Exploring Phosphabicyclononane Ligands in Suzuki-Miyaura and Mizoroki-Heck Reactions

Ntombenhle M. Masanabo[1], Paseka T. Moshapo[1], Cedric W. Holzapfel[1] and Munaka C. Maumela[1,2]*

[1] *Research Centre for Synthesis and Catalysis, Department of Chemical Sciences, University of Johannesburg, Johannesburg, South Africa.*
[2]*Research & Technology, Sasol, Sasolburg, South Africa.*

ABSTRACT

Herein, we report a first screening and reaction optimization of Pd and 9-eicosyl-9-phosphabicyclononane (phoban) catalysts possessing a C-20 alkyl chain for Suzuki-Miyaura and Mizoroki-Heck cross-coupling reactions. In general, the optimal reactions were conducted in dioxane at 95 °C in the presence of Cs_2CO_3 and low catalyst loadings of 1.5 mol% Pd and 3.6 mol% ligand for the Suzuki coupling of a wide array of electronically and structurally diverse aryl bromides, chlorides, and boronic acids. Aryl bromides afforded 13 products in 82% average GC yield, whilst aryl chlorides afforded 9 products in 74% average GC yield. Variation of the aryl boronic acids yielded 10 products with an average GC yield of 58%. A ligand comparative study demonstrated better activity of the phosphabicyclononane ligands compared to triphenylphosphine and tris(*o*-tolyl)phosphine under the reported Suzuki cross-coupling reaction conditions. However, dialkylbiaryl phosphine ligands developed by Buchwald were superior. In addition, 2 mol% Pd and 4 mol% ligand, in dioxane solvent and K_2CO_3 at 120 °C, were required to afford 15 Heck cross-coupling products with average GC yields of 81%. The optimized protocols were also used to synthesize industrially valuable products 8n, 10o, 12a, and 12b.

KEYWORDS

Suzuki-Miyaura, Mizoroki-Heck, Palladium, Phosphine ligands, Cross-coupling

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INTRODUCTION

Carbon-carbon and carbon-heteroatom bond-forming reactions are essential for the synthesis of natural products, agrochemicals, polymers, and pharmaceutical compounds.[1,2,3] Thus, these reactions have undergone continuous research and development to establish reaction conditions that are sustainable and compatible with a broad range of substrates at ambient reaction temperatures.[4,5] Some of these improvements have been achieved through the development of new ligands that generate more active catalyst systems, which can efficiently produce cross-coupling products at low catalyst loading. Ligand properties such as steric bulk and electronic properties around the phosphorus atom have often been found to influence the performance of phosphine ligands in various metal-catalyzed reactions.[6] This has been realized with biaryl ligands reported by Buchwald, as well as bulky trialkyl ligands such as tri-*tert*-butylphosphine and tricyclohexylphosphine, which have been reported to generate highly active palladium catalysts.[7,8,9,10] However, there are still challenges associated with some active catalysts, including the need for inert working conditions due to poor air stability and the higher cost of more stable ligands. Thus, there remains a need to design, synthesize, and evaluate alternative phosphine ligand systems with structural and electronic features similar to those of the parent phosphine ligand to improve stability, catalytic activity, and affordability.[11,12]

Since its discovery in 1979, the Suzuki-Miyaura reaction has been utilized to construct carbon-carbon bonds between aryl or vinyl boronic acids and various aryl halides or equivalent substrates.[13] Although biaryl phosphine ligands have provided stable and active catalysts for effective cross-coupling reactions, trialkyl phosphine ligands such as those reported by Capretta and co-workers have equally demonstrated Suzuki-Miyaura cross-coupling activity under mild reaction conditions.[14] A study on C-C and C-N coupling reactions catalyzed by a variety of ligands, including those possessing the phosphabicyclononane (phoban) structural unit, prompted us to explore phoban ligands as potential candidates for application in palladium-catalyzed cross-coupling reactions.[15] In addition, phoban ligands have demonstrated potential for application in metal-catalyzed reactions such as hydroformylation and alkene metathesis.[16,17] This class of ligands can be obtained through the radical addition of primary phosphine **1** to a relatively inexpensive cis,cis-1,5-cyclooctadiene **2**, affording products as a mixture of [3.3.1] and [4.2.1] cyclooctyl bicyclic regioisomers **3** and **4** in a 2:1 ratio (Scheme 1).[18, 19] The phosphine substituent R can be various functional groups such as carbonyl, amino, hydroxyl, or an alkyl chain. Following our recent reports on the catalytic activities of biaryl phosphabicyclononane ligands and other related *P*-bridged ligands,[20,21,22,23] in this study, we explore the application of phosphabicyclononane ligands possessing a 20-carbon alkyl chain (Phoban-C20) in Suzuki-Miyaura and Mizoroki-Heck cross-coupling reactions.

EXPERIMENTAL

General methods and chemicals

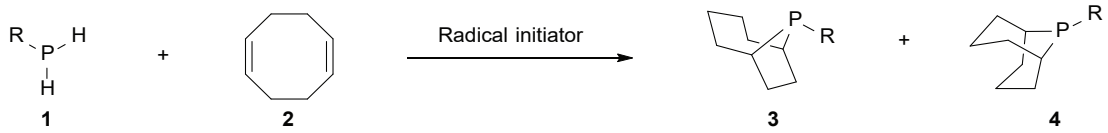
All compounds were synthesised under inert conditions in pressure tubes. The reactions were monitored using a Shimadzu GC-FID-2010. NMR spectra (^{1}H and ^{13}C) were obtained from a Bruker Ultrashield 400 MHz magnet and an Avance III 400 MHz Console, using $CDCl_3$ as the solvent. All chemicals used in this study were purchased from Merck and used without further purification. All solvents were anhydrous and were of the highest purity available. Phoban-C20 was supplied by Sasol Research and Technology (RSA) in a 1:0.4 ratio ([3.3.1]:[4.2.1]) and used without further purification.

General procedure for the Suzuki-Miyaura coupling reactions

A pressure tube containing aryl halide (2.833 mmol), boronic acid (2.875 mmol), Pd source (1.5 mol %), phoban-C20 (3.6 mol %), and Cs_2CO_3 (2 eq.) were dissolved in 5 mL anhydrous dioxane and stirred for 24 hr at 95 °C under argon. After 24 hours, the reaction mixture was cooled to room temperature. Once cooled, 30 mL of ethyl acetate

*To whom correspondence should be addressed
Email: chris.maumela@sasol.com

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Scheme 1: General synthesis of phosphabicyclononane ligands **3** and **4**.

was added to the reaction mixture, which was then washed 3-5 times with deionised water (10 mL each). The organic layer was dried over $MgSO_4$ and then filtered. The solvent was then removed under vacuum, yielding a crude product. Purification of the product was conducted using column chromatography to yield the corresponding products:

4-Methoxybiphenyl (7a/ 8a)

7a: GC yield = 84%, isolated yield = 76%; **8a**: GC yield = 65%, isolated yield = 55%. δ_H (400 MHz, $CDCl_3$): 7.58 (m, 4H), 7.45 (t, *J* 7.6 Hz, 2H), 7.34 (m, 1H), 7.01 (d, *J* 8.4 Hz, 2H), 3.86 (s, 3H); δ_c (100 MHz, $CDCl_3$): 159.2, 140.9, 133.8, 128.8, 128.2, 126.8, 126.7, 114.2 (Ar), 55.4 (OCH_3). Spectroscopic data agreed with the reported literature data.[24]

2-Methylbiphenyl (7b/ 8b)

7b: GC yield = 84%, isolated yield = 60%; **8b**: GC yield = 47% Isolated yield = 34%. δ_H (400 MHz, $CDCl_3$): 7.45 (t, *J* 7.3 Hz, 2H), 7.39-7.35 (m, 3H), 7.28-7.27 (m, 4H), 2.19 (s, 3H); δ_c (100 MHz, $CDCl_3$): 139.6, 138.6, 130.9, 130.7, 129.6, 128.6, 128.0, 127.0, 125.5, 120.9 (Ar), 20.1 (CH_3). Spectroscopic data agreed with the reported literature data.[25]

3-Methylbiphenyl (7c)

GC yield = 86%, isolated yield = 67%. δ_H (400 MHz, $CDCl_3$): 7.66-7.62 (m, 2H), 7.51-7.30 (m, 6H), 7.24-7.12 (m, 1H), 2.46 (s, 3H); δ_c (100 MHz, $CDCl_3$): 141.3, 141.2, 138.3, 128.7, 128.6, 128.0, 127.9, 127.1, 124.2 (Ar), 21.52 (CH_3). Spectroscopic data agreed with the reported literature data.[25]

4-Methylbiphenyl (7d/ 8d)

7d: GC yield = 84%, isolated yield = 71%; **8d**: GC yield = 69%, isolated yield = 59%. δ_H (400 MHz, $CDCl_3$): 7.64 (d, *J* 7.6 Hz, 2H,), 7.54 (d, *J* 8.0 Hz, 2H), 7.48 (t, *J* 7.6 Hz, 2H), 7.34 (d, *J* 7.2 Hz, 1H), 7.30 (d, *J* 4.8 Hz, 2H), 2.43 (s, 3H); δ_c (100 MHz, $CDCl_3$): 141.2, 138.4, 137.0, 129.5, 128.7, 127.1, 127.0, 127.0 (Ar), 21.1 (CH_3). Spectroscopic data agreed with the reported literature data.[24]

2-Isopropylbiphenyl (7e)

GC yield = 88%, isolated yield = 76%. δ_H (400 MHz, $CDCl_3$): 7.90 (d, *J* 6.0 Hz, 1H), 7.77-7.71 (m, 2H), 7.50-7.14 (m, 6H), 3.08-2.99 (m, 1H), 1.15 (d, *J* 5.6 Hz, 6H); δ_c (100 MHz, $CDCl_3$): 146.3, 141.0, 129.9, 129.3, 128.7, 12.7.9, 127.6, 127.2, 127.2, 126.7 (Ar), 29.3 (CH), 24.26 (CH_3). Spectroscopic data agreed with the reported literature data.[25]

Biphenyl-4-ol (7f)

GC yield = 74%, isolated yield = 58%. δ_H (400 MHz, $CDCl_3$): 7.53-7.20 (m, 7H), 6.90 (d, *J* 8.4 Hz, 2H), 4.70 (s, 1H); δ_c (100 MHz, $CDCl_3$): 155.1 (C-O), 140.8, 134.1, 128.7, 128.4, 126.7, 126.7, 115.7 (Ar). Spectroscopic data agreed with the reported literature data.[26]

Biphenyl-4-carbaldehyde (7g/ 8g)

7g: GC yield = 78%, isolated yield = 52%; **8g**: GC yield = 95%, isolated yield = 54%. δ_H (400 MHz, $CDCl_3$): 10.05 (s, 1H), 7.95 (d, *J* 8.0 Hz, 2H), 7.75 (d, *J* 8.0 Hz, 2H), 7.63 (d, *J* 7.2 Hz, 2H), 7.50-7.35 (m, 3H); δ_c (100 MHz, $CDCl_3$): 191.8 (CHO), 147.1, 139.7, 135.2, 130.2, 129.0, 128.4, 127.6, 127.3 (Ar). Spectroscopic data agreed with the reported literature data.[24]

4-Phenylacetophenone (7h/ 8h)

7h: GC yield = 95%, isolated yield = 88%; **8h**: GC yield = 86%, isolated yield = 79%. δ_H (400 MHz, $CDCl_3$): 8.03 (d, *J* 8.0 Hz, 2H), 7.68 (d, *J* 8.0 Hz, 2H), 7.60-7.45 (m, 5H), 2.63 (s, 3H); δ_c (100 MHz, $CDCl_3$): 145.5 (C=O), 134.0, 133.8, 133.7, 132.7, 130.02, 129.9, 129.4, 128.6 (Ar), 21.21 (CH_3). Spectroscopic data agreed with the reported literature data.[24]

2-Nitrobiphenyl (7i)

GC yield = 74%, isolated yield = 69%. δ_H (400 MHz, $CDCl_3$): 7.89 (d, *J* 8.0 Hz, 1H), 7.67 (t, *J* 8.0 Hz, 1H), 7.53 (m, 5H), 7.36 (m, 2H); δ_c (100 MHz, $CDCl_3$): 149.3, 137.4, 136.4, 132.3, 132.0, 128.7, 128.2, 128.2, 127.9, 124.1 (Ar). Spectroscopic data agreed with the reported literature data.[27]

4-Nitrobiphenyl (7j/ 8j)

7j: GC yield = 73%, isolated yield = 69%; **8j**: GC yield = 66%, isolated yield = 57%. δ_H (400 MHz, $CDCl_3$): 8.30 (d, *J* 8.4 Hz, 2H), 7.73 (d, *J* 8.4 Hz, 2H), 7.62 (m, 2H), 7.50-7.41 (m, 3H); δ_c (100 MHz, $CDCl_3$): 147.6, 147.2, 138.8, 129.1, 128.9, 127.8, 127.37, 124.1 (Ar). Spectroscopic data agreed with the reported literature data.[27]

Biphenyl-2-carbonitrile (7k/ 8k)

7k: GC yield = 77%, isolated yield = 66%; **8k**: GC yield = 80%, isolated yield = 65%. δ_H (400 MHz, $CDCl_3$): 7.67 (d, *J* 8.0 Hz, 2H), 7.65-7.47 (m, 5H), 7.34-7.33 (m, 2H); δ_c (100 MHz, $CDCl_3$): 136.9, 133.9, 133.8, 132.8, 130.0, 128.7, 128.7, 128.0, 127.5, 127.1, 113.4 (Ar), 115.9 (CN). Spectroscopic data agreed with the reported literature data.[28]

Biphenyl-4-carbonitrile (7l/ 8l)

7l: GC yield = 74%, isolated yield = 62%, **8l**: GC yield = 74%, isolated yield = 60%. δ_H (400 MHz, $CDCl_3$) δ: 7.70-7.65 (m, 4H), 7.58-7.57 (m, 2H), 7.49-7.47 (m, 2H), 7.45-7.39 (m, 1H); δ_c (100 MHz, $CDCl_3$): 145.6, 139.1, 132.5, 129.1, 128.6, 127.7, 127.2 (Ar), 118.9 (CN), 110.9 (Ar). Spectroscopic data agreed with the reported literature data.[27]

4-(Trifluoromethyl)biphenyl (7m/ 8m)

7m: GC yield = 84%, isolated yield = 62%, **8m**: GC yield = 83%, isolated yield = 72%. δ_H (400 MHz, $CDCl_3$): 7.69-7.58 (m, 4H), 7.49-7.48 (m, 2H), 7.45-7.42 (m, 2H), 7.41-7.40 (m, 1H); δ_c (100 MHz, $CDCl_3$): 144.7, 139.8, 129.2, 128.2, 127.4, 127.3, 127.2, 125.7, 125.7 (Ar). Spectroscopic data agreed with the reported literature data.[27]

4-Fluoro-4'-methoxylbiphenyl (7n)

GC yield = 77%, isolated yield = 64%. δ_H (400 MHz, $CDCl_3$): 7.51-7.46 (m, 4H), 7.18-7.13 (m, 2H), 7.10-6.96 (m, 2H), 3.84 (s, 3H); δ_c (100 MHz, $CDCl_3$): 159.12(C-F), 137.00, 132.84, 128.28, 128.20, 128.06, 115.67, 114.27 (Ar), 55.37 (OCH_3). Spectroscopic data agreed with the reported literature data.[29]

4.4'-Dimethoxybiphenyl (7o)

GC yield = 57%, isolated yield = 52%. δ_H (400 MHz, $CDCl_3$): 7.58-7.40 (m, 4H), 7.02-6.90 (m, 4H), 3.87 (s, 6H); δ_c (100 MHz, $CDCl_3$): 158.7, 133.5, 127.7, 114.2 (Ar), 55.3 (OCH_3). Spectroscopic data agreed with the reported literature data.[30]

***4-Methoxy-2'-methylbiphenyl* (7p)**

GC yield = 67%, isolated yield = 51%. δ_H (400 MHz, $CDCl_3$): 7.29-7.25 (m, 6H), 6.99-6.97 (m, 2H), 3.89 (s,3H), 2.31 (s, 3H); δ_c (100 MHz, $CDCl_3$): 158.5, 141.6, 135.2, 134.4, 130.3, 130.2, 129.9, 126.9, 125.7, 113.5 (Ar), 55.26 (OCH_3), 20.45 (CH_3). Spectroscopic data agreed with the reported literature data.[31]

***4-Methoxy-4'-methylbiphenyl* (7q)**

GC yield = 78%, isolated yield = 56%. δ_H (400 MHz, $CDCl_3$): 7.40 (d, *J* 6.8 Hz, 2H), 7.34 (d, *J* 8.0 Hz, 2H), 7.11 (d, *J* 8.0 Hz, 2H), 6.85 (d, *J* 8.8 Hz, 2H), 3.70 (s, 3H), 2.26 (s, 3H); δ_c (100 MHz, $CDCl_3$): 158.7 (C-O), 137.9, 133.6, 129.4, 127.9, 127.7, 126.7, 114.1 (Ar), 55.2 (OCH_3), 21.0 (CH_3). Spectroscopic data agreed with the reported literature data.[31]

***4'-Methoxy-[1,1'biphenyl]-4-carbonitrile* (7t)**

GC yield = 58%, isolated yield = 42%. δ_H (400 MHz, $CDCl_3$): **δ** 7.73 (d, *J* 8.0 Hz, 2H), 7.67 (d, *J* 8.0 Hz, 2H), 7.60 (d, *J* 8.0 Hz, 2H), 7.01 (d, *J* 8.0 Hz, 2H), 3.86 (s, 3H); δ_c (100 MHz, $CDCl_3$): 159.5 (C-O), 145.3, 133.1, 132.8, 130.1, 127.7, 118.7 (CN), 115.0, 111.5, 55.8 (CH_3). Spectroscopic data agreed with the reported literature data.[32]

***4'-Methyl-[1,1'biphenyl]-4-carbonitrile* (7u)**

GC yield = 81%, isolated yield = 57%. δ_H (400 MHz, $CDCl_3$): 7.90-7.65 (m, 4H), 7.49 (d, *J* 8.0 Hz, 2H), 7.28 (d, *J* 8.0 Hz, 2H), 2.40 (s, 3H); δ_c (100 MHz, $CDCl_3$): 145.6 (CN), 138.7, 136.2, 132.5, 129.80, 127.4, 127.0, 119.0, 110.5 (Ar), 21.1 (CH_3). Spectroscopic data agreed with the reported literature data.[31]

***2-Cyno-4-methylbiphenyl* (8n)**

GC yield = 80%, isolated yield = 65%. δ_H (400 MHz, $CDCl_3$): 7.63 (d, *J* 6.8 Hz, 1H), 7.29 (d, *J* 8.0 Hz, 2H), 7.72 (d, *J* 8.0 Hz, 1H), 7.51-7.43 (m, 3H), 7.60 (d, *J* 6.8 Hz, 1H), 2.40 (s, 3H); δ_c (100 MHz, $CDCl_3$): 145.5, 138.7, 133.9, 133.8, 132.7, 132.7, 130.0, 129.9, 129.4, 128.6, 127.2, 127.1 (Ar), 111.2 (CN), 21.2 (CH_3). Spectroscopic data agreed with the reported literature data.[33]

General procedure for the Mizoroki-Heck coupling reactions

A pressure tube containing a mixture of aryl halide (2.5 mmol), olefin (3 mmol), base (3 mmol), Pd source (0.05 mmol), phoban-C20 (0.10 mmol), and anhydrous dioxane (2.5 mL) was stirred under argon for 24 hr at 120 °C. After 24 hr, the reaction mixture was cooled to room temperature. Once cooled, 30 mL of ethyl acetate was added to the reaction mixture, which was then washed 3-5 times with deionized water (10 mL each). The organic layer was dried over $MgSO_4$ and then filtered. The solvent was removed under vacuum, yielding a crude product containing the desired product. Purification of the product was conducted using column chromatography to yield the corresponding products:

***(E)-Butyl 3-(4-methoxyphenyl)acrylate* (10a)**

GC yield = 93%, isolated yield = 74 %. δ_H (400 MHz, $CDCl_3$): 7.62 (d, *J* 16.0 Hz, 1H), 7.45 (d, *J* 7.2 Hz, 2H), 6.88 (d, *J* 6.4 Hz, 2H), 6.31 (d, *J* 16.0 Hz, 1H), 4.19 (t, *J* 6.6 Hz, 2H), 3.81 (s, 3H), 1.68-1.64 (m, 2H), 1.44-1.39 (m, 2H), 0.95 (t, *J* 7.3 Hz, 3H); δ_c (100 MHz, $CDCl_3$): 167.3 (C=O), 161.3 (C-O), 144.2 (CH), 129.6, 127.3 (Ar), 115.8 (CH), 114.7, 64.2 (CH_2), 55.3 (O-CH_3), 30.8 (CH_2), 19.1 (CH_2), 13.6 (CH_3). Spectroscopic data agreed with the reported literature data.[34]

***(E)-Butyl 3-(2-methoxyphenyl)acrylate* (10b)**

GC yield = 80 %, isolated yield = 72%. δ_H (400 MHz, $CDCl_3$): 7.92 (d, *J* 16.4 Hz, 1H), 7.40-7.39 (m, 1H), 7.22-7.21 (m, 1H), 6.84-6.74 (m, 2H), 6.48 (d, *J* 16.4 Hz, 1H), 4.12 (t, *J* 6.7 Hz, 2H), 3.76 (s, 3H), 1.60-1.57 (m, 2H), 1.34-1.33 (m, 2H), 0.88 (t, *J* 6.0 Hz, 3H); δ_c (100 MHz, $CDCl_3$): 167.7 (C=O), 158.3 (C-O), 140.0 (CH), 131.4, 128.9, 123.6, 120.7 (Ar), 118.8 (CH), 111.2, 64.2, 55.5 (O-CH_3), 30.9 (CH_2), 19.2 (CH_2), 13.8 (CH_3). Spectroscopic data agreed with the reported literature data.[34]

***(E)-Butyl 3-(4-methylphenyl)acrylate)* (10c)**

GC yield = 87%, isolated yield = 73%. δ_H (400 MHz, $CDCl_3$): 7.65 (d, *J* 16.0 Hz, 1H), 7.41 (d, *J* 6.0 Hz, 2H), 7.18 (d, *J* 6.4 Hz, 2H), 6.40 (d, *J* 16.0 Hz, 1H), 4.2 (t, *J* 6.6 Hz, 2H), 2.35 (s, 3H), 1.70-1.64 (m, 2H), 1.56-1.38 (m, 2H), 0.96 (t, *J* 7.3 Hz, 3H); δ_c (100 MHz, $CDCl_3$): 167.3 (C=O), 140.6 (CH), 140.5, 131.8, 129.5, 128.0 (Ar), 117.2 (CH), 64.2, 30.7 (CH_2), 21.4 (CH_3), 19.2 (CH_2), 13.8 (CH_3). Spectroscopic data agreed with literature.[35]

***(E)-Butyl 3-mesitylacrylate* (10d)**

GC yield = 90%, isolated yield 81%. δ_H (400 MHz, $CDCl_3$): 7.88 (d, *J* 16.0 Hz, 1H), 6.92 (s, 2H), 6.09 (d, *J* 16.0 Hz, 1H), 4.25 (t, *J* 6.6 Hz, 2H), 2.35 (s, 6H), 2.18 (s, 3H), 1.75-1.70 (m, 2H), 1.56-1.44 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H); δ_c (100 MHz, $CDCl_3$): 166.7 (C=O), 162.3 (CH), 144.0 (CH), 137.7, 134.5, 134.4, 128.9 (Ar), 65.2 (CH_2), 30.9 (CH_2), 22.0 (CH_3), 20.0 (CH_3), 19.2 (CH_3), 13.8 (CH_3). The spectroscopic data agreed with the reported literature data.[36]

***(E)-Butyl 3-(4-hydroxyphenyl)acrylate* (10e)**

GC yield = 58%, isolated yield = 45%. δ_H (400 MHz, $CDCl_3$): 7.63 (d, *J* 16.0 Hz, 1H), 7.40 (d, *J* 6.8 Hz, 2H), 6.85 (d, *J* 6.8 Hz, 2H), 6.30 (d, *J* 16.0 Hz, 1H), 4.20 (t, *J* 6.6 Hz, 2H), 2.04 (m, 2H), 1.45-1.20 (m, 2H), 0.95 (t, *J* 6.0 Hz, 3H); δ_c (100 MHz, $CDCl_3$): 168.3 (C=O), 158.4 (C-O), 145.0 (CH), 130.2, 127.2, 116.2 (CH), 115.6 (Ar), 64.8 (CH_2), 31.0 (CH_2), 19.4 (CH_2), 14.4 (CH_3). The spectroscopic data agreed with the reported literature data.[36]

***(E)-Butyl 3-(4- fluorophenyl)acrylate* (10f)**

GC yield = 80%, isolated yield = 72%. δ_H (400 MHz, $CDCl_3$): 7.66 (d, *J* 16.0 Hz, 1H), 7.52-7.49 (m, 2H), 7.09-7.05 (m, 2H), 6.35 (d, *J* 16.0 Hz, 1H), 4.22 (t, *J* 6.7 Hz, 2H), 1.72-1.66 (m, 2H), 1.46-1.42 (m, 2H), 0.98 (t, *J* 7.4 Hz, 3H); δ_c (100 MHz, $CDCl_3$): 165.0 (C=O), 163.1 (C-F), 143.4 (CH), 131.0, 130.1, 116.3 (CH), 116.1 (Ar), 64.6 (CH_2), 31.0 (CH_2), 19.4 (CH_2), 13.9 (CH_3). The spectroscopic data agreed with the reported literature data.[35]

***(E)-Butyl 3-(2-fluorophenyl)acrylate* (10g)**

GC yield = 77%, isolated yield = 57%. (400 MHz, $CDCl_3$): 8.01 (d, *J* 12.4 Hz, 1H), 7.54-7.33 (m, 1H), 7.32-7.28 (m, 1H), 7.17-7.04 (m, 2H), 6.56 (d, *J* 16.0 Hz, 1H), 4.24 (t, *J* 6.8 Hz, 2H), 1.71-1.67 (m, 2H), 1.47-1.41 (m, 2H), 0.99 (t, *J* 7.2 Hz, 3H); δ_c (100 MHz, $CDCl_3$): 166.5 (C=O), 162.5 (C-F), 147.2 (CH), 129.2, 129.2, 124.6, 122.7 (Ar), 116.4 (CH), 116.2 (Ar), 64.6 (CH_2), 30.9 (CH_2), 19.3 (CH_2), 13.8 (CH_3). The spectroscopic data agreed with the reported literature data.[35]

***(E)-Butyl 3-(4-acetylphenyl)acrylate* (10h)**

GC yield = 96%, isolated yield = 83%. δ_H (400 MHz, $CDCl_3$): 7.98 (d, *J* 6.8 Hz, 2H), 7.72 (d, *J* 16.0 Hz, 1H), 7.62 (d, *J* 5.6 Hz, 2H), 6.55 (d, *J* 16.0 Hz, 1H), 4.25 (t, *J* 6.6 Hz, 2H), 2.62 (s, 3H), 1.72-1.69 (m, 2H), 1.47-1.43 (m, 2H), 0.92 (t, *J* 7.4 Hz, 3H); δ_c (100 MHz, $CDCl_3$): 197.2 (C=O), 166.5 (C=O), 142.9 (CH), 138.8, 138.0, 128.8, 128.1 (CH), 120.9 (Ar), 64.6 (CH_2), 30.8 (CH_2), 26.6 (CH_3), 19.2 (CH_2), 13.7 (CH_3). The spectroscopic data agreed with the reported literature data.[34]

***(E)-Butyl 3-(4-formylphenyl)acrylate* (10i)**

GC yield = 82%, isolated yield = 69%. δ_H (400 MHz $CDCl_3$): 9.90 (s, 1H), 7.78 (d, *J* 16.0 Hz, 2H), 7.58-7.54 (m, 3H), 6.44 (d, *J* 16.0 Hz, 1H),

4.11 (t, *J* 6.6 Hz, 2H), 1.71-1.58 (m, 2H), 1.41-1.31 (m, 2H), 0.86 (t, *J* 7.3 Hz, 3H); δ_c (100 MHz $CDCl_3$): 191.4 (C=O), 166.4 (C=O), 142.8 (CH), 140.2, 137.2, 130.1, 128.5 (Ar), 121.6 (CH), 64.7 (CH_2), 30.7 (CH_2), 19.2 (CH_2), 13.7 (CH_3). The spectroscopic data agreed with the reported literature data.[36]

(E)-Butyl 3-(3-formylphenyl)acrylate (10j)

GC yield = 78%, isolated yield = 66 %. δ_H (400 MHz $CDCl_3$): 9.90 (s, 1H), 7.97 (s, 1H), 7.84 (d, *J* 16.0 Hz, 1H) 7.73-7.68 (m, 2H), 7.54-7.50 (m, 1H), 6.50 (d, *J* 16.0 Hz, 1H), 4.19 (t, *J* 6.8 Hz, 2H), 1.68 (m, 2H), 1.43 (m, 2H), 0.93 (t, *J* 7.2 Hz, 3H); δ_c (100 MHz $CDCl_3$): 191.8 (C=O), 166.7 (C=O), 142.8 (CH), 136.9, 135.5, 133.6, 131.1, 129.7, 128.9 (Ar), 120.2 (CH), 65.0 (CH_2), 30.7 (CH_2), 19.2 (CH_2), 13.8 (CH_3). The spectroscopic data agreed with the reported literature data.[36]

***(E)-1-Methoxy-4-styrylbenzene* (10k)**

GC yield = 81%, isolated yield = 74%. δ_H (400 MHz, $CDCl_3$): 7.48-7.43 (m, 5H). 7.35 (t, *J* 6.0 Hz, 2H), 7.22 (m, 1H), 7.07 (d, *J* 15.0 Hz, 1H), 6.98-6.80 (m, 2H), 3.82 (s, 3H); δ_c (100 MHz $CDCl_3$): 159.3 (C-O), 137.7, 130.1, 128.6, 128.2, 127.7, 127.2, 126.7, 126.3, 114.2 (Ar), 55.3 (OCH_3). The spectroscopic data agreed with the reported literature data.[37]

***(E)- 1-Methoxy-4-(4-methylstyryl)benzene* (10l)**

GC yield = 75%, isolated yield = 69%. δ_H (400 MHz, $CDCl_3$): 7.43 (d, *J* 8.8 Hz, 2H), 7.37 (d, *J* 8.8 Hz, 2H), 7.14 (d, *J* 6.4 Hz, 2H), 7.02-6.98 (m, 4H), 3.81 (s, 3H), 2.37 (s, 3H); δ_c (100 MHz $CDCl_3$): 159.2, 137.0, 134.9, 129.3, 127.6, 127.3, 126.6, 126.2, 114.1 (Ar), 55.3 (OCH_3), 21.2 (CH_3). The spectroscopic data agreed with the reported literature data.[38]

***(E)-Methyl 3-(4-methoxyphenyl)-2-methylacrylate* (10m)**

GC yield = 71%, isolated yield = 61%. δ_H (400 MHz, $CDCl_3$): 7.62 (s, 1H), 7.36 (d, *J* 6.4 Hz, 2H), 6.90 (d, *J* 6.4 Hz, 2H), 3.79 (d, *J* 5.6, 6H), 2.11 (s, 3H); δ_c (100 MHz $CDCl_3$): 169.4, 159.7, 138.6, 131.4, 128.5, 126.1, 113.9 (Ar), 55.2 (OCH_3), 51.9 (OCH_3), 14.04 (CH_3). The spectroscopic data agreed with the reported literature data.[38]

***(E)- tert-Butyl-3-(4-methoxyphenyl)acrylate* (10n)**

GC yield = 68%, isolated yield = 54%. δ_H (400 MHz, $CDCl_3$): 7.54 (d, *J* 15.6 Hz, 1H), 7.44 (d, *J* 8.8 Hz, 2H), 6.87 (d, *J* 8.8 Hz, 2H), 6.24 (d, *J* 16.0 Hz, 1H), 3.81 (s, 3H), 1.51 (s, 9H). δ_c (100 MHz $CDCl_3$): 166.9 (C=O), 161.4 (C-O), 143.4, 129.8, 127.7, 118.0, 114.5 (Ar), 80.4 (CH), 55.5 (OCH_3), 28.8 (CH_3). The spectroscopic data agreed with the reported literature data.[38]

***(E)-2-Ethylhexyl 4-methyoxycinnamate (Octinoxate)* (10o)**

GC yield = 94%, isolated yield = 86%. δ_H (400 MHz, $CDCl_3$): 7.63 (d, *J* 16.0 Hz, 1H,), 7.47 (d, *J* 6.4 Hz, 2H), 6.89 (d, *J* 6.4 Hz, 2H), 6.29 (dd, *J* 17.2 Hz and 1.2 Hz, 1H), 4.10-4.08 (m, 2 H), 3.82 (s, 3H,), 2.15-1.61 (m, 1H), 1.41-1.29 (m, 8H), 0.92-0.89 (m, 6H). δ_c (101 MHz, $CDCl_3$): 161.3 (C=O), 144.1 (CH), 129.7, 127.3, 115.9 (CH), 114.4 (Ar), 66.8, 55.4 (OCH_3), 38.9, 30.5, 29.0, 23.9 (CH_2), 23.0 (CH_2), 14.0 (CH_3), 11.0 (CH_3). The spectroscopic data agreed with the literature data.[39]

***4-(4-Methoxyphenyl)-2-butanone (Flavouring agent)* (12a)**

GC yield = 51%, isolated yield = 41%. δ_H (400 MHz, $CDCl_3$): 7.09-7.07 (m, 2H), 6.81-6.79 (m, 2H), 3.77 (s, 3H, OCH_3), 2.91-2.78 (m, 2H), 2.70-2.61 (m, 2H), 2.11 (s, 3H); δ_c (100 MHz, $CDCl_3$): 208.2 (C=O), 158.3, 133.3, 129.4, 114.2 (Ar), 55.5 (OCH_3), 45.7 (CH_2), 30.3 (CH_3), 29.2 (CH_2). The spectroscopic data agreed with the literature data.[40]

***4-Phenyl-2-butanone* (12b)**

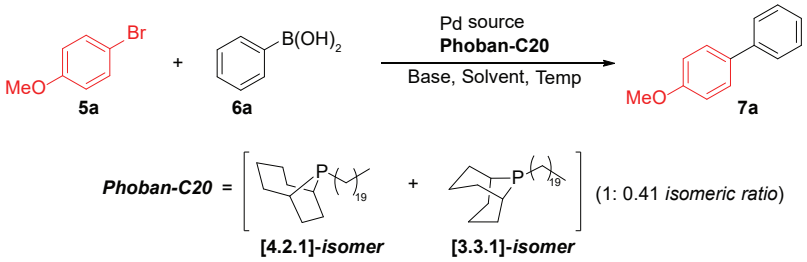
GC yield = 56%, isolated yield = 48%. δ_H (400 MHz, $CDCl_3$): 7.22-7.05 (m, 5H), 2.83 (m, 2H, CH_2), 2.69 (m, 2H, CH_2), 2.06 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$): 207.8 (C=O), 141.0, 128.5, 128.3, 126.1 (Ar), 45.2 (CH_2), 30.0 (CH_3), 29.8 (CH_2). The spectroscopic data agreed with the reported literature data.[41]

RESULTS AND DISCUSSION

We commenced the study by performing an extensive screening of the reaction parameters to establish the optimum Suzuki-Miyaura reaction conditions. 4-Bromoanisole and phenylboronic acid were used as model substrates, while phoban-C20 ligands were used as a 1:0.4 isomeric mixture of the [4.2.1] and [3.3.1] isomers. As highlighted in Table 1 (entries 6-8), no product formation was observed in reactions conducted using organic bases. On the other hand, inorganic bases afforded the desired product, with Cs_2CO_3 providing the highest product yield of 82% (Table 1, entry 3). Product yields also increased slightly to 84% when the Pd source was changed from $Pd(OAc)_2$ to $Pd(dba)_2$ (entry 10). Unfortunately, other Pd sources did not provide better yields (entries 9, 11, and 12). Solvents play an important role in the catalytic outcome of cross-coupling reactions. For instance, studies conducted by Littke and Fu showed that parameters such as solvent and temperature can lead to homocoupling of either the electrophile or nucleophile.[42] In our case, changing the solvent from dioxane (entries 13 and 14) and lowering the reaction temperature (entries 15-17) resulted in lower product yields. Therefore, the optimum temperature for this study was 95 °C, with dioxane being the preferred solvent, affording the desired product in 84% yield (Table 1, entry 10).

Following the optimisation studies, we established the scope and limitations of our catalytic system by conducting reactions with an electronically diverse range of aryl bromides and aryl chlorides. The results of these reactions are summarised in Scheme 2. Aryl bromide substrates possessing electron-donating substituents afforded the products **7a-7e** in excellent yields. Similarly, aryl bromides bearing electron-withdrawing groups afforded products **7g-7m** in yields of 73% to 95%. In general, aryl chlorides afforded lower yields than their bromide derivatives (example, **7a** vs **8a**, **7b** vs **8b**, and **7m** vs **8m**). This observed trend stems from the ease with which aryl bromides undergo the oxidative addition reaction step compared to the aryl chloride derivatives.[43,44] Interestingly, reactions with a free alcohol substituent also afforded the desired coupling product **7f** in good yields. Aldehydes and ketones were also tolerated by this protocol, affording products **7g**, **8g**, **7h**, and **8h** in excellent yields. Substituent positions (*ortho* or *para*) on the aryl bromides did not have a significant influence on the reaction outcome (example **7a** vs **7c**, **7h** vs **7i**). In addition, product **7e**, bearing an *ortho*-isopropyl group, was obtained in excellent yield. Substrates with coordinating groups at the *ortho* position afforded slightly improved product yields compared to the *para*-substituted derivatives. For example, the coupling between 2-chlorobenzonitrile and phenylboronic acid afforded 80% yield of product **8k**, while coupling with its *para*-substituted analogue, 4-chlorobenzonitrile, afforded 74% yield of product **8m**. A similar trend is observed with products **7l** and **7m**, which are obtained from the bromide derivatives. Reacting various aryl boronic acids with 4-bromoanisole resulted in lower product yields. For example, compound **7n**, bearing an electron-withdrawing group on the phenylboronic acid ring, was obtained in lower yield than compound **7a**. A similar trend was observed for boronic acids bearing electron-donating substituents **7o-7r**. In addition, the position of substituents on the boronic acids seems to influence the reaction outcome, with the *ortho*-substituted substrate **7p** obtained in a moderate yield of 67% compared to the 78% of the *para*-substituted derivative **7q**. Further

Table 1: Optimisation of the Phoban-C20 catalyzed Suzuki–Miyaura cross-coupling reaction between 4-bromoanisole **5a** and phenylboronic acid **6a**.



Entry	Base	Pd source	Solvent	Temp (°C)	Yield (%) [a]
1	TBAF	$Pd(OAc)_2$	dioxane	95	75
2	KOH	$Pd(OAc)_2$	dioxane	95	71
3	Cs_2CO_3	$Pd(OAc)_2$	dioxane	95	82
4	K_3PO_4	$Pd(OAc)_2$	dioxane	95	51
5	K_2CO_3	$Pd(OAc)_2$	dioxane	95	53
6	NEt_3	$Pd(OAc)_2$	dioxane	95	0
7	i-Pr_2NEt	$Pd(OAc)_2$	dioxane	95	0
8	$(C_6H_{11})_2NCH_3$	$Pd(OAc)_2$	dioxane	95	0
9	Cs_2CO_3	$Pd(COD)Cl_2$	dioxane	95	63
10	Cs_2CO_3	$Pd(dba)_2$	dioxane	95	84
11	Cs_2CO_3	$Pd_2(dba)_3$	dioxane	95	80
12	Cs_2CO_3	$PdCl_2$	dioxane	95	74
13	Cs_2CO_3	$Pd(dba)_2$	toluene	95	54
14	Cs_2CO_3	$Pd(dba)_2$	DMF	95	65
15	Cs_2CO_3	$Pd(dba)_2$	dioxane	80	73
16	Cs_2CO_3	$Pd(dba)_2$	dioxane	60	63
17	Cs_2CO_3	$Pd(dba)_2$	dioxane	40	0
18	Cs_2CO_3	$Pd(dba)_2$	dioxane	95	18

Reaction conditions: Boronic acid (0.875 mmol), 4-bromoanisole (0.833 mmol), Pd (1.5 mol%), ligand (3.6 mol%), (1:0.41 isomeric ligand ratio [4.2.1]:[3.3.1]), base (1.67 mmol), 2.5 mL solvent at 95 °C for 24 hr. Reactions were performed in duplicate using *n*-decane as an internal standard. [a] GC yield.

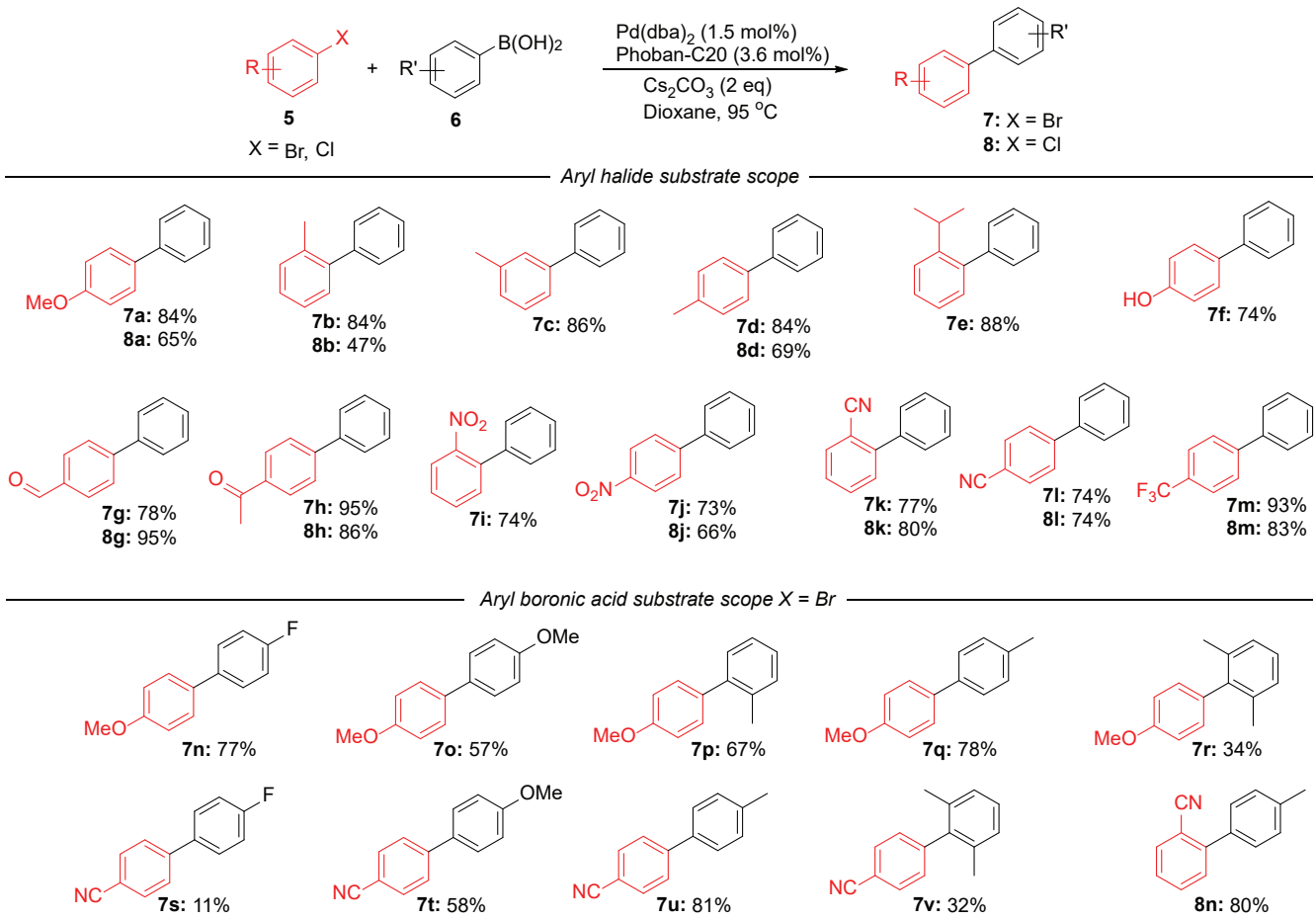
increasing the steric effects around the boron atom resulted in lower product yields of compound **7r**. Reacting 4-bromobenzonitrile with various aryl boronic acids afforded products **7s**-**7v** in yields ranging from low to excellent. The reaction between 4-tolyboronic acid and 2-bromobenzonitrile to afford product **8n** was of great interest to the study, as it is an industrially valuable intermediate commonly used in the synthesis of antihypertensive agents such as Sartan derivatives, and thus highlights the potential industrial applicability of the protocol.[45]

A series of commercially available ligands was also compared to the catalytic performance of phoban-C20, as shown in Scheme 3 below. The use of PPh_3 resulted in a homo-coupling product of phenylboronic acid, with no conversion of 2-chlorotoluene. When P(*p*-tolyl)$_3$ was used, 38% of the product was obtained. The isomeric phoban-C20 demonstrated superiority over P(*p*-tolyl)$_3$ in our hands, but fell short when compared to Buchwald ligands, SPhos, and DavePhos. Although phoban-C20 is less effective for 2-chlorotoluene compared to SPhos and DavePhos, phoban-C20 can still be employed to couple other aryl chlorides and bromides.

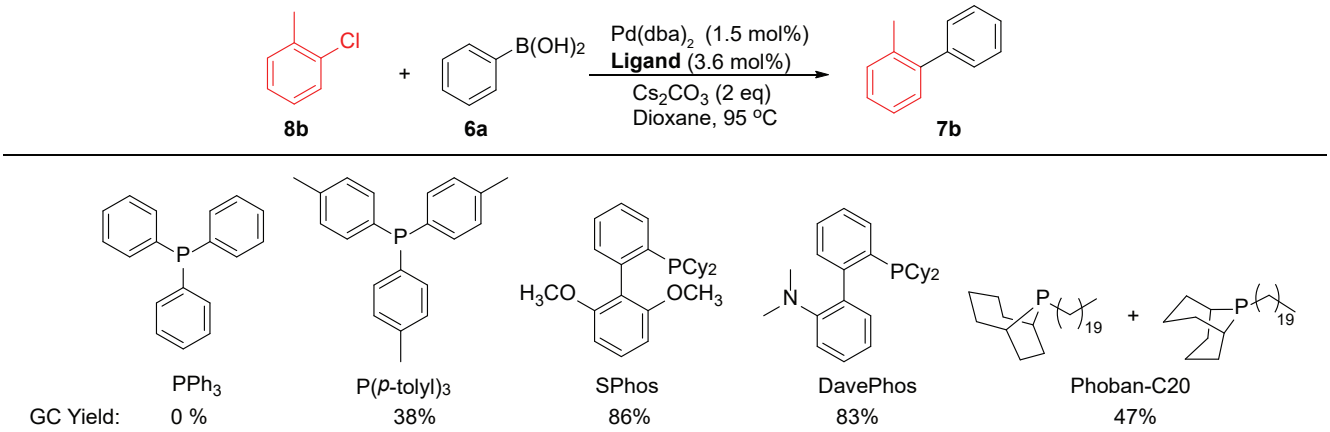
Motivated by the results obtained in the Suzuki-Miyaura cross-coupling reactions, we then investigated the efficiency of phoban-C20 ligands in Mizoroki-Heck reactions. To achieve this, reaction conditions were adopted from those reported by Beller *et al.* and optimized using 4-bromoanisole and *n*-butyl acrylate as model substrates.[39] Parameters, including the Pd source, base, solvent, and reaction temperature, were investigated and are summarized in Table 2. $Pd(dba)_2$ was the most effective palladium source at 2 mol% and 4 mol% of the ligand, using K_2CO_3 as a base in dioxane at 120 °C. Reducing the Pd catalyst loading to 1 mol% resulted in a reduced product yield (Table 2, entry 1 vs entry 5). Using organic bases did not improve reaction yields (Table 2, entry 10), and changing the solvent also led to lower product yields (Table 2, entries 11 - 13). Reactions at lower temperatures also produced lower product yields (Table 2, entries 14 and 15).

With the optimal reaction conditions in hand, structurally diverse aryl bromides were coupled to butyl acrylate, yielding products **10a**-**10j** (Scheme 4). Reactions with electron-donating functional groups **10a**-**10d** afforded products in 80-93% yield. However, 4-bromophenol afforded product **10e** in 58% yield, probably due to side reactions emanating from the free hydroxyl group. Reactions with electron-withdrawing aryl bromides afforded the desired products in yields between 78% and 96%. The reactions were compatible with aryl bromides possessing functional groups such as ketones and aldehydes **10h**-**10j**. Variation of the alkene electrophile afforded products **10k**-**10o** in good to excellent yields. The reactions with styrene and 4-methyl styrene afforded products **10k** and **10l** in 81% and 75%, respectively. The lower product yield of **10l** could be attributed to the alkene's reduced electrophilicity due to the electron-donating nature of the methyl group. Similarly, methyl methacrylate afforded the product **10m** in lower yield than **10a**. Bulkier *tert*-butyl acrylate led to lower product yields for **10n**. The optimized protocol was also used to synthesize octinoxate **10o**, a UV absorber found in sunscreens, in 94% yield.[46]

The catalyst system was further explored for the synthesis of flavoring and fragrance agents, raspberry ketone methyl ether **12a** and its analog **12b** (Scheme 5).[47] These compounds are commonly synthesized *via* a two-step reaction pathway that involves a Heck coupling between an aryl halide and a suitable acrylate. This is then followed by an alkene reduction to afford the desired compound.[48] In



Scheme 2. Reaction conditions: Boronic acid (2.875 mmol), aryl halide (2.833 mmol), Pd (1.5 mol%), ligand (3.6 mol%), (1:0.41 isomeric ligand ratio [4.2.1]:[3.3.1]), Cs_2CO_3 (2 eq.), 5 ml dioxane for 24 hrs at 95 °C. Using *n*-decane as an internal standard. Yields reported are from GC analysis. Isolated yields are reported in the experimental section.



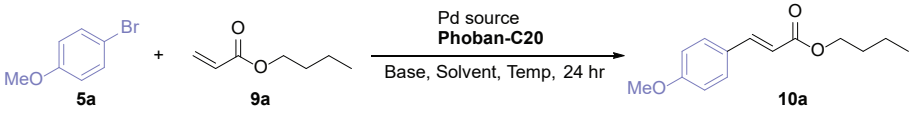
Scheme 3. Reaction conditions: Phenylboronic acid (0.875 mmol), 2-chlorotoluene (0.833 mmol), Pd (1.5 mol%), ligand (3.6 mol%), Cs_2CO_3 (2 eq.), 2.5 ml dioxane for 24 hrs at 95 °C. Using *n*-decane as an internal standard.

this study, the target alkyl ketones were synthesized by reacting the respective aryl bromides **5a** and **5w** with the alkenol **11**. The products were obtained in 51% and 56% yields, demonstrating potential for further optimization and applicability of the catalyst system in the synthesis of alkyl ketones in this manner.

CONCLUSION

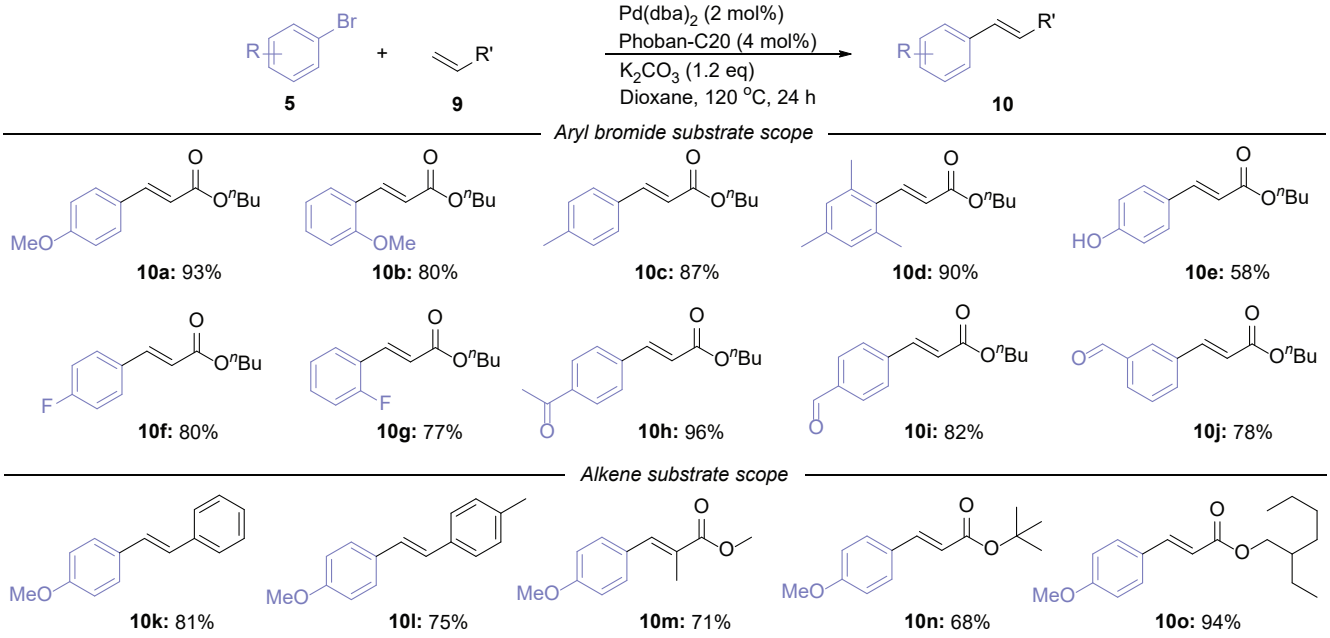
This study demonstrated the application of isomeric phoban-C20 as an alternative ligand in Pd-catalyzed Suzuki-Miyaura reactions by coupling electronically diverse aryl bromides and chlorides with boronic acids at low catalyst loading. Overall, aryl bromides demonstrated better activities compared to aryl chlorides. The effect of steric hindrance was observed when *ortho*-substituted aryl boronic acid substrates were used, as slightly lower yields were obtained in comparison to when *para*-substituted substrates were used. A ligand comparison study showed that phoban-C20 was superior to traditional triphenylphosphine ligands but inferior to Buchwald's dialkylbiarylphosphines. In addition, the ligand was applied in the Mizoroki-Heck coupling of a diverse array of aryl bromides and alkenes, affording the desired products in good to excellent yields.

Table 2: Optimisation of the Phoban-C20 catalyzed Mizoroki-Heck cross-coupling reaction between 4-bromoanisole **5a** and *n*-butyl acrylate **9a**.

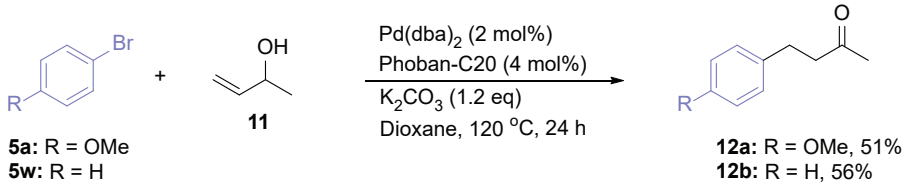


Entry	Pd source	Base	Solvent	Temp (°C)	GC yield (%)
1	$Pd(dba)_2$	K_3PO_4	dioxane	120	80
2	$Pd(COD)_2Cl_2$	K_3PO_4	dioxane	120	60
3	$PdCl_2$	K_3PO_4	dioxane	120	33
4	$Pd(OAc)_2$	K_3PO_4	dioxane	120	62
5	$Pd(dba)_2$[a]	K_3PO_4	dioxane	120	38
6	$Pd(dba)_2$	KOH	dioxane	120	59
7	$Pd(dba)_2$	K_2CO_3	dioxane	120	93
8	$Pd(dba)_2$	Na_2CO_3	dioxane	120	36
9	$Pd(dba)_2$	Cs_2CO_3	dioxane	120	85
10	$Pd(dba)_2$	NEt_3	dioxane	120	24
11	$Pd(dba)_2$	K_2CO_3	toluene	120	88
12	$Pd(dba)_2$	K_2CO_3	DMA	120	52
13	$Pd(dba)_2$	K_2CO_3	DMF	120	59
14	$Pd(dba)_2$	K_2CO_3	dioxane	100	64
15	$Pd(dba)_2$	K_2CO_3	dioxane	80	2

Conditions: 4-Bromoanisole (2.5 mmol), butyl acrylate (3 mmol), base (3 mmol), Pd source (0.05 mmol), phoban-C20 (0.10 mmol), and anhydrous solvent (2.5 mL) stirred under argon for 24 hr at 120 °C. [a] The Pd source was 0.025 mmol. *n*-Decane was used as an internal standard. For reproducibility, the experiments were carried out in duplicate.



Scheme 4. Reaction conditions: ArBr (2.5 mmol), butyl acrylate (3 mmol), K_2CO_3 (3 mmol), $Pd(dba)_2$ (2 mol%), phoban-C20 (4 mol%) and anhydrous dioxane (2.5 mL), argon, 24 hr at 120 °C. Using *n*-decane as an internal standard.



Scheme 5. Synthesis of (flavor and fragrance agent) raspberry ketone methyl ether **12a** and its analog **12b**.

The optimized protocol was used to synthesize the UV absorber, octinoxate. Further optimization for the synthesis of raspberry ketone and its derivatives using this catalyst system will be conducted and reported in the future. In addition, a comparative study of the catalytic efficiency of the phoban-C20 isomers will be conducted in the future.

SUPPLEMENTARY INFORMATION

Supplementary information for this article is provided in the online supplement.

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AUTHORS CONTRIBUTIONS

Ntombenhle M. Masanabo: Investigation, Methodology, Data Curation, Writing-Original Draft, Validation, Formal Analysis. Paseka T Moshapo: Supervision, Conceptualization, Validation, Writing - Original Draft, Writing - Review & Editing, Project administration. Cedric W. Holzapfel: Supervision, Conceptualization, Validation, Resources. Munaka Christopher Maumela: Supervision, Conceptualization, Validation, Resources, Writing - Review & Editing, Project administration, Funding acquisition.

DECLARATION OF COMPETING OR FINANCIAL INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

The authors declare that no generative AI or AI-assisted technologies were used for the purpose of the research conducted or for the preparation of the manuscript.

ORCID IDS

Ntombenhle M. Masanabo: https://orcid.org/0000-0002-9482-489X
Paseka T. Moshapo: https://orcid.org/0000-0002-4003-9853
Munaka C. Maumela: https://orcid.org/0000-0001-7372-1974

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