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Synthesis of 3-aryl-1-phosphinoimidazo[1,5-a]pyridine ligands for use in Suzuki–Miyaura cross-coupling reactions†‡

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3-Aryl-1-phosphinoimidazo[1,5-a]pyridine ligands were synthesized from 2-aminomethylpyridine as the initial substrate *via* two complementary routes. The first synthetic pathway underwent the coupling of 2-aminomethylpyridine with substituted benzoyl chlorides, followed by cyclization, iodination and palladium-catalyzed cross-coupling phosphination reactions sequence to give our phosphorus ligands. In the second route, 2-aminomethylpyridine was cyclized with aryl aldehydes, followed by the iodination and palladium-catalyzed cross-coupling phosphination reactions to yield our phosphorus ligands. The 3-aryl-1-phosphinoimidazo[1,5-a]pyridine ligands were evaluated in palladium-catalyzed sterically-hindered biaryl and heterobiaryl Suzuki–Miyaura cross-coupling reactions.

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Palladium-catalyzed cross-coupling methodologies have become common themes in modern organic synthesis.^{1–5} A decade before his death, Snieckus presented in his 2010 Nobel Prize review that privileged ligands 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.⁶ In the last two decades, 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. The overall rate of the reaction was increased with bulky trialkylphosphine or N-heterocyclic carbene ligands, which facilitated the oxidative addition processes of electron-rich, unactivated substrates like aryl chlorides.^{7,8} Monophosphine ligands have found widespread use in metal-catalyzed cross-coupling reactions.^{9–13} Privileged ligands such as Buchwald’s biarylphosphines,^{14–17} Stradiotto’s biaryl P–N phosphines,^{18–21} Fu/Koie/Shaugnessy’s trialkylphosphines,^{7,8,22} Hartwig’s ferrocenes,^{23,24} Ackermann’s diaminochlorophosphines,^{25,26} Beller’s bis(adamantyl)phosphines²⁷ and *N*-aryl(benz)imidazolyl- or *N*-pyrrolyl-monophosphines,^{28–30} Kwong’s indolyl-based monophosphines,^{31–35} Zhang’s ClickPhos ligands,^{36,37} Singer’s bippyPhos ligands,^{38,39} Rodriguez/Tang’s oxaphospholes,^{40,41} and Verkade’s proaza-phosphatranes^{42,43} have found wide-spread use in Suzuki–Miyaura, Corriu–Kumada, Heck, Negishi, Sonagashira, carbon–

heteroatom cross-coupling and Buchwald–Hartwig amination reactions (Fig. 1). Preformed catalysts with these ligands attached to the palladium metal center are also recognized in cross-coupling methodologies.^{44,45}

Our group is interested in a long-standing research program directed at the use of unexplored heterocyclic potential phosphorus ligands for cross-coupling reactions. Our first entry into the use of new heterocyclic phosphorus ligands was our

Fig. 1 Representative monophosphine ligands for palladium-catalyzed cross-coupling reactions.

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† This article is dedicated in memory of Professor Victor Snieckus.

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Previous work:

This current work:

Fig. 2 Our previous and current syntheses of imidazopyridine phosphorus ligands.

Scheme 1 Preparation of 1-phosphinoimidazo[1,5-*a*]pyridine ligands 7a–c from 2-aminomethylpyridine (3).

previously developed complementary synthetic routes for the preparation of 3-aryl-2-phosphino[1,2-*a*]pyridine ligands 2 from 2-aminopyridine (1) (Fig. 2).⁴⁶ In this current work, we have developed synthetic protocols to access 3-aryl-1-phosphinoimidazo[1,5-*a*]pyridine ligands 4 from 2-aminomethylpyridine (3) as our starting material.

The parent 1-phosphinoimidazo[1,5-*a*]pyridine ligands 7a–c were synthesized from imidazo[1,5-*a*]pyridine (5). Imidazo[1,5-*a*]pyridine (5), which is commercially available, was conveniently prepared in a two-step sequence *via* formylation and cyclization with phosphorus oxychloride from 2-aminomethylpyridine (3, Scheme 1).⁴⁷ Reaction of imidazo[1,5-*a*]pyridine (5) with *N*-iodosuccinimide (NIS) afforded 1-iodoimidazo[1,5-*a*]pyridine (6),⁴⁸ which underwent palladium-catalyzed reactions with different phosphines in the presence of 1,1'-bis(diisopropylphosphino)ferrocene (DIPPF) to deliver our 1-phosphinoimidazo[1,5-*a*]pyridine 7a–c ligands.⁴⁹

We were then interested in the preparation of various methoxy-substituted aryl imidazo[1,5-*a*]pyridine phosphorus ligands. 2-Aminomethylpyridine (3) reacted with various mono-, di-, and trimethoxy-substituted benzoyl chlorides, prepared from the corresponding benzoic acids with oxalyl chloride, to afford *N*-[(pyridin-2-yl)methyl]arylamides 8c–i in excellent yields (Scheme 2, Route A).⁵⁰ The arylamides 8c–i were then cyclized to generate 3-arylimidazo[1,5-*a*]pyridines 9c–i in the presence of phosphorus oxychloride under reflux in good yields, which were very pure and carried onto the next step

Scheme 2 Preparation of 3-aryl-1-phosphinoimidazo[1,5-*a*]pyridine ligands 4a–s from 2-aminomethylpyridine (3) *via* Routes A and B.

without further purification.⁵¹ Route B showed that 2-methoxy-, 3-methoxy- and 3,4,5-trimethoxybenzaldehydes were reacted with 2-aminomethylpyridine (3) in the presence of TBHP and I₂ in DMF at 70 °C to afford 3-arylimidazo[1,5-*a*]pyridines 9a–b/j in moderate yields.⁵² We found that Route A was more convenient compared to Route B in terms of yields, time, and purification.

With intermediates 9a–j obtained from Routes A and B in hand, two different conditions to iodinate at the C-1 position were explored. Substrates 9a–j were successfully iodinated at the C-1 position using either NIS in acetonitrile⁴⁸ at room temperature or I₂ in THF under reflux to give 1-iodo-3-arylimidazo[1,5-*a*]pyridines 10a–j in low to excellent yields.⁵³ It was noted that mono- and dimethoxy substrates must be iodinated with NIS in acetonitrile within 3 h. Otherwise, the compounds would be over-iodinated on multiple carbons. However, the trimethoxy substrates were unsuccessful with NIS in acetonitrile within 3 h, but successful with I₂ in THF under reflux to give moderate yields. The trimethoxy substrates could be iodinated with NIS in acetonitrile but the time of the reaction needed to be 24 h at room temperature as shown for compound 9h (Table 1). As from our previous investigations, we successfully synthesized our phosphorus ligands *via* the palladium-catalyzed cross-coupling phosphination reaction using the iodo precursors with DIPPF ligand in the presence of Cs₂CO₃ as the base in 1,4-dioxane under reflux.⁴⁶ Iodo substrates 10a–j were successfully phosphinated at the C-1 position *via* the palladium-catalyzed reaction with diphenylphosphine and dicyclohexylphosphine to give new ligands 4a–s in low to moderate yields.⁴⁹ Many attempts to attach a di-*tert*-butylphosphine group to the iodo

Table 1 Iodination and palladium-catalyzed phosphination sequence reactions of 2-iodoimidazo[1,5-*a*]pyridines **9** and **10**

Entry	R	Ar	Route/substrate	Iodination (% yield)	Phosphination ^c (% yield)
1	Cy	Ph	B, 9a	10a (96) ^a	4a (68)
2	Ph	Ph	B, 9a	10a (96) ^a	4b (38)
3	Cy	2-OMeC ₆ H ₄	B, 9b	10b (99) ^a	4c (78)
4	Ph	2-OMeC ₆ H ₄	B, 9b	10b (82) ^a	4d (62)
5	Cy	3-OMeC ₆ H ₄	B, 9c	10c (82) ^a	4e (58)
6	Ph	3-OMeC ₆ H ₄	B, 9c	10c (82) ^a	4f (33)
7	Cy	4-OMeC ₆ H ₄	A, 9d	10d (72) ^a	4g (44)
8	Ph	4-OMeC ₆ H ₄	A, 9d	10d (72) ^a	4h (65)
9	Cy	2,4-DiOMeC ₆ H ₃	A, 9e	10e (99) ^a	4i (41)
10	Ph	2,4-DiOMeC ₆ H ₃	A, 9e	10e (99) ^a	4j (65)
11	Cy	2,5-DiOMeC ₆ H ₃	A, 9f	10f (50) ^a	4k (90)
12	Ph	2,5-DiOMeC ₆ H ₃	A, 9f	10f (50) ^a	4l (63)
13	Cy	2,6-DiOMeC ₆ H ₃	A, 9g	10g (94) ^a	4m (51)
14	Ph	2,6-DiOMeC ₆ H ₃	A, 9g	10g (94) ^a	4n (54)
15	Cy	2,3,4-TriOMeC ₆ H ₂	A, 9h	10h (95) ^d	4o (40)
16	Cy	2,4,5-TriOMeC ₆ H ₂	A, 9i	10i (64) ^b	4p (52)
17	Ph	2,4,5-TriOMeC ₆ H ₂	A, 9i	10i (64) ^b	4q (56)
18	Cy	3,4,5-TriOMeC ₆ H ₂	A, 9j	10j (50) ^b	4r (48)
19	Ph	3,4,5-TriOMeC ₆ H ₂	A, 9j	10j (50) ^b	4s (49)

^a Reaction conditions: NIS, CH₃CN, 25 °C, 3 h. ^b I₂, THF, reflux. ^c HPR₂ (1 equiv.), Pd(OAc)₂ (2 mol%), Cs₂CO₃ (1.2 equiv.), DIPPF (2.5 mol%), 1,4-dioxane, 80 °C. ^d NIS, CH₃CN, 25 °C, 24 h.

intermediates met with complete failure. Our early attempts to perform the metal–halogen exchange of the iodo intermediates followed by trapping with disubstituted chlorophosphines failed to yield any trace of phosphinated products.

We have investigated numerous routes to prepare our regioisomeric, 1-aryl-3-phosphinoimidazo[1,5-*a*]pyridine ligands which all succumbed to our synthetic efforts, including chemistry that involved utilization of 1,3-diiodoimidazo[1,5-*a*]pyridine. Our success in achieving excellent selectivity with our 2,3-diiodoimidazo[1,2-*a*]pyridine in our previous work did not translate well to this system.⁴⁶ No selectivity was observed when attempting to phosphinate or to couple an aryl ring onto the 1,3-diiodoimidazo[1,5-*a*]pyridine system, usually yielding a rough 1 : 1 ratio of inseparable regioisomers.

With our library of functionalized imidazo[1,5-*a*]pyridine phosphorus ligands **4a–s** 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 (**11**) and 2-methoxyphenylboronic acid (**12**) to give 2,6-dimethyl-(2-methoxy)biphenyl (**13**) as our model reaction as outlined in Table 2. 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 20 and 21). With the GC conditions validated, we screened selected ligands **7a–7b** and **4a–s**. It was clearly evident that the di-*tert*-butyl and diphenyl phosphorus ligands represented by **7b**, **4d** and **4n** were ineffective ligands in our model reaction (entries 2, 5, and 10). However, the dicyclohexyl phosphorus ligands shown by **4k** and **4m** showed greater than 99%

Table 2 Screening of reaction conditions for the Suzuki–Miyaura cross-coupling model reaction

Entry	Ligand	Conditions	Conversion ^a (%)
1	7a		8
2	7b		3
3	4a		68
4	4b		40
5	4d		11
6	4g		62
7	4h		43
8	4k		>99
9	4m		>99 ^{b,c}
10	4n		4
11	4o		13
12	4p		7
13	4q		31
14	4r		69
15	4m	K ₃ PO ₄ was used as a base	65
16	4m	Reaction was performed at 25 °C	4
17	4m	Reaction was stirred for 3 h at 80 °C	47
18	4m	No base	0
19	—	No ligand	0
20	SPhos		>99
21	XPhos		>99

^a Based on GC analyses of consumed **11** and formation of **13**. ^b Isolated yield of 96% was obtained. ^c Isolated yield of 88% was obtained, when the reaction was scaled to 16.2 mmol of **11** with 0.5 mol% of **4m** and 0.25 mol% of Pd(OAc)₂.

Table 3 Selected Suzuki–Miyaura cross-coupling reactions with hetero(aryl) halides with hetero(aryl)boronic acids

conversions by GC analyses (entries 8 and 9). Further exploration of ligand **4m** with K_3PO_4 as the base, stirring the reaction overnight at room temperature or for 3 h at 80 °C showed inferior conversions (entries 15–17). There was no conversion when a base or a ligand were not used in the model reaction (entries 18 and 19). The reaction was scaled up to 3.0 g of **11** (16.2 mmol) with lower catalyst and ligand loadings (0.25 mol% and 0.50 mol%, respectively), and we were gratified that an 88% isolated yield was obtained (Table 2, entry 9, footnote c).

With ligand **4m** under optimized conditions, we explored a short preliminary study of palladium-catalyzed Suzuki–Miyaura cross-coupling reactions as shown in Table 3. 4-Chlorobenzonitrile and 2-bromoaniline were reacted with 2-methoxybenzeneboronic acid to deliver biaryls **14** and **15** in 92% and 88%, respectively, under our optimized reaction conditions. Sterically-encumbered biaryls **16** and **17** were synthesized from bromoarenes with 2,3-dimethoxybenzeneboronic acids in good yields. Heterocyclic halides with pyridine and pyrimidine cores reacted with furan, pyridine, benzothiophene, and thiophene boronic acids to deliver biheteroaryls **18–21** in all good yields.

In conclusion, two complementary synthetic routes to 3-aryl-1-phosphinoimidazo[1,5-a]pyridine ligands **4** from 2-aminomethylpyridine (**3**) as our starting material are reported. The first synthetic pathway underwent the coupling of 2-aminomethylpyridine with substituted benzoyl chlorides, followed by cyclization, iodination and palladium-catalyzed cross-coupling phosphination reactions sequence to give our phosphorus ligands. In the second route, 2-aminomethylpyridine was

cyclized with substituted benzaldehydes, followed by the iodination and palladium-catalyzed cross-coupling phosphination reactions to give our phosphorus ligands. Our optimization screening studies revealed ligand **4m** were active in palladium-catalyzed sterically-hindered biaryl and heterobiaryl Suzuki–Miyaura cross-coupling reactions. We are currently exploiting the further use of our phosphorus ligands in the scope and limitations of the Suzuki–Miyaura and Buchwald–Hartwig cross-coupling reactions, and these full efforts will be reported in future publications.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 A. Biffis, P. Centomo, A. Del Zotto and M. Zecca, *Chem. Rev.*, 2018, **118**, 2249–2295.
- 2 *New Trends in Cross-Coupling: Theory and Applications*, ed. T. J. Colacot, The Royal Society of Chemistry, Cambridge, UK, 2015.
- 3 In Special Issue on Cross-Coupling, ed. S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1439–1564, entire issue.
- 4 In Special Issue on Frontiers in Transition Metal Catalyzed Reactions, ed. J. A. E. Gladysz, *Chem. Rev.*, 2011, **111**, 1170–2485, entire issue.
- 5 *Metal-Catalyzed Cross-Coupling Reactions and More*, ed. A. de Meijere, S. Bräse and M. Oestreich, 3 volume set, Wiley-VCH, Weinheim, 2014.
- 6 C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062–5085.
- 7 A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176–4211.
- 8 C. A. Fleckenstein and H. Plenio, *Chem. Soc. Rev.*, 2010, **39**, 694–711.
- 9 S. M. Wong, C. M. So and F. Y. Kwong, *Synlett*, 2012, 1132–1153.
- 10 R. J. Lundgren and M. Stradiotto, *Chem.–Eur. J.*, 2012, **18**, 9758–9769.
- 11 K. H. Shaughnessy, *Curr. Org. Chem.*, 2020, **24**, 231–264.
- 12 E. A. Onoabedje and U. C. Okoro, *Synth. Commun.*, 2019, **49**, 2117–2146.
- 13 *Ligand Design in Metal Chemistry*, ed. R. J. Lundgren and M. Stradiotto, John Wiley & Sons, Ltd, West Sussex, United Kingdom, 2016.
- 14 R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461–1473.
- 15 D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338–6361.

- 16 D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27–50.
- 17 B. T. Ingoglia, C. C. Wagen and S. L. Buchwald, *Tetrahedron*, 2019, **75**, 4199–4211.
- 18 R. J. Lundgren, B. D. Peters, P. G. Alsabeh and M. Stradiotto, *Angew. Chem., Int. Ed.*, 2010, **49**, 4071–4074.
- 19 R. J. Lundgren, A. Sappong-Kumankumah and M. Stradiotto, *Chem.–Eur. J.*, 2010, **16**, 1983–1991.
- 20 B. J. Tardiff, R. McDonald, M. J. Ferguson and M. Stradiotto, *J. Org. Chem.*, 2012, **77**, 1056–1071.
- 21 B. J. Tardiff and M. Stradiotto, *Eur. J. Org. Chem.*, 2012, 3972–3977.
- 22 G. C. Fu, *Acc. Chem. Res.*, 2008, **41**, 1555–1564.
- 23 A. Fihri, P. Meunier and J.-C. Hierso, *Coord. Chem. Rev.*, 2007, **251**, 2017–2055.
- 24 J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534–1544.
- 25 L. Ackermann, J. H. Spatz, C. J. Gschrei, R. Born and A. Althammer, *Angew. Chem., Int. Ed.*, 2006, **45**, 7627–7630.
- 26 L. Ackermann, H. K. Potukuchi, A. Althammer, R. Born and P. Mayer, *Org. Lett.*, 2010, **12**, 1004–1007.
- 27 A. Zapf, A. Ehrentraut and M. Beller, *Angew. Chem., Int. Ed.*, 2000, **39**, 4153–4155.
- 28 S. Harkal, F. Rataboul, A. Zapf, C. Fuhrmann, T. Riermeier, A. Monsees and M. Beller, *Adv. Synth. Catal.*, 2004, **346**, 1742–1748.
- 29 A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen and M. Beller, *Chem. Commun.*, 2004, 38–39.
- 30 T. Schulz, C. Torborg, B. Schäffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 918–921.
- 31 C. M. So, C. P. Lau and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2008, **47**, 8059–8063.
- 32 C. M. So, Z. Zhou, C. P. Lau and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2008, **47**, 6402–6406.
- 33 C. M. So, H. W. Lee, C. P. Lau and F. Y. Kwong, *Org. Lett.*, 2009, **11**, 317–320.
- 34 P. Y. Choy, O. Y. Yuen, M. P. Leung, W. K. Chow and F. Y. Kwong, *Eur. J. Org. Chem.*, 2020, **2020**, 2846–2853.
- 35 C. M. So, W. K. Chow, P. Y. Choy, C. P. Lau and F. Y. Kwong, *Chem.–Eur. J.*, 2010, **16**, 7996–8001.
- 36 D. Liu, W. Gao, Q. Dai and X. Zhang, *Org. Lett.*, 2005, **7**, 4907–4910.
- 37 Q. Dai, W. Gao, D. Liu, L. M. Kapes and X. Zhang, *J. Org. Chem.*, 2010, **71**, 3928–3934.
- 38 R. A. Singer, M. Doré, J. E. Sieser and M. A. Berliner, *Tetrahedron Lett.*, 2006, **47**, 3727–3731.
- 39 G. J. Withbroe, R. A. Singer and J. E. Sieser, *Org. Process Res. Dev.*, 2008, **12**, 480–489.
- 40 W. Tang, A. G. Capacci, X. Wei, W. Li, A. White, N. D. Patel, J. Savoie, J. J. Gao, S. Rodriguez, B. Qu, N. Haddad, B. Z. Lu, D. Krishnamurthy, N. K. Yee and C. H. Senanayake, *Angew. Chem., Int. Ed.*, 2010, **49**, 5879–5883.
- 41 S. Rodriguez, B. Qu, N. Haddad, D. C. Reeves, W. Tang, H. Lee, D. Krishnamurthy and C. H. Senanayake, *Adv. Synth. Catal.*, 2011, **353**, 533–537.
- 42 S. Ugaonkar, M. Nagarajan and J. G. Verkade, *Tetrahedron Lett.*, 2002, **43**, 8921–8924.
- 43 S. Ugaonkar, J.-H. Xu and J. G. Verkade, *J. Org. Chem.*, 2003, **68**, 8416–8423.
- 44 H. Li, C. C. C. J. Seechurn and T. J. Colacot, *ACS Catal.*, 2012, **2**, 1147–1164.
- 45 P. G. Gildner and T. J. Colacot, *Organometallics*, 2015, **34**, 5497–5508.
- 46 R. Q. Tran, S. A. Jacoby, K. E. Roberts, W. A. Swann, N. W. Harris, L. P. Dinh, E. L. Denison and L. Yet, *RSC Adv.*, 2019, **9**, 17778–17782.
- 47 M. Mihorianu, M. H. Franz, P. G. Jones, M. Freytag, G. Kelter, H.-H. Fiebig, M. Tamm and I. Neda, *Appl. Organomet. Chem.*, 2016, **30**, 581–589.
- 48 S. Fuse, T. Ohuchi, Y. Asawa, S. Sato and H. Nakamura, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 5887.
- 49 M. Murata and S. L. Buchwald, *Tetrahedron*, 2004, **60**, 7397–7403.
- 50 G. Pelletier and A. B. Charette, *Org. Lett.*, 2013, **15**, 2290–2293.
- 51 V. Arvapalli, G. Chen, S. Kosarev, E. Tan, D. Xie and L. Yet, *Tetrahedron Lett.*, 2010, **51**, 284–286.
- 52 H. Ludan, G. Lingfeng, W. Changfeng and W. Zhiyong, *Acta Chim. Sin.*, 2013, **71**, 1603–1606.
- 53 F. Shibahara, E. Yamaguchi, A. Kitagawa, A. Imai and T. Murai, *Tetrahedron*, 2009, **65**, 5062–5073.