as synthesis of natural products,[3] active pharmaceutical ingredients (API),[4] agrochemicals,[5] and materials for electronic applications[6] are showcased. Snieckus described in his 2010 Nobel Prize review that privileged ligand scaffolds represented the "third wave" in the cross-coupling reactions where the "first wave" was the investigation of the metal catalyst-the rise of palladium and the "second wave" was the exploration of the organometallic coupling partner.[1] In the last twenty years, it was recognized that the choice of ligand facilitated the oxidative addition and reductive-elimination steps of the catalytic cycle of transition metal-catalyzed cross-coupling reactions, increasing the overall rate of the reaction. For example, bulky trialkylphosphines facilitated the oxidative addition processes of electron-rich, unactivated substrates such as aryl chlorides.[7,8] Sterically demanding ligands also provided enhanced rates of reductive elimination from [(L)$_n$Pd(aryl)(R), R = aryl, amido, phenoxo, *etc.*] species by alleviation of steric congestion.[9] Privileged ligands such as Buchwald's biarylphosphines,[10,11] Fu's trialkylphosphines,[7,8,12] Nolan–Hermann's *N*-heterocyclic carbenes (NHC),[13–15] Hartwig's ferrocenes,[16,17] Beller's bis(adamantyl)phosphines[18,19] and *N*-aryl(benz)imidazolyl or *N*-pyrrolylphosphines,[20,21] Zhang's ClickPhos ligands,[22,23] and Stradiotto's biaryl P–N phosphines,[24,25] to mention a few, have found wide-spread use in

Suzuki–Miyaura, Corriu–Kumada, Heck, Negishi, Sonogashira, C–X (X = S, O, P) cross-coupling and Buchwald–Hartwig amination reactions (Fig. 1). Preformed catalysts with these ligands attached to the palladium metal center are also recognized as well-defined entities in cross-coupling reactions.[26]

The term privileged structure was first coined by Evans *et al.* in 1988 and was defined as "a single molecular framework able
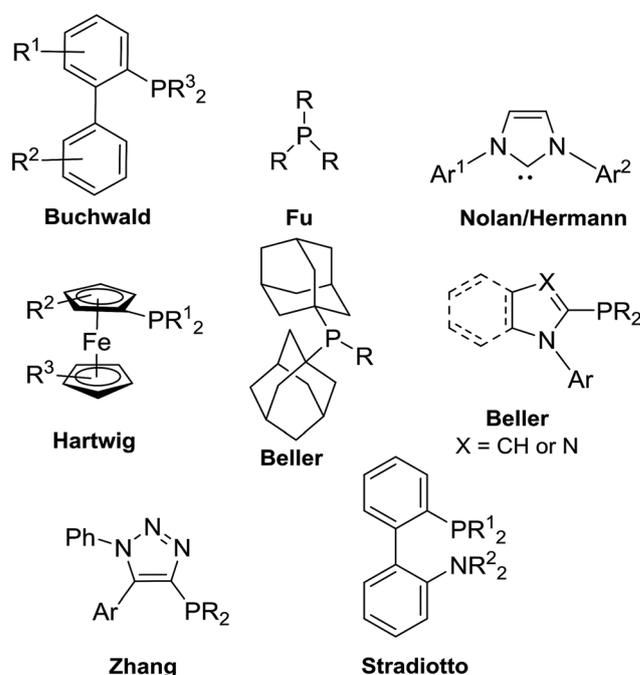

Fig. 1 Privileged ligands for palladium-catalyzed cross-coupling reactions.

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to provide ligands for diverse receptors".[27] In the last three decades, it is clear that privileged structures are exploited as opportunities in drug discovery programs.[28–31] For example, imidazo[1,2-a]pyridines are privileged structures in medicinal chemistry programs (Fig. 2).[32] Imidazo[1,2-a]pyridines are a represented motif in several drugs on the market such as zolpidem, marketed as Ambien™ for the treatment of insomnia,[33] minodronic acid, marketed as Bonoteo™ for oral treatment of osteoporosis,[34] and olprinone, sold as Coretec™ as a cardiotonic agent.[35]

Our group is interested in a long-term research program directed at the use of key privileged structures that are employed in drug discovery programs as potential phosphorus ligands for cross-coupling reactions. In our entry into the use of privileged structures from the medicinal chemistry literature for our investigation into new phosphorus ligands, we have developed two complementary synthetic routes for the preparation of 3-aryl-2-phosphinoimidazo[1,2-a]pyridine ligands from 2-aminopyridine as our initial substrate.

Our first synthetic route for the preparation of 3-aryl-2-phosphinoimidazo[1,2-a]pyridine ligands 3a–3l required the copper(II) acetate iodine-mediated double oxidative C–H amination of 2-aminopyridine (1) with arylacetylenes under an oxygen atmosphere to give 3-aryl-2-iodoimidazo[1,2-a]pyridines 2a–2d (Scheme 1).[36,37]
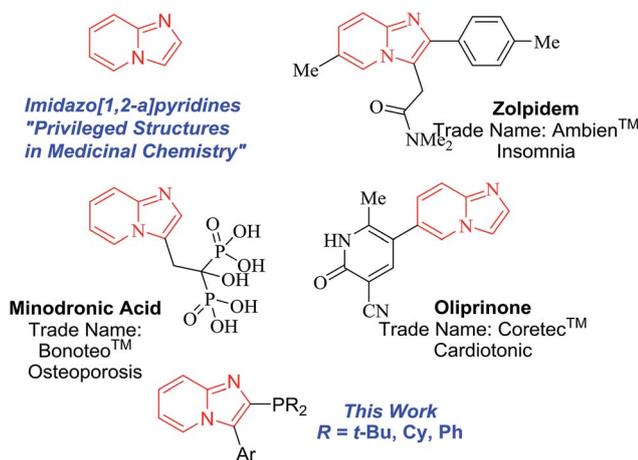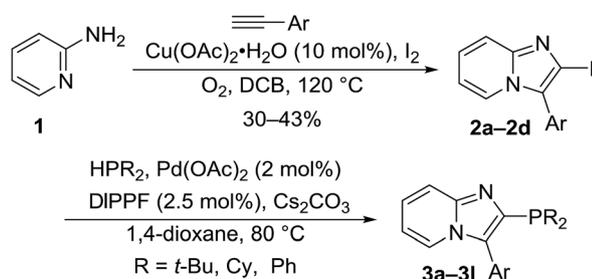
Phenylacetylene and 2-/3-/4-methoxyphenylacetylenes were commercially available reagents. With intermediates 2a–d in hand, we explored several cross-coupling phosphination reactions and we found that palladium-catalyzed phosphination with DIPPF ligand in the presence of cesium carbonate as the base in 1,4-dioxane under reflux provided twelve new ligands 3a–3l as shown in Table 1.[38] Moderate to good yields were obtained under these cross-coupling conditions. There are few commercially available dimethoxyphenylacetylenes, and most are prohibitively expensive, and so an alternative synthetic strategy was explored.
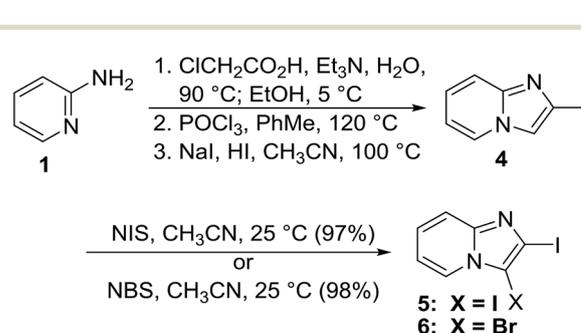
2-Iodoimidazo[1,2-a]pyridine (4) was conveniently prepared in three steps from 2-aminopyridine (1) following literature procedures, which was then converted into either iodo 5 or bromo 6 with NIS or NBS, respectively (Scheme 2).[39,40]

When the phosphorus ligands 3 contained tert-butyl or cyclohexyl groups, method 1 was followed where 2,3-diiodoimidazo[1,2-a]pyridine (5) underwent Suzuki cross-coupling reactions with arylboronic acids to yield aryl intermediates 7a–7f, which was followed by palladium-catalyzed cross-coupling phosphination reactions with di-tert-butylphosphine or dicyclohexylphosphine to give C-2 substituted phosphorus ligands 3m–3u in low to moderate yields (Scheme 3, Table 2).[38] The phosphorus ligands 3v–3ab were prepared from 3-bromo-2-iodoimidazo[1,2-a]pyridine (6) via a palladium-catalyzed

Fig. 2 Imidazo[1,2-a]pyridines as privileged structures in medicinal chemistry and in our cross-coupling reactions approach.

Table 1 Palladium-catalyzed phosphination of 3-aryl-2-iodoimidazo[1,2-a]pyridines 2a–2d[a]

Entry	Ar	R	3 (% yield)
1	Ph (2a)	t-Bu	3a (41)
2	Ph (2a)	Cy	3b (50)
3	Ph (2a)	Ph	3c (61)
4	2-OMeC$_6$H$_4$ (2b)	t-Bu	3d (53)
5	2-OMeC$_6$H$_4$ (2b)	Cy	3e (83)
6	2-OMeC$_6$H$_4$ (2b)	Ph	3f (69)
7	3-OMeC$_6$H$_4$ (2c)	t-Bu	3g (62)
8	3-OMeC$_6$H$_4$ (2c)	Cy	3h (72)
9	3-OMeC$_6$H$_4$ (2c)	Ph	3i (79)
10	4-OMeC$_6$H$_4$ (2d)	t-Bu	3j (73)
11	4-OMeC$_6$H$_4$ (2d)	Cy	3k (55)
12	4-OMeC$_6$H$_4$ (2d)	Ph	3l (59)

[a] Reaction conditions: 2a–2d (1 equiv.), HPR$_2$ (1 equiv.), Pd(OAc)$_2$ (2 mol%), Cs$_2$CO$_3$ (1.2 equiv.), DIPPF (2.5 mol%), 1,4-dioxane, 80 °C.

Scheme 1 Preparation of 3-aryl-2-phosphinoimidazo[1,2-a]pyridine ligands 3a–3l from 2-aminopyridine via copper-catalyzed arylacetylene cyclizations/palladium-catalyzed phosphination reactions sequences.

Scheme 2 Preparation of 2,3-diiodoimidazo[1,2-a]pyridine (5) and 3-bromo-2-iodoimidazo[1,2-a]pyridine (6).
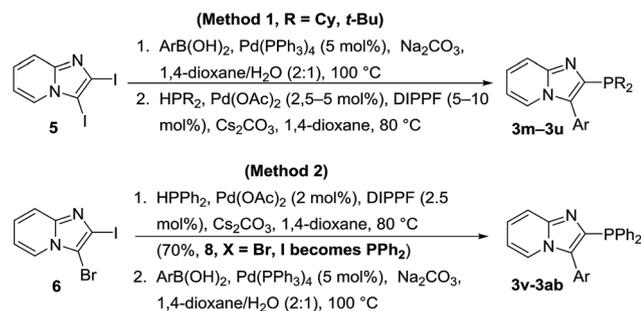
Scheme 3 Preparation of 3-aryl-2-phosphinoimidazo[1,2-a]pyridine ligands **3m–3ab** from 2-iodo-3-iodo(or bromo)imidazo[1,2-a]pyridines **5** or **6** via palladium-catalyzed Suzuki/phosphination or a phosphination/Suzuki cross-coupling reactions sequences.

phosphination with diphenylphosphine (method 2) to give intermediate **8** (X = Br, I becomes PPh₂) followed by Suzuki palladium-catalyzed cross-coupling reactions with arylboronic acids. Note that the change in reactivity of the core when switching between bromo and iodo at C3 results in a change in the order of cross-coupling steps.

With our library of functionalized imidazo[1,2-a]pyridine phosphorus ligands **3a–3ab** in hand, we began to screen these ligands in Suzuki–Miyaura cross-coupling reactions to prepare sterically-hindered biaryl compounds. We chose the Suzuki–Miyaura cross-coupling reactions of *m*-bromo-xylene (**9**) and 2-methoxyphenylboronic acid (**10**) to give 2,6-dimethyl-(2-methoxy)biphenyl (**11**) as our model reaction as outlined in Table 3. Our initial screening conditions included 5.0 mol% ligand, 2.5 mol% palladium(II) acetate with 2.5 equivalents of base in 1,4-dioxane at 80 °C for 12–24 h. As expected, SPhos and XPhos were employed as our initial ligands to confirm our GC analyses of >99% conversion in our chosen model reaction (Entries 14–15). With the GC conditions validated, we screened selected ligands from **3a–3ab**. It was clearly evident that the di-

tert-butyl phosphorus ligands represented by **3a**, **3m**, and **3p** were ineffective ligands in our model reactions (Entries 1–3). Furthermore, the diphenyl phosphorus ligands such as **3w**, **3y**, **3z**, and **3ab** showed low to moderate conversions in the model cross-coupling reactions (Entries 6–9). However, the dicyclohexyl phosphorus ligands shown by **3r** and **3t** showed greater than 99% conversions by GC analyses (Entries 4–5). Further exploration of ligand **3r** with K₃PO₄ as the base, stirring the reaction overnight at room temperature or for 3 h at 80 °C showed inferior conversions (Entries 10–12). There was no conversion when a ligand was not used in the model reaction (Entry 13).

Furthermore, a Buchwald–Hartwig amination model study was investigated with our new imidazo[1,2-a]pyridine phosphorus ligands **3a–3ab**. The Buchwald–Hartwig amination reaction of 4-chlorotoluene (**12**) with aniline (**13**) to give 4-methyl-*N*-phenylaniline (**14**) was screened with our ligands (Table 4). Our screening conditions were exactly as used in the optimization of the Suzuki cross-coupling reactions of *m*-bromo-xylene (**9**) and 2-methoxyphenylboronic acid (**10**) to give 2,6-dimethyl-(2-methoxy)biphenyl (**11**). *Tert*-butyl phosphine ligands **3a**, **3d**, **3g**, **3n**, and **3p** were all ineffective in the amination reactions (Entries 1–2, 4, 7–8). However, as expected, the dicyclohexyl phosphorus ligands **3e**, **3q**, and **3s** showed >99% conversion (Entries 3, 9, and 11) in the model screening reaction conditions. Phosphorus ligand **3s** were screening against other bases such as K₃PO₄, K₂CO₃, KOt-Bu, and NaOt-Bu (Entries 12–15) where all gave >99% conversions except for K₂CO₃ which was ineffective. Finally, ligands **3h** and **3k** showed moderate conversions (Entries 5–6).
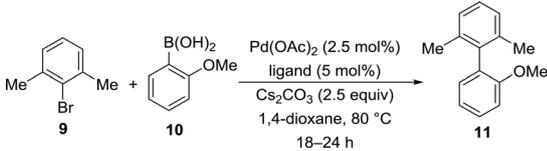
In summary, we have disclosed two complementary synthetic routes to 3-aryl-2-phosphinoimidazo[1,2-a]pyridine ligands **3a–3ab** from 2-aminopyridine (**1**). In one method, 2-aminopyridine (**1**) underwent a copper-catalyzed iodine-mediated cyclization with arylacetylenes followed by

Table 2 Palladium-catalyzed Suzuki/phosphination or phosphination/Suzuki reactions sequences of 2,3-diiodoimidazo[1,2-a]pyridine (**5**) or 3-bromo-2-iodoimidazo[1,2-a]pyridine (**6**)[a]

Entry	R	Ar	Method/substrate	Step 1 (% yield)	Step 2 (% yield)
1	*t*-Bu	2,3-diOMeC₆H₃	1, 5	**7a** (59)	**3m** (64)
2	*t*-Bu	3,4-diOMeC₆H₃	1, 5	**7b** (54)	**3n** (31)
3	*t*-Bu	2,5-diOMeC₆H₃	1, 5	**7c** (58)	**3o** (61)
4	*t*-Bu	3,4,5-triOMeC₆H₂	1, 5	**7d** (50)	**3p** (62)
5	Cy	2,3-diOMeC₆H₃	1, 5	**7a** (59)	**3q** (46)
6	Cy	2,6-diOMeC₆H₃	1, 5	**7e** (40)	**3r** (52)
7	Cy	3,4-diOMeC₆H₃	1, 5	**7b** (54)	**3s** (52)
8	Cy	2,3,4-triOMeC₆H₂	1, 5	**7f** (58)	**3t** (21)
9	Cy	3,4,5-triOMeC₆H₂	1, 5	**7d** (50)	**3u** (55)
10	Ph	2,3-diOMeC₆H₃	2, 6	**8** (70)	**3v** (52)
11	Ph	2,5-diOMeC₆H₃	2, 6	**8** (70)	**3w** (68)
12	Ph	3,4-diOMeC₆H₃	2, 6	**8** (70)	**3x** (67)
13	Ph	2,3,4-triOMeC₆H₂	2, 6	**8** (70)	**3y** (52)
14	Ph	3,4,5-triOMeC₆H₂	2, 6	**8** (70)	**3z** (64)
15	Ph	4-FC₆H₄	2, 6	**8** (70)	**3aa** (40)
16	Ph	3-F,5-OMeC₆H₃	2, 6	**8** (70)	**3ab** (39)

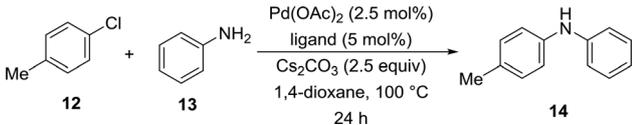[a] Reaction conditions: **5**, ArB(OH)₂, Pd(PPh₃)₄ (5 mol%), Na₂CO₃ (2 equiv.), 1,4-dioxane/H₂O (2 : 1) and HPR₂ (1 equiv.), Pd(OAc)₂ (2.5–5 mol%), Cs₂CO₃ (1.2 equiv.), DIPPF (2.5–10 mol%), 1,4-dioxane, 80 °C or **6**, reverse sequence of reactions.

Table 3 Optimization of conditions for the Suzuki–Miyaura cross-coupling model reaction

Entry	Ligand	Conditions	Conversion[a] (%)
1	3a		12
2	3m		20
3	3p		14
4	3r		>99[b]
5	3t		>99
6	3w		21
7	3y		55
8	3z		46
9	3ab		11
10	3r	K$_3$PO$_4$ was used as base	91
11	3r	reaction was performed at	4
12	3r	25 °C reaction was stirred	39
13	—	for 3 h no ligand	0
14	SPhos		>99
15	XPhos		>99

[a] Based on GC analyses of consumed 9. [b] Isolated yield of 96% was obtaisned.

Table 4 Screening of conditions for the Buchwald–Hartwig amination cross-coupling model reaction

Entry	Ligand	Conditions	Conversion[a] (%)
1	3a		38
2	3d		26
3	3e		>99[b]
4	3g		29
5	3h		54
6	3k		71
7	3n		0
8	3p		0
9	3q		>99
10	3r		92
11	3s		>99
12	3s	K$_3$PO$_4$ was used as base	83
13	3s	K$_2$CO$_3$ was used as base	0
14	3s	KOt-Bu was used as base	>99
15	3s	NaOt-Bu was used as base	>99

[a] Based on GC analyses of consumed 13. [b] Isolated yield of 76% was obtained.

palladium-catalyzed cross-coupling reactions with phosphines. In the second protocol, 2,3-diiodoimidazo[1,2-a]pyridine (5) or 3-bromo-2-iodoimidazo[1,2-a]pyridine (6) were prepared from 2-aminopyridine (1) followed by palladium-catalyzed phosphination/Suzuki or Suzuki/phosphination reactions sequences, respectively. We are currently exploring the scope and limitations of the 3-aryl-2-phosphinoimidazo[1,2-a]pyridine ligand 3r and 3e in our Suzuki–Miyaura and Buchwald–Hartwig amination cross-coupling reactions, respectively.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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