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Development of Unimolecular Tetrakis(piperidin-4-ol) as a Ligand for Suzuki–Miyaura Cross-Coupling Reactions: Synthesis of Incrustoporin and Preclamol

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A domino aza-Cope/aza-Prins cascade enabled the synthesis of a new class of 4-hydroxypiperidine-appended mono, bis, tris, and tetrakis unimolecular compounds that served as efficient ligands to catalyze Suzuki–Miyaura cross-coupling reactions under aerobic conditions. Various biaryls, terphenyls, and heterocyclic biphenyls were obtained in good to excellent yields. The ligands were also capable of catalyzing the Heck–Mizoroki reaction. As an application, the Suzuki–Miyaura coupling reaction was used in the synthesis of incrustoporin, its analogs, and the drug molecule preclamol.

Introduction

The utility of C–C bond-forming reactions such as the Heck–Mizoroki,[1] Negishi,[2] Kumada,[3] and Suzuki–Miyaura[4] reactions is undeniable. One of the many methods known for biaryl synthesis, the Suzuki–Miyaura cross-coupling reaction may be used for the efficient construction of aryl C_{sp2}–C_{sp2} bonds under mild conditions. The wide functional-group tolerance and commercial availability of boronic acids have made this reaction cost effective ever since it was initially reported in 1979.[4a] Apart from C_{sp2}–C_{sp2} bond formation, it has been used in C_{sp2}–C_{sp3} and C_{sp3}–C_{sp3} coupling between various halide electrophiles and nucleophilic boronic acids.[5] The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction has been used in the synthesis of target molecules including natural products such as alkaloids, agrochemicals, polymers, ligands, pharmaceutically important drug precursors, and biaryl targets, and it has been used in industrially viable processes for large-scale synthesis.[6] Remarkable examples in which the coupling reaction was used include the large-scale synthesis of such key intermediates as: i) *o*-tolylbenzonitrile (**1a**; Figure 1), an intermediate for the preparation of Losartan (**2a**) [7a] (an antihypertensive drug) and other compounds of the sartan drug family;[7b–7d] ii) 3-amino-2-phenylpyridine (**1b**), an important intermediate for the preparation of potent nonpeptidic NK1 receptor antagonists such as CP-99,994 (**2b**) and GR203040 (**2c**);[7e] and iii) 2-(4-formylphenyl)pyridine (**1c**), an important unit for the synthesis of Atazanavir (**2d**; Reyataz, Figure 1).[7f]

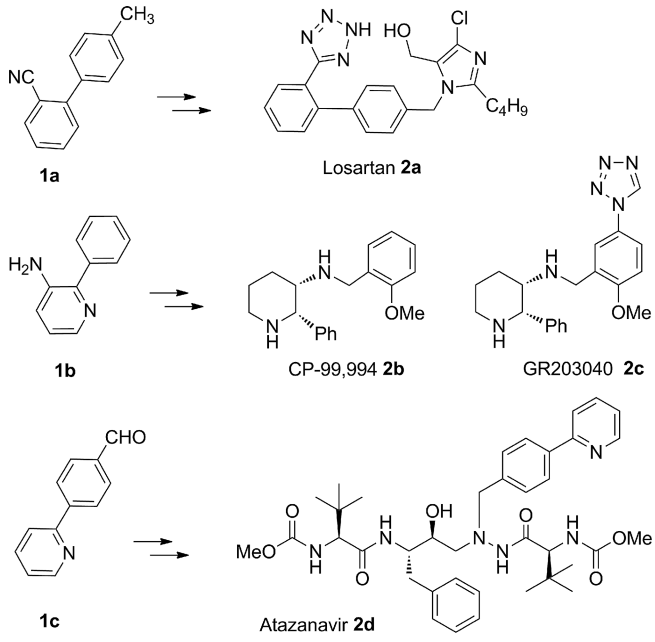

Figure 1. Applications of Suzuki–Miyaura coupling in drug synthesis.

In the past few decades, palladium complexes containing tertiary phosphines, phosphates, and phosphine oxides have been extensively used in Suzuki–Miyaura cross-coupling reactions.[8] However, their use is sometimes limited due to the high costs involved, and their sensitivity to air and moisture, which demands an inert atmosphere and specialized techniques like the use of a glove box to conduct the coupling reactions. Furthermore, phosphines form phosphine oxides and phosphine-bridged complexes, which are responsible for early termination of the catalytic cycle.[9] Therefore, to replace phosphine ligands, a new class of nitrogen-based ligands has been developed. These ligands

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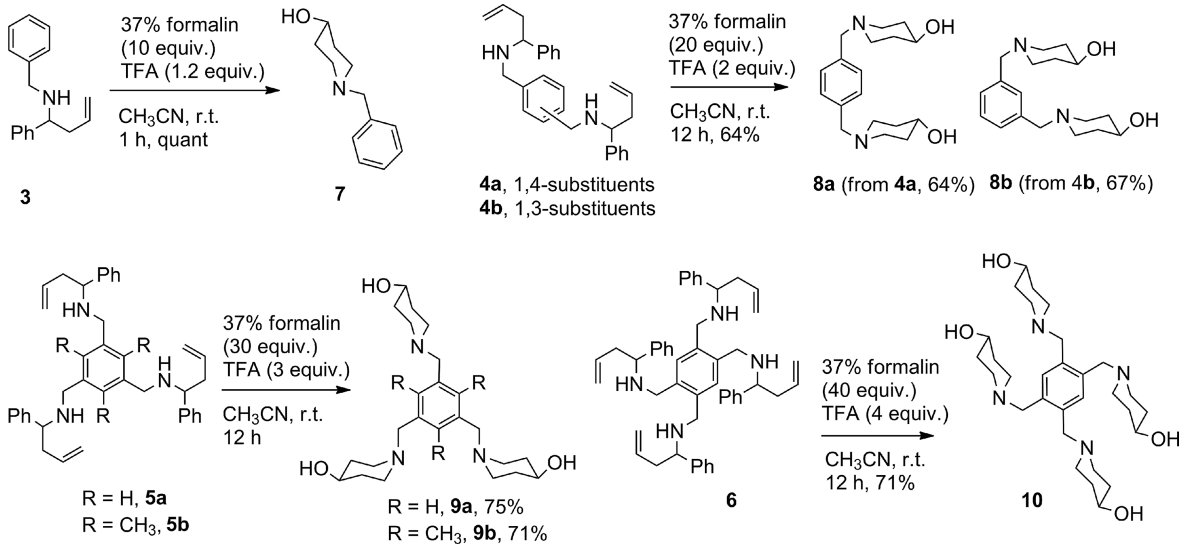


Scheme 1. Cascade aza-Cope/aza-Prins cyclization to give 4-hydroxypiperidines[16] (TFA = trifluoroacetic acid).

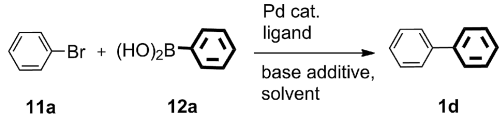
give Pd complexes with high stability and high catalytic activity for coupling reactions.[10] *N*-Heterocyclic moieties have been extensively used as ligands for the synthesis of biaryls through C–C coupling reactions. These include the *N*-heterocyclic carbenes (NHCs),[11] piperizine-based ligands,[12] diamino-substituted aryloximes,[13] bisamides,[14] and other *N*-heterocyclic systems.[10,15]

Recently, we reported the synthesis of 4-hydroxypiperidines through cascade aza-Cope/aza-Prins cyclizations from homoallylamines.[16] The mono-homoallylamine **3** and unimolecular bis-, tris-, and tetrakis-homoallylamines **4**–**6** delivered the mono, bis, tris (tripod), and tetrakis (crucifix) flanked piperidinols **7**–**10** (Scheme 1).[16] We have explored the use of these compounds as ligands in the Suzuki–Miyaura cross-coupling reaction, and we report our results in this paper. The coupling reaction was used in the synthesis of incrustoporin, its analogs and the drug molecule preclamol.

Results and Discussion

The optimization study was conducted for the coupling of bromobenzene (**11a**) and phenylboronic acid (**12a**), as shown in Table 1. The reactions were carried out with **11a** (1.0 mmol, 1.0 equiv.) and $PhB(OH)_2$ (**12a**; 1.5 mmol, 1.5 equiv.) using $PdCl_2$ (1 mol-%). We tested ligands **7**–**10**, using water as the solvent (Table 1, entries 1–6). Of the six ligands tested, **10** gave the best results. Considering the most common solvents used in Suzuki–Miyaura coupling reactions, we then checked MeOH, EtOH. and an EtOH/H_2O mixture (Table 1, entries 7–9). The latter solvent combination proved to be better, giving **1d** in 84% yield (Table 1, entry 9). We worked back and tested this solvent combination for the other ligands (Table 1, entries 10–14). However, ligand **10** was still the best. Next, we checked various Pd catalysts commonly used in this reaction (Table 1, entries 15–20), and we found that $Pd(OAc)_2$ delivered **1d** in

Table 1. Optimization of the Suzuki–Miyaura cross-coupling reaction between **11a** and $PhB(OH)_2$ (**12a**) (dba = dibenzylideneacetone).[a]



ligands: **7**, **8a**, **8b**, **9a**, **9b** and **10**

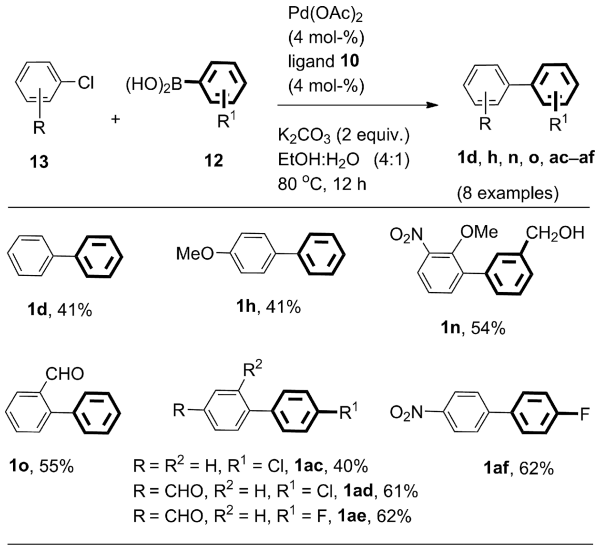
Entry	Catalyst (mol-%)	Ligand (mol-%)	Base (2 equiv.)	Solvent[b]	Temp. [°C]	t [h]	Yield [%][c]
1	$PdCl_2$ (1)	**7** (10)	Na_2CO_3	H_2O	95	24	22
2	$PdCl_2$ (1)	**8a** (10)	Na_2CO_3	H_2O	95	24	28
3	$PdCl_2$ (1)	**8b** (10)	Na_2CO_3	H_2O	95	24	32
4	$PdCl_2$ (1)	**9a** (10)	Na_2CO_3	H_2O	95	24	49
5	$PdCl_2$ (1)	**9b** (10)	Na_2CO_3	H_2O	95	24	38
6	$PdCl_2$ (1)	**10** (10)	Na_2CO_3	H_2O	95	24	60
7	$PdCl_2$ (1)	**10** (10)	Na_2CO_3	MeOH	95	24	76
8	$PdCl_2$ (1)	**10** (10)	Na_2CO_3	EtOH	95	24	78
9	$PdCl_2$ (1)	**10** (10)	Na_2CO_3	EtOH/H_2O	95	24	84
10	$PdCl_2$ (1)	**7** (10)	Na_2CO_3	EtOH/H_2O	95	24	79
11	$PdCl_2$ (1)	**8a** (10)	Na_2CO_3	EtOH/H_2O	95	24	78
12	$PdCl_2$ (1)	**8b** (10)	Na_2CO_3	EtOH/H_2O	95	24	64
13	$PdCl_2$ (1)	**9a** (10)	Na_2CO_3	EtOH/H_2O	95	24	82
14	$PdCl_2$ (1)	**9b** (10)	Na_2CO_3	EtOH/H_2O	95	24	82
15	$Pd_2(dba)_3$ (1)	**10** (10)	Na_2CO_3	EtOH/H_2O	95	24	10
16	$Pd(Ph_3P)_4$ (1)	**10** (10)	Na_2CO_3	EtOH/H_2O	95	24	68
17	$Pd(OCOCF_3)_2$ (1)	**10** (10)	Na_2CO_3	EtOH/H_2O	95	24	87
18	Pd/C (1)	**10** (10)	Na_2CO_3	EtOH/H_2O	95	24	61
19	$[Pd(allyl)Cl]_2$ (1)	**10** (10)	Na_2CO_3	EtOH/H_2O	95	24	52
20	$Pd(OAc)_2$ (1)	**10** (10)	Na_2CO_3	EtOH/H_2O	95	6	92
21	$Pd(OAc)_2$ (1)	**10** (10)	K_2CO_3	EtOH/H_2O	r.t.	1	quant.
22	$Pd(OAc)_2$ (1)	**10** (10)	K_3PO_4	EtOH/H_2O	r.t.	2	78
23	$Pd(OAc)_2$ (1)	**10** (10)	Cs_2CO_3	EtOH/H_2O	r.t.	2	75
24	$Pd(OAc)_2$ (1)	**10** (5)	K_2CO_3	EtOH/H_2O	r.t.	1.5	quant.
25	**$Pd(OAc)_2$ (1)**	**10 (1)**	**K_2CO_3**	**EtOH/H_2O**	**r.t.**	**1.5**	**quant.**
26	$Pd(OAc)_2$ (1)	**10** (0.5)	K_2CO_3	EtOH/H_2O	r.t.	7	68
27	$Pd(OAc)_2$ (0.50)	**10** (1)	K_2CO_3	EtOH/H_2O	r.t.	7	57
28	$Pd(OAc)_2$ (0.25)	**10** (1)	K_2CO_3	EtOH/H_2O	r.t.	7	68
29	$Pd(OAc)_2$ (1)	–	K_2CO_3	EtOH/H_2O	r.t.	24	39[d]

[a] Ar–X (1.0 mmol), $ArB(OH)_2$ (1.5 mmol), M_2CO_3 or K_3PO_4 (2.0 mmol), Pd source (0.25–1.0 mol-%), ligand (0.5–10 mol-%), solvent, r.t. (room temperature) to 95 °C. [b] EtOH/H_2O (4:1). [c] Isolated yield. [d] Without ligand..

92% yield in 6 h (Table 1, entry 20). Inspection of various base additives (Table 1, entries 21–23) indicated K_2CO_3 to be superior, giving **1d** in quantitative yield at room temperature in 1 h (Table 1, entry 21). Varying the ligand concentration from 10 mol-% to 0.5 mol-% (Table 1, entries 24–26) indicated that 1 mol-% was the optimal amount (Table 1, entry 25). Further lowering the Pd catalyst loading to 0.5 and 0.25 mol-% (Table 1, entries 27 and 28) resulted in lower yields of **1d**. The reaction without any ligand was very sluggish (24 h), and gave only 39% of **1d** (Table 1, entry 29), which indicates that a ligand is necessary. Thus we chose to use $Pd(OAc)_2$ (1 mol-%), ligand **10** (1 mol-%), K_2CO_3 (2.0 equiv.) in EtOH/H_2O (4:1) at room temperature as the optimum conditions.

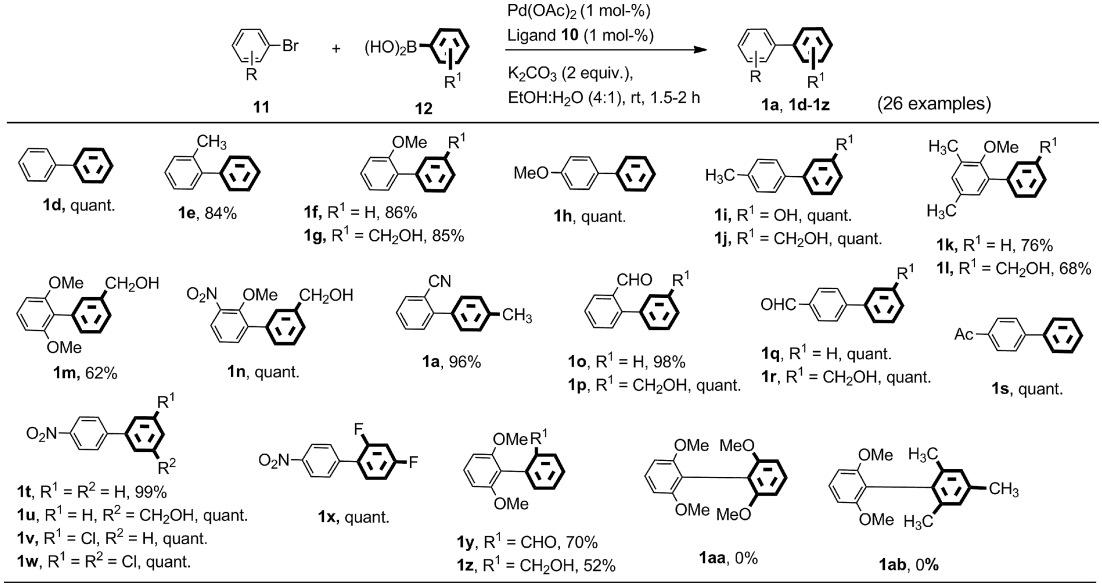
Using the optimized conditions, we explored the scope and limitations of this method with various aryl, heteroaryl and vinyl halides for Suzuki–Miyaura cross-coupling reactions. It has been observed that electronic and steric factors play a major role on the yields of the coupling reaction.[17] Aryl halides with electron-donating groups (and no *ortho* substituents) gave the coupled products (i.e., **1d**, **1h**, **1i**, and **1j**) in quantitative yields (Scheme 2). The aryl halides with electron-donating groups but that were sterically hindered in that they had *ortho* substituents gave the biphenyls [i.e., **1e** (84%), **1f** (86%), **1g** (85%), **1k** (76%), **1l** (68%), **1m** (62%), and **1n** (quant.)] in moderate to good yields (Scheme 2). We turned our attention to aryl halides bearing electron-withdrawing groups, and we found that they underwent smooth coupling reactions to deliver the various substituted biphenyls (i.e., **1a**, **1o**–**1x**) in 96% to quantitative yields (Scheme 2). Biphenyl **1a** is as an important intermediate for the synthesis of the sartan family of drugs, which comprises Losartan, Irbesartan, Valsartan, Candesartan, etc., and which show angiotension II acceptor depressant activity (Scheme 2, Figure 1).[7a–7d] We also used sterically hindered aryl bromides and boronic acids to obtain tri-*ortho*- and tetra-*ortho*-substituted biaryls. We could successfully prepare tri-*ortho*-substituted biaryls **1y** and **1z** in good yields, 70 and 52%, respectively, tetra-*ortho*-substituted biaryls **1aa** and **1ab** could not be obtained (Scheme 2).

We also investigated whether the less reactive aryl chlorides **13** could be coupled with various boronic acids **12** under these conditions. Biaryls **1d**, **1h**, **1n**, **1o**, and **1ac**–**1af** were obtained in moderate to good yields (40–62%, Scheme 3). In these reactions, we used $Pd(OAc)_2$ and ligand **10**, each in 4 mol-%, the reaction was carried out at 80 °C.



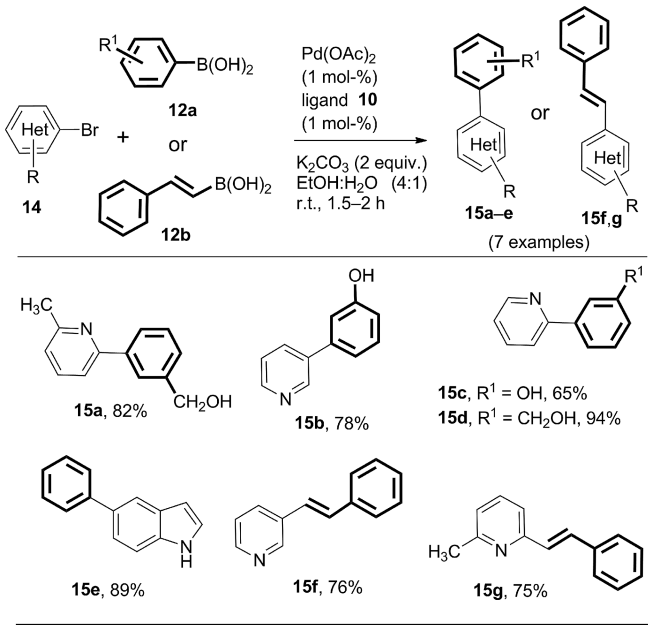
Scheme 3. Synthesis of biaryls using aryl chlorides **13**.

N-Heterocyclic structures are privileged architectures in many natural products and drug molecules. Pyridyl and indoyl halides (**14**) coupled with **12** (either aryl or styryl) to give the coupled products (i.e., **15a**–**15g**) by Suzuki–Mi-



Scheme 2. Substrate scope of the Suzuki–Miyaura cross-coupling reaction.

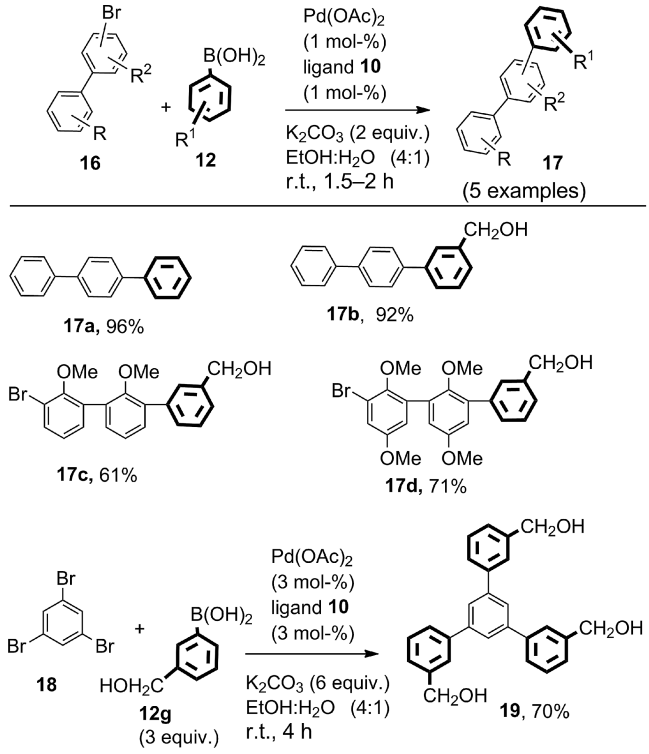
yaura cross-coupling in moderate to good yields (65–94%, Scheme 4).



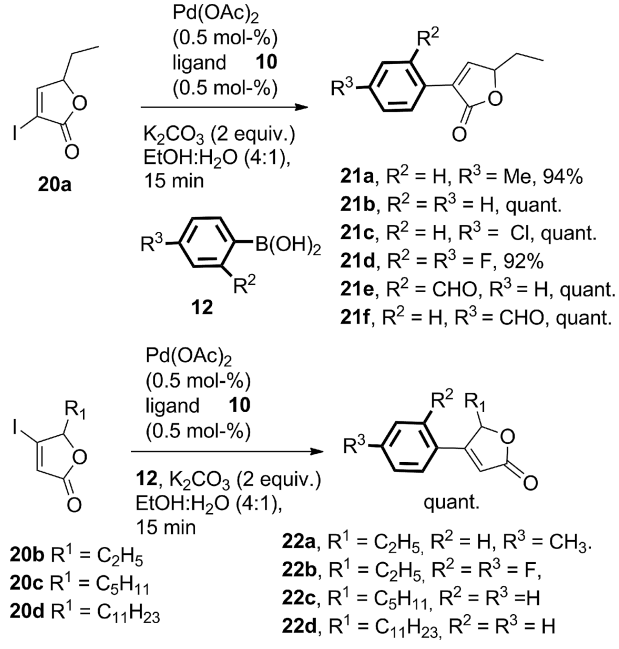
Scheme 4. Synthesis of *N*-heterocyclic biphenyls **15a**–**15g**.

We also used this coupling strategy to synthesize terphenyls **17a** (96%), **17b** (92%), **17c** (61%), and **17d** (71%) in moderate to good yields (Scheme 5). The dibromobiaryl compounds delivered monoboronic acid coupled products **17c** and **17d** in good yields, along with small amounts of the dicoupled products. It was difficult to separate the latter from the self-coupled boronic acid products. Hence we could not characterize the dicoupled products. However in the case of 1,3,5-tribromobenzene (**18**), the coupling reaction with **12g** delivered the tripod compound (i.e., **19**) in 70% yield (Scheme 5). In this case also, a small amount of the self-coupled boronic acid product was obtained, and this could easily be separated from **19**.

The Suzuki–Miyaura reaction using ligand **10** was used in an efficient coupling of butenolide-derived α-vinyl iodide **20a** with **12** for the synthesis of (±)-incrustoporin (**21a**) and its analogs **21b**–**21f** (Scheme 6). Incrustoporin is an antifungal compound that shows prominent cytotoxic activity against *Absidia glauca*, *Botrytis cinerea*, *Mucor miehei*, and *Rhodotorulaglutinis*.[18] The analogs with halide substituents on the aryl ring have been shown to have improved activity.[18c] The reaction of **20a** with **12** (R^3 = Me, R^2 = H) delivered (±)-incrustoporin (**21a**) in 94% yield.[16] Similarly, coupling of **20a** with the various boronates produced analogs **21b**–**21f** in 92% to quantitative yield.[16] The regioisomeric butenolide-derived β-vinyl iodides **20b**–**20d** coupled with **12** to give isomeric analogs **22a**–**22d** in quantitative yield in each case (Scheme 6). Here, the ligand and Pd source was used in only 0.5 mol-% in each case. The reactions were complete in less than 15 min. When 1.0 mol-% of the Pd source was used, the results were comparable, but the reaction time decreased to around 10 min.



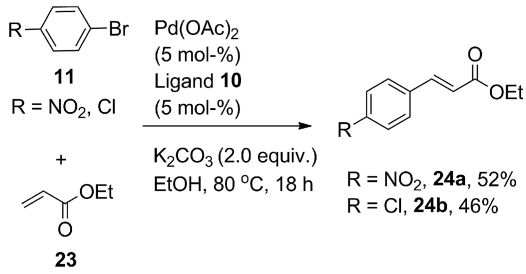
Scheme 5. Synthesis of terphenyls **17a**–**17d** and tripod compound **19**.



Scheme 6. Synthesis of incrustoporin and its analogs.

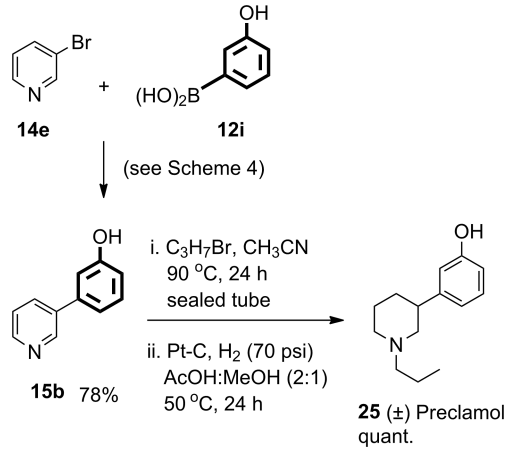
We further investigated our protocol in Heck–Mizoroki[1] cross-coupling reactions between aryl bromides **11** and ethyl acrylate (**23**), and we found that *trans*-3-arylacrylates **24a** and **24b** were formed in moderate yields (Scheme 7). Here, we used 5 mol-% each of $Pd(OAc)_2$ and ligand **10** at 80 °C in EtOH as solvent. The use of EtOH/H_2O (4:1) re-

sulted in partial hydrolysis of **24** into the acid. This coupling requires further optimization, which is ongoing in our laboratory.



Scheme 7. Heck–Mizoroki coupling using ligand **10**.

The drug molecule (±)-preclamol (**25**) shows selective Dopamine autoreceptor (DA) agonistic properties.[19] In recent decades, preclamol has been synthesized through Ni-catalyzed coupling[20] between a Grignard reagent and 3-bromoanisole, or by direct C–H arylation of pyridine[21] with 3-bromoanisole, followed by reduction with the Adams catalyst and demethylation. Heterobiaryl compound **15b** (obtained in 78% yield from **14e** and **12i**; Scheme 4) was efficiently transformed into the drug molecule (±)-preclamol (**25**) through *N*-quaternization followed by pyridyl ring hydrogenation, in quantitative yield (Scheme 8) without protection of the OH group.



Scheme 8. Synthesis of preclamol.

Conclusions

In conclusion, the unimolecular tetrakis-4-hydroxypiperidinol obtained by domino aza-Cope/aza-Prins cyclization was found to catalyze Suzuki–Miyaura cross-coupling reaction under aerobic conditions for the synthesis of biaryls, terphenyls, and heterocyclic biaryls in good to excellent yields. The Suzuki coupling strategy has been elegantly used for the synthesis of (±)-incrustoporin and its analogs, and also in an efficient synthesis of the drug molecule (±)-preclamol. A preliminary investigation showed that ligand **10** also catalyzes Heck–Mizoroki coupling. Further applications of the ligands prepared (Scheme 1) in other coupling reactions are under investigation in our laboratory.

Experimental Section

General Information: Solvents were dried by standard procedures. Thin-layer chromatography was carried out on EM 250 Kieselgel 60 F254 silica gel plates. Spots were visualized by staining with $KMnO_4$ or by using a UV lamp. ^1H and ^{13}C NMR spectra were recorded with Varian 400, and Bruker Avance^{III} 400 and 500 spectrometers, and the chemical shifts were calibrated using the tetramethylsilane peak at $\delta = 0.00$ ppm for ^1H NMR spectra, and the $CDCl_3$ peak at $\delta = 77.00$ ppm (t) in ^{13}C NMR spectra. IR spectra were obtained with a Perkin–Elmer Spectrum One FTIR spectrometer. HRMS and LRMS spectra were recorded with a Micromass Q-Tof micro (YA-105) spectrometer. For the synthesis of **3**–**10**, and characterization data for compounds **21a**–**21f**, see the literature report.[16]

General Procedure for the Synthesis of Biaryls, 4-Arylbutenolides, and 3-Arylacrylates: Arylboronic acid **12** (1.5 mmol, 1.5 equiv.) or **23** (6.0 mmol, 6.0 equiv.), K_2CO_3 (276.4 mg, 2.0 mmol, 2.0 equiv.), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1.0 mol-%), and ligand **10** (3.6 mg, 0.01 mmol, 1.0 mol-%) were added sequentially to a solution of aryl halide **11**, **13**, **14**, or **16**, or vinyl halides **20** (1.0 mmol) in EtOH/H_2O (4:1; 3.0 mL). The reaction mixture was stirred at room temperature for 1.5 h, or until the halide had been consumed. The reaction mixture was then filtered through a small pad of Celite, which was washed with CH_2Cl_2 (2 × 15 mL). The filtrate was concentrated, and the residue was purified by column chromatography (petroleum ether/EtOAc) to give biphenyls, *N*-heterocyclic biphenyls, terphenyls, or other coupled products in good to excellent yields.

For coupling reactions of aryl chlorides **13** with **12**, we used 4 mol-% each of $Pd(OAc)_2$ and ligand **10** at 80 °C. In the reaction of compound **18**, compound **12g** (3.0 equiv.), K_2CO_3 (6.0 equiv.), $Pd(OAc)_2$ (3.0 mol-%), and ligand **10** (3.0 mol-%) were used. In the reaction of vinyl halides **20** with **12**, $Pd(OAc)_2$ (0.5 mol-%), and ligand **10** (0.5 mol-%) were used. In the Heck–Mizoroki coupling between **11** and **23**, we used 5 mol-% each of $Pd(OAc)_2$ and ligand **10** at 80 °C in EtOH as solvent.

Biphenyl (1d):[22] White solid (quant., 154 mg), m.p. 68–70 °C. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$ (t, $J = 7.4$ Hz, 2 H), 7.45 (t, $J = 7.6$ Hz, 4 H), 7.62 (d, $J = 8.2$ Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 127.1, 127.2, 128.7, 141.2$ ppm. IR (KBr): $\tilde{\nu} = 3033, 2921, 2850, 1568, 1478, 1428, 1343, 1169, 1090, 1005, 902, 728, 696$ cm^{-1}.

2-Methylbiphenyl (1e):[22] Colorless oil (84%, 141 mg). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.34$ (s, 3 H), 7.29–7.33 (m, 4 H), 7.38–7.42 (m, 3 H), 7.45–7.52 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.4, 125.7, 126.7, 127.2, 128.0, 128.7, 129.2, 129.8, 130.3, 135.3, 141.9$ ppm.

2-Methoxybiphenyl (1f):[22] Colorless oil (86%, 158.2 mg). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.82$ (s, 3 H), 6.99–7.06 (m, 2 H), 7.31–7.35 (m, 3 H), 7.40 (t, $J = 7.6$ Hz, 2 H), 7.54 (d, $J = 7.4$ Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.4, 111.1, 120.8, 126.9, 127.9, 128.6, 129.5, 130.8, 133.3, 138.5, 156.4$ ppm.

(2′-Methoxybiphenyl-3-yl)methanol (1g): Colorless oil (85%, 182 mg). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.74$ (br. s, 1 H), 3.81 (s, 3 H), 4.74 (s, 2 H), 6.98–7.05 (m, 2 H), 7.33–7.52 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.5, 65.5, 111.1, 120.8, 125.6,$

128.16, 128.2, 128.7, 129.0, 130.4, 130.8, 138.8, 140.5, 156.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3399, 3016, 2939, 2835, 1599, 1499, 1464, 1424, 1240, 1180, 1122, 1056, 1028, 668 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{14}H_{14}O_2 + Na]^+$ 237.0886; found 237.0887.

4-Methoxybiphenyl (1h):[22] White solid (quant., 184 mg), m.p. 90–92 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 6.97 (d, J = 8.8 Hz, 2 H), 7.29 (d, J = 7.4 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 2 H), 7.52 (t, J = 8.2 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2, 114.1, 126.6, 126.7, 128.1, 128.7, 133.7, 140.7, 159.1 ppm. IR (KBr): $\tilde{\nu}$ = 3056, 2962, 2937, 2836, 1606, 1582, 1522, 1488, 1464, 1287, 1270, 1250, 1201, 1184, 1035, 834, 715, 687 cm^{-1}.

4′-Methylbiphenyl-3-ol (1i): White solid (quant., 184 mg), m.p. 74–76 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 4.91 (s, 1 H, OH), 6.78–6.81 (m, 1 H), 7.04 (t, J = 2.1 Hz, 1 H), 7.14–7.17 (m, 1 H), 7.25–7.31 (m, 3 H), 7.46 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 113.85, 113.9, 119.6, 126.9, 129.4, 129.9, 137.3, 137.8, 142.9, 155.7 ppm. IR (KBr): $\tilde{\nu}$ = 3300, 3028, 2915, 2853, 1588, 1568, 1478, 1446, 1324, 1299, 1214, 1192, 1164, 1127, 1039, 884, 816, 690 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{13}H_{12}O + H]^+$ 185.0961; found 185.0955.

(4′-Methylbiphenyl-3-yl)methanol (1j): White solid (quant., 198 mg), m.p. 72–74 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.75 (br. s, 1 H, OH), 2.40 (s, 3 H), 4.76 (s, 2 H), 7.24–7.25 (m, 2 H), 7.32–7.36 (m, 1 H), 7.41 (t, J = 7.6 Hz, 1 H), 7.50–7.59 (m, 3 H), 7.59–7.61 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 65.3, 125.5, 126.2, 126.9, 128.9, 129.5, 137.1, 138.0, 141.3, 141.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3372, 3016, 2923, 2872, 1607, 1518, 1483, 1438, 1187, 1021, 908, 823, 706, 668 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{14}H_{14}O + Na]^+$ 221.0937; found 221.0937.

2-Methoxy-3,5-dimethylbiphenyl (1k): Colorless oil (76%, 161 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 6 H), 3.34 (s, 3 H), 6.98 (s, 2 H), 7.34 (d, J = 7.4 Hz, 1 H), 7.40 (t, J = 7.2 Hz, 2 H), 7.55 (d, J = 7.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2, 20.7, 59.9, 126.9, 128.1, 129.1, 129.3, 131.0, 131.2, 133.2, 134.5, 138.9, 153.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3013, 2934, 1501, 1475, 1415, 1248, 1163, 1014, 930, 864, 699 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{15}H_{16}O + H]^+$ 213.1274; found 213.1268.

(2′-Methoxy-3′,5′-dimethylbiphenyl-3-yl)methanol (1l): Colorless oil (68%, 164.5 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.75 (br. s, 1 H, OH), 2.31 (s, 6 H), 3.35 (s, 3 H), 4.76 (d, J = 3.8 Hz, 2 H), 6.99 (s, 2 H), 7.34–7.36 (m, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.50 (dt, J = 7.6, 1.5 Hz, 1 H), 7.55 (d, J = 0.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 20.7, 60.0, 65.4, 125.6, 127.7, 128.35, 128.4, 129.2, 131.1, 131.2, 133.3, 134.2, 139.1, 140.7, 153.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3399, 3005, 2927, 2868, 1604, 1471, 1407, 1374, 1252, 1226, 1111, 1015, 908, 735, 651 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{16}H_{18}O_2 + Na]^+$ 265.1199; found 265.1199.

(2′,6′-Dimethoxybiphenyl-3-yl)methanol (1m): White solid (62%, 151.3 mg), m.p. 72–74 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.73 (s, 6 H), 4.73 (s, 2 H), 6.65 (d, J = 8.4 Hz, 2 H), 7.26–7.41 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 65.5, 104.1, 119.1, 125.5, 127.9, 128.7, 129.5, 130.2, 134.4, 140.2, 157.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3419, 3011, 2937, 2838, 1590, 1471, 1429, 1275, 1247, 1034, 910, 706, 668 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{15}H_{16}O_3 + Na]^+$ 267.0992; found 267.0991.

(2′-Methoxy-3′-nitrobiphenyl-3-yl)methanol (1n): Colorless oil (quant., 259 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.90–2.01 (br. s, 1 H, OH), 3.53 (s, 3 H), 4.77 (s, 2 H), 7.24 (t, J = 7.9 Hz, 1 H), 7.41–7.51 (m, 3 H), 7.55–7.57 (m, 2 H), 7.72 (dd, J = 8.1, 1.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.8, 64.7, 123.97, 124.0, 126.6, 127.3, 127.9, 128.7, 135.1, 136.4, 137.3, 141.3, 144.9, 150.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3433, 3020, 1603, 1532, 1466, 1416, 1362, 1045, 999, 928, 850, 705, 669 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{14}H_{13}NO_4 + Na]^+$ 282.0737; found 282.0736.

2-(4-Methylphenyl)benzonitrile (1a):[23] White solid (96%, 185.3 mg), m.p. 53–55 °C, ref.[23] = 50–52 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 7.30 (d, J = 7.8 Hz, 2 H), 7.41 (t, J = 7.6 Hz, 1 H), 7.47 (d, J = 7.5 Hz, 2 H), 7.50 (d, J = 7.9 Hz, 1 H), 7.62 (t, J = 7.2 Hz, 1 H), 7.75 (d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 111.1, 118.8, 127.2, 128.5, 129.4, 129.9, 132.7, 133.6, 135.2, 138.6, 145.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3021, 2923, 2868, 2226, 1613, 1597, 1518, 1478, 1444, 1265, 1187, 1047, 1006, 928, 822, 669 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{14}H_{11}N + Na]^+$ 216.0784; found 216.0784.

Biphenyl-2-carbaldehyde (1o):[24] Colorless oil (98%, 178.3 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.66 (m, 8 H), 8.04 (d, J = 7.8 Hz, 1 H), 10.0 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.0, 127.5, 127.7, 128.0, 128.3, 130.0, 130.7, 133.5, 137.6, 145.9, 192.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3021, 2853, 2755, 1692, 1598, 1475, 1394, 1255, 1197, 1074, 829, 703, 669 cm^{-1}.

3′-(Hydroxymethyl)biphenyl-2-carbaldehyde (1p): Colorless oil (quant., 212 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.89 (br. s, 1 H, OH), 4.78 (s, 2 H), 7.29 (dt, J = 4.2, 2.0 Hz, 1 H), 7.39–7.52 (m, 5 H), 7.62 (td, J = 7.5, 1.4 Hz, 1 H), 8.02 (dd, J = 7.8, 1.1 Hz, 1 H), 9.97 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.5, 126.5, 127.5, 127.7, 128.3, 128.4, 129.1, 130.6, 133.4, 133.6, 137.7, 141.2, 145.7, 192.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3442, 3020, 2977, 2933, 2875, 2758, 1690, 1653, 1598, 1524, 1474, 1449, 1425, 1394, 1333, 1258, 1104, 1044, 928, 878, 849, 824, 708, 669 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{14}H_{12}O_2 + Na]^+$ 235.0730; found 235.0718.

Biphenyl-4-carbaldehyde (1q):[25] Colorless oil (quant., 182 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, J = 7.4 Hz, 1 H), 7.47 (t, J = 7.3 Hz, 2 H), 7.64 (d, J = 7.6 Hz, 2 H), 7.75 (d, J = 8.3 Hz, 2 H), 7.95 (d, J = 8.4 Hz, 2 H), 10.06 (s, 1 H) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ = 127.3, 127.6, 128.4, 128.9, 130.2, 135.1, 139.6, 147.1, 191.9 ppm.

3′-(Hydroxymethyl)biphenyl-4-carbaldehyde (1r): Colorless oil (quant., 212 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.75 (br. s, 1 H, OH), 4.80 (d, J = 4.6 Hz, 2 H), 7.41 (dt, J = 7.6, 1.4 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 1 H), 7.56 (dt, J = 7.6, 1.5 Hz, 1 H), 7.66 (s, 1 H), 7.76 (d, J = 8.2 Hz, 2 H), 7.95 (d, J = 8.4 Hz, 2 H), 10.06 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.6, 125.6, 126.3, 126.9, 127.5, 129.0, 130.1, 134.9, 139.6, 141.7, 146.8, 192.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3433, 3019, 2928, 2741, 1701, 1605, 1568, 1482, 1409, 1388, 1306, 1172, 1017, 929, 834, 669 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{14}H_{12}O_2 + Na]^+$ 235.0730; found 235.0718.

4-Acetylbiphenyl (1s):[22] White solid (quant., 196 mg), m.p. 115–117 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.64 (s, 3 H), 7.41 (d, J = 7.3 Hz, 1 H), 7.45 (t, J = 7.6 Hz, 2 H), 7.62 (d, J = 7.0 Hz, 2 H), 7.68 (d, J = 8.0 Hz, 2 H), 8.03 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7, 127.2, 127.24, 128.2, 128.9, 128.93, 135.8, 139.8, 145.8, 197.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3154, 3033, 1677, 1604, 1560, 1467, 1403, 1358, 1267, 1189, 1096, 912, 845, 741, 650 cm^{-1}.

4-Nitrobiphenyl (1t):[22] White solid (99%, 197 mg), m.p. 110–112 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.61 (m, 3 H), 7.62–7.64 (m, 2 H), 7.72 (d, J = 8.9 Hz, 2 H), 8.30 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.0, 127.3, 127.7, 128.9, 129.1, 138.7, 147.0, 147.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2975, 2929, 1598, 1578, 1518, 1482, 1348, 1318, 1106, 1046, 856, 771, 697 cm^{-1}.

(4′-Nitrobiphenyl-3-yl)methanol (1u): Yellow solid (quant., 229 mg), m.p. 68–70 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.88–1.98 (br. s,

1 H, OH), 4.81 (s, 2 H), 7.43–7.57 (m, 3 H), 7.65 (s, 1 H), 7.74 (d, J = 8.9 Hz, 2 H), 8.29 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.6, 123.9, 125.6, 126.4, 127.3, 127.6, 129.2, 138.7, 141.8, 146.8, 147.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3434, 3020, 2976, 2932, 2885, 1597, 1522, 1481, 1442, 1349, 1400, 1109, 1047, 929, 856, 698, 670 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{13}H_{11}NO_3 + Na]^+$ 252.0631; found 252.0624.

3-Chloro-4′-nitrobiphenyl (1v): White solid (quant., 233 mg), m.p. 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.46 (m, 2 H), 7.49–7.52 (m, 1 H), 7.61–7.62 (m, 1 H), 7.71 (d, J = 9.0 Hz, 2 H), 8.31 (d, J = 9.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.1, 125.5, 127.4, 127.8, 128.8, 130.4, 135.1, 140.5, 146.0, 147.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2977, 1595, 1569, 1521, 1476, 1431, 1393, 1349, 1221, 1102, 1036, 929, 877, 855, 689, 670 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{12}H_8ClNO_2 + Na]^+$ 256.0136; found 256.0134.

3,5-Dichloro-4′-nitrobiphenyl (1w): White solid (quant., 268 mg), m.p. 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, J = 1.9 Hz, 1 H), 7.50 (d, J = 1.9 Hz, 2 H), 7.69 (d, J = 8.9 Hz, 2 H), 8.31 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.30, 125.9, 128.0, 128.7, 135.8, 141.7, 144.7, 147.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2977, 1561, 1523, 1477, 1428, 1349, 1046, 929, 850, 670 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{12}H_7Cl_2NO_2 + H]^+$ 267.9932; found 267.9941.

2,4-Difluoro-4′-nitrobiphenyl (1x): White solid (quant., 235 mg), m.p. 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95–7.03 (m, 2 H), 7.42 (td, J = 8.4, 6.3 Hz, 1 H), 7.67 (dd, J = 8.9, 1.5 Hz, 2 H), 8.29 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 104.6 and 105.1 ($J_{C,F}$ = 26 Hz), 112.0 and 112.3 ($J_{C,F}$ = 4.0 Hz), 123.8, 129.67, 129.7, 131.3 and 131.5 ($J_{C,F}$ = 4.0 Hz), 141.5, 147.2, 158.5 and 161.0 ($J_{C,F}$ = 12.0 Hz), 161.9 and 164.5 ($J_{C,F}$ = 260.0 Hz) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2976, 1620, 1605, 1522, 1488, 1436, 1399, 1350, 1299, 1263, 1143, 1101, 1046, 967, 929, 855, 670 cm^{-1}. HRMS calcd. mass $[C_{12}H_7F_2NO_2 + Na]^+$ 258.0337; found mass 258.0341.

2′,6′-Dimethoxybiphenyl-2-carbaldehyde (1y): Colorless oil (70%, 167 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (s, 6 H), 6.67 (d, J = 8.3 Hz, 2 H), 7.34–7.38 (m, 2 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.63 (t, J = 7.5 Hz, 1 H), 8.01 (d, J = 7.8 Hz, 1 H), 9.74 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 103.9, 114.6, 126.4, 127.5, 130.0, 132.3, 133.3, 134.3, 138.1, 157.7, 192.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3021, 2931, 2840, 1694, 1600, 1472, 1434, 1384, 1286, 1251, 1197, 1172, 1113, 1019, 945, 912, 898, 887, 830, 786, 651 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{15}H_{14}O_3 + Na]^+$ 265.0835; found 265.0843.

(2′,6′-Dimethoxybiphenyl-2-yl)methanol (1z): Colorless oil (52%, 127.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92 (br. s, 1 H, OH), 3.68 (s, 6 H), 4.37 (br. s, 2 H), 6.67 (d, J = 8.4 Hz, 2 H), 7.16 (dd, J = 7.2, 1.3 Hz, 1 H), 7.31–7.42 (m, 3 H), 7.56 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 64.1, 104.4, 117.9, 127.5, 127.9, 128.9, 129.2, 131.1, 133.3, 139.7, 157.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3317, 2930, 2847, 1583, 1470, 1441, 1430, 1248, 1107, 1028, 1005, 913, 784, 737 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{15}H_{16}O_3 + Na]^+$ 267.0992; found 267.0991.

4-Chlorobiphenyl (1ac): White solid (40%, 75 mg), m.p. 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.57 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 139.7, 133.4, 129.0, 128.9, 128.4, 127.6, 127.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3028, 2927, 2854, 1659, 1478, 1449, 1398, 1093, 1019, 1007, 931, 833, 814, 697 cm^{-1}. LRMS (ESI–TOF): m/z = 189.95 $[C_{12}H_9Cl + H]^+$.

4′-Chlorobiphenyl-4-carbaldehyde (1ad): White solid (61%, 132.2 mg), m.p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 8.6 Hz, 2 H), 7.58 (dd, J = 8.7, 5.2 Hz, 2 H), 7.69 (d, J = 8.2 Hz, 2 H), 7.93 (d, J = 8.4 Hz, 2 H), 10.05 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.5, 128.6, 129.2, 130.3, 134.7, 135.4, 138.1, 145.8, 191.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2832, 2737, 1701, 1606, 1579, 1560, 1514, 1482, 1423, 1392, 1308, 1286, 1182, 1169, 1095, 1016, 1005, 928, 840, 815, 669 cm^{-1}. LRMS (ESI–TOF): m/z = 231.06 $[C_{13}H_9OCl + H]^+$.

4′-Fluorobiphenyl-4-carbaldehyde (1ae): White solid (62%, 124.1 mg), m.p. 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (t, J = 8.7 Hz, 2 H), 7.58 (dd, J = 8.7, 5.2 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H), 7.93 (d, J = 8.4 Hz, 2 H), 10.05 (s, 1 H), ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.9 and 116.1 (d, $J_{C,F}$ = 22.0 Hz), 127.5, 129.0 and 129.1 (d, $J_{C,F}$ = 8.0 Hz), 130.3, 135.2, 135.78, 135.8, 146.1, 161.9 and 164.3 (d, $J_{C,F}$ = 245 Hz), 191.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3055, 2987, 2924, 2850, 1701, 1604, 1567, 1521, 1497, 1423, 1265, 1234, 1171, 1160, 1098, 1022, 896, 845, 821, 704, 669 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{13}H_9OF + H]^+$ 201.0710; found 201.0714.

4-Fluoro-4′-nitrobiphenyl (1af): Yellow solid (62%, 134.7 mg), m.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, J = 8.6 Hz, 2 H), 7.58 (dd, J = 8.8, 5.2 Hz, 2 H), 7.68 (d, J = 8.9 Hz, 2 H), 8.28 (d, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.1 and 116.3 (d, $J_{C,F}$ = 22.0 Hz), 124.2, 127.6, 129.1 and 129.2 (d, $J_{C,F}$ = 8.0 Hz), 134.9, 146.5, 147.1, 162.1 and 164.6 (d, $J_{C,F}$ = 248.0 Hz) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3077, 3021, 2920, 2849, 1601, 1509, 1486, 1396, 1342, 1295, 1236, 1160, 1111, 1019, 857, 846, 831, 729, 692, 670 cm^{-1}. LRMS (ESI–TOF): m/z = 257.14 $[C_{12}H_8O_2FN + K]^+$.

[3-(6-Methylpyridin-2-yl)phenyl]methanol (15a): Colorless oil (82%, 163.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.05 (br. s, 1 H), 2.63 (s, 3 H), 4.76 (s, 2 H), 7.1 (d, J = 7.5 Hz, 1 H), 7.38–7.48 (m, 3 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.63 (t, J = 7.7 Hz, 1 H), 7.85 (dd, J = 7.5, 1.3 Hz, 1 H), 7.97 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 64.7, 118.0, 121.7, 125.5, 126.0, 127.2, 128.7, 137.0, 139.7, 141.5, 156.9, 158.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3369, 3063, 3018, 2927, 2873, 1698, 1575, 1451, 1378, 1309, 1162, 1097, 1041, 927, 892, 706, 669 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{13}H_{14}NO]^+$ 200.1070; found 200.1070.

3-(Pyridin-3-yl)phenol (15b):[26] Yellow solid (78%, 133.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.96–6.98 (m, 1 H), 7.11 (dd, J = 7.6, 0.7 Hz, 1 H), 7.23–7.28 (m, 1 H), 7.36 (t, J = 7.9 Hz, 1 H), 7.42 (dd, J = 7.9, 4.9 Hz, 1 H), 7.95 (dt, J = 6.4, 1.6 Hz, 1 H), 8.59 (d, J = 4.5 Hz, 1 H), 8.93 (br. s, 1 H), 9.01 (d, J = 2.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 114.3, 116.0, 118.4, 124.2, 130.6, 135.4, 137.5, 138.5, 147.2, 147.5, 157.8 ppm.

3-(Pyridin-2-yl)phenol (15c):[26] Colorless oil (65%, 111 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88–6.91 (m, 1 H), 7.24–7.28 (m, 1 H), 7.29 (t, J = 7.9 Hz, 1 H), 7.39 (dt, J = 7.8, 1.1 Hz, 1 H), 7.55 (t, J = 2.0 Hz, 1 H), 7.67 (d, J = 8.0 Hz, 1 H), 7.75 (td, J = 7.7, 1.5 Hz, 1 H), 8.65–8.66 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.5, 116.7, 118.8, 121.6, 122.4, 130.0, 137.4, 140.2, 148.9, 157.0, 157.4 ppm.

[3-(Pyridin-2-yl)phenyl]methanol (15d): Colorless oil (94%, 174 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98–2.09 (br. s, 1 H, OH), 4.78 (s, 2 H), 7.23–7.36 (m, 1 H), 7.41–7.52 (m, 2 H), 7.61–7.79 (m, 2 H), 7.88 (dt, J = 7.5, 1.6 Hz, 1 H), 8.0 (s, 1 H), 8.69–8.71 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.0, 120.8, 122.2, 125.5, 126.0, 127.5, 128.9, 136.9, 139.4, 141.7, 149.5, 157.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3370, 3018, 2928, 1590, 1567, 1466, 1437, 1044, 927, 669 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{12}H_{11}NO + H]^+$ 186.0913; found 186.0917.

5-Phenylindole (15e):[22] White solid (89%, 172 mg), m.p. 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.61 (dd, J = 3.2, 2.0 Hz, 1 H), 7.24–7.25 (m, 1 H), 7.29–7.33 (m, 1 H), 7.42–7.46 (m, 4 H), 7.64–7.67 (m, 2 H), 7.86 (d, J = 1.5 Hz, 1 H), 7.87 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.9, 111.2, 119.2, 121.8, 124.9, 126.3, 127.3, 128.3, 128.6, 133.3, 135.2, 142.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3425, 3013, 2926, 1600, 1470, 1457, 1415, 1307, 1091, 884, 699, 667 cm^{-1}.

(*E*)-3-Styrylpyridine (15f): Colorless oil (76%, 138 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.06 (d, J = 16.4 Hz, 1 H), 7.16 (d, J = 16.4 Hz, 1 H), 7.28–7.32 (m, 2 H), 7.34 (t, J = 7.5 Hz, 2 H), 7.53 (d, J = 7.3 Hz, 2 H), 7.83 (dt, J = 8.0, 1.8 Hz, 1 H), 8.49 (d, J = 3.7 Hz, 1 H), 8.73 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 123.5, 124.8, 126.6, 128.2, 128.4, 128.7, 130.8, 132.6, 132.9, 136.6, 148.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3013, 2973, 1599, 1586, 1567, 1477, 1446, 1419, 1399, 1187, 1025, 954, 921, 868, 807, 762, 666 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{13}H_{11}N + H]^+$ 182.0964; found 182.0961.

(*E*)-2-Methyl-6-styrylpyridine (15g):[27] Yellow oil (75%, 146.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (s, 3 H), 7.01 (d, J = 7.6 Hz, 1 H), 7.15 (d, J = 16.2 Hz, 1 H), 7.23 (d, J = 7.8 Hz, 1 H), 7.27 (t, J = 7.34 Hz, 1 H), 7.35 (t, J = 7.4 Hz, 2 H), 7.54–7.66 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.6, 118.7, 121.7, 127.0, 128.1, 128.4, 128.6, 132.3, 136.6, 136.7, 155.0, 158.2 ppm.

***p*-Terphenyl (17a):**[28] White solid (96%, 221 mg), m.p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (t, J = 7.4 Hz, 2 H), 7.45 (t, J = 7.6 Hz, 4 H), 7.65 (d, J = 7.2 Hz, 4 H), 7.69 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.0, 127.3, 127.5, 128.8, 140.1, 140.7 ppm. IR (KBr): $\tilde{\nu}$ = 3057, 3033, 2919, 1595, 1576, 1479, 1454, 1403, 1258, 1168, 1074, 1027, 1002, 909, 838, 687 cm^{-1}.

***p*-Terphenyl-3-ylmethanol (17b):** White solid (92%, 239 mg), m.p. 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (t, J = 6.0 Hz, 1 H), 4.78 (d, J = 5.9 Hz, 2 H), 7.35–7.39 (m, 2 H), 7.45 (t, J = 7.7 Hz, 3 H), 7.57 (dt, J = 7.7, 1.4 Hz, 1 H), 7.64–7.69 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.3, 125.6, 125.9, 126.3, 127.0, 127.4, 127.5, 128.8, 129.1, 139.8, 140.2, 140.6, 141.0, 141.4 ppm. IR (KBr): $\tilde{\nu}$ = 3374, 3294, 2916, 2884, 2850, 1580, 1478, 1452, 1401, 1349, 1260, 1184, 1078, 1025, 1006, 839, 764, 692 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{19}H_{16}O + Na]^+$ 283.1093; found 283.1093.

(3′′-Bromo-2′,2′′-dimethoxy-[1,1′:3′,1′′-terphenyl]-3-yl)methanol (17c): Colorless oil (61%, 243.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.15 (s, 3 H), 3.58 (s, 3 H), 4.78 (s, 2 H), 7.03 (t, J = 7.80 Hz, 1 H), 7.18–7.45 (m, 6 H), 7.55–7.65 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.6, 60.7, 65.4, 117.6, 123.8, 124.8, 125.9, 127.8, 128.5, 130.6, 130.9, 131.0, 132.0, 132.8, 134.2, 135.0, 138.9, 140.9, 154.8, 155.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3427, 2928, 2851, 1606, 1456, 1415, 1263, 1231, 1083, 1010, 910, 705 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{21}H_{19}BrO_3 + Na]^+$ 421.0410; found 421.0411.

(3′′-Bromo-2′,2′′,5′,5′′-tetramethoxy-[1,1′:3′,1′′-terphenyl]-3-yl)-methanol (17d): Colorless oil (71%, 326 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.15 (s, 3 H), 3.58 (s, 3 H), 3.79 (s, 3 H), 3.82 (s, 3 H), 4.76 (s, 2 H), 6.84 (d, J = 3.2 Hz, 1 H), 6.87 (d, J = 3.0 Hz, 1 H), 6.92 (d, J = 3.2 Hz, 1 H), 7.12 (d, J = 3.1 Hz, 1 H), 7.36–7.44 (m, 2 H), 7.54 (d, J = 7.5 Hz, 1 H), 7.61 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.7, 55.8, 60.8, 61.0, 65.3, 115.3, 116.2, 116.3, 117.6, 117.8, 126.0, 127.7, 128.46, 128.5, 132.7, 134.2, 135.8, 138.7, 140.9, 148.9, 155.1, 155.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 3012, 2935, 2835, 1698, 1595, 1564, 1470, 1416, 1343, 1294, 1176, 1115, 1041, 1007, 854, 706, 667 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{23}H_{23}BrO_5 + Na]^+$ 481.0621; found 481.0628.

[5′-(3-Hydroxymethylphenyl)-3′′-hydroxymethyl-[1,1′:3′,1′′-terphenyl]-3-yl]methanol (19): White solid (70%, 278 mg), m.p. 218–220 °C. ^{1}H NMR (400 MHz, CD_3OD): δ = 4.70 (br. s, 3 H), 4.78 (s, 6 H), 7.44 (d, J = 7.6 Hz, 3 H), 7.52 (t, J = 7.6 Hz, 3 H), 7.70 (d, J = 7.7 Hz, 3 H), 7.81 (s, 3 H), 7.89 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 65.3, 126.0, 127.0, 127.4, 127.43, 130.2, 142.6, 143.6, 143.8 ppm. IR (KBr): $\tilde{\nu}$ = 3270, 3035, 2865, 1595, 1582, 1487, 1454, 1399, 1263, 1197, 1172, 1033, 1011, 1000, 879, 799, 786, 710 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{27}H_{24}O_3 + Na]^+$ 419.1618; found 419.1616.

Vinyl iodides **20a**–**20d** were synthesized by following the literature procedure.[29] The analytical data for α- or β-iodobutenolides **20a**–**20d** is given below.

5-Ethyl-3-iodofuran-2(5*H*)-one (20a): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.4 Hz, 3 H), 1.70–1.88 (m, 2 H), 4.95 (t, J = 1.4 Hz, 1 H), 7.72 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8, 26.3, 85.4, 86.3, 161.0, 170.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2961, 2928, 1739, 1640, 1462, 1380, 1017, 960, 875, 669 cm^{-1}. LRMS (ESI–TOF): m/z = 238.96 $[C_6H_7IO_2 + H]^+$.

5-Ethyl-4-iodofuran-2(5*H*)-one (20b): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.4 Hz, 3 H), 1.66–1.73 (m, 1 H), 2.08–2.14 (m, 1 H), 4.94–4.97 (m, 1 H), 6.53 (d, J = 1.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.5, 25.4, 88.6, 124.8, 130.3, 171.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3010, 2972, 2928, 2851, 1752, 1585, 1459, 1401, 1325, 1237, 1157, 1047, 913, 746 cm^{-1}. LRMS (ESI–TOF): m/z = 238.96 $[C_6H_7IO_2 + H]^+$.

5-Pentyl-4-iodofuran-2(5*H*)-one (20c): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 6.9 Hz, 3 H), 1.30–1.42 (m, 6 H), 1.55–1.64 (m, 1 H), 1.99–2.07 (m, 1 H), 4.94–4.97 (m, 1 H), 6.51 (d, J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.3, 23.3, 31.2, 32.4, 88.0, 125.3, 130.0, 171.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3101, 3016, 2952, 2929, 2860, 1755, 1587, 1464, 1376, 1332, 1244, 1161, 1090, 1039, 1014, 926, 880, 853, 699 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_9H_{13}O_2I + Na]^+$ 302.9858; found 302.9863.

5-Undecyl-4-iodofuran-2(5*H*)-one (20d): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 6.9 Hz, 3 H), 1.25–1.43 (m, 18 H), 1.53–1.65 (m, 1 H), 1.99–2.07 (m, 1 H), 4.94–4.97 (m, 1 H), 6.51 (d, J = 1.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 23.7, 29.28, 29.3, 29.4, 29.6, 31.9, 32.5, 88.0, 125.3, 130.0, 171.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2925, 2854, 1768, 1572, 1465, 1377, 1327, 1264, 1185, 987, 705 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{15}H_{25}IO_2I + H]^+$ 365.0978; found 365.0987.

5-Ethyl-4-*p*-tolylfuran-2(5*H*)-one (22a): Colorless oil (quant., 202 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, J = 7.40 Hz, 3 H), 1.63–1.72 (m, 1 H), 2.09–2.16 (m, 1 H), 2.43 (s, 3 H), 5.48–5.50 (m, 1 H), 6.26 (d, J = 1.3 Hz, 1 H), 7.28 (d, J = 7.6 Hz, 2 H), 7.37 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 8.2, 21.5, 26.4, 82.9, 113.7, 127.0, 127.4, 129.9, 141.9, 167.3, 173.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2972, 2928, 1744, 1618, 1511, 1454, 1316, 1168, 1083, 1017, 921, 770, 669 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{13}H_{14}O_2 + Na]^+$ 225.0886; found 225.0879.

4-(2,4-Difluorophenyl)-5-ethylfuran-2(5*H*)-one (22b): Colorless oil (quant., 224 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.3 Hz, 3 H), 1.55–1.61 (m, 1 H), 2.02–2.05 (m, 1 H), 5.49–5.50 (m, 1 H), 6.36 (s, 1 H), 6.93–7.03 (m, 2 H), 7.38 (td, J = 8.5, 6.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 26.1, 83.53 and 83.57 ($J_{C,F}$ = 4.0 Hz), 105.14 and 105.65 ($J_{C,F}$ = 26 Hz), 112.49 and 112.74 ($J_{C,F}$ = 3.0 Hz), 114.93 and 115.06 ($J_{C,F}$ = 4.0 Hz), 117.58 and 117.65 ($J_{C,F}$ = 7.0 Hz), 130.23 and 130.33 ($J_{C,F}$ =

5.0 Hz), 159.49 and 162.05 ($J_{C,F}$ = 12.0 Hz), 163.17 and 165.71 ($J_{C,F}$ = 210.0 Hz), 172.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2972, 2934, 1754, 1624, 1588, 1505, 1456, 1432, 1267, 1176, 1144, 1100, 979, 965, 856, 741 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{12}H_{10}O_2F_2 + H]^+$ 225.0727; found 225.0721.

5-Pentyl-4-phenylfuran-2(5*H*)-one (22c): Colorless oil (quant., 230 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.3 Hz, 3 H), 1.18–1.30 (m, 4 H), 1.37–1.47 (m, 2 H), 1.53–1.62 (m, 1 H), 1.95–2.03 (m, 1 H), 5.48–5.51 (m, 1 H), 6.26 (d, J = 1.1 Hz, 1 H), 7.45–7.49 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 24.2, 31.3, 33.4, 82.3, 114.3, 127.1, 129.2, 130.2, 131.2, 167.8, 173.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2926, 2851, 1755, 1599, 1492, 1448, 1338, 1275, 1118, 1026, 963, 894, 792, 694 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{15}H_{18}O_2 + H]^+$ 231.1385; found 231.1390.

5-Undecyl-4-phenylfuran-2(5*H*)-one (22d): Colorless oil (quant., 314 mg). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.0 Hz, 3 H), 1.21–1.28 (m, 16 H), 1.34–1.46 (m, 2 H), 1.54–1.60 (m, 1 H), 1.95–2.02 (m, 1 H), 5.48–5.51 (m, 1 H), 6.27 (d, J = 1.4 Hz, 1 H), 7.44–7.50 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.7, 24.5, 29.2, 29.3, 29.32, 29.4, 29.6, 31.9, 33.5, 82.3, 114.3, 127.1, 129.2, 130.2, 131.2, 167.8, 173.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2925, 2851, 1756, 1596, 1492, 1448, 1341, 1264, 1118, 1023, 963, 891, 856, 792, 694 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{21}H_{30}O_2 + H]^+$ 315.2324; found 315.2321.

(*E*)-Ethyl-3-(4-nitrophenyl)acrylate (24a): White solid (52%, 115 mg), m.p. 138–140 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 7.1 Hz, 3 H), 4.27 (q, J = 7.1 Hz, 2 H), 6.54 (d, J = 16.0 Hz, 1 H), 7.66 (d, J = 8.8 Hz, 2 H), 7.68 (d, J = 16.2 Hz, 1 H), 8.24 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 61.0, 122.6, 124.2, 128.6, 140.6, 141.6, 148.5, 166.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 1712, 1599, 1522, 1421, 1347, 1044, 928, 846, 669 cm^{-1}. LRMS (ESI–TOF): m/z = 222.07 $[C_{11}H_{11}O_4N + H]^+$.

(*E*)-Ethyl-3-(4-chlorophenyl)acrylate (24b): Colorless oil (46%, 97 mg). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, 3 H), 4.24 (q, J = 7.1 Hz, 2 H), 6.34 (d, J = 16.0 Hz, 1 H), 7.34 (d, J = 8.5 Hz, 2 H), 7.44 (d, J = 8.5 Hz, 1 H), 7.61 (d, J = 16.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 60.6, 118.9, 129.1, 129.2, 132.9, 136.1, 143.1, 166.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2979, 2935, 2908, 1710, 1640, 1594, 1492, 1368, 1312, 1273, 1203, 1184, 1091, 1042, 982, 880, 824, 669 cm^{-1}. LRMS (ESI–TOF): m/z = 211.05 $[C_{11}H_{11}O_2Cl + H]^+$.

Synthesis of Preclamol (25):[20,21] Propyl bromide (43 mg, 0.351 mmol, 2.0 equiv.) was added to a solution of compound **15b** (30 mg, 0.1754 mmol) in dry CH_3CN (2 mL) in a sealed tube at room temperature. The reaction mixture was stirred at 90 °C for 24 h. The solvent was removed under vacuum to give propyl pyridinium bromide as a yellow solid.

The resulting salt (47.3 mg) was dissolved in MeOH/AcOH (1:2; 2 mL), and Pt/C (10%; 4.1 mg, 0.0175 mmol, 10 mol-%) was added. The mixture was stirred under a hydrogen atmosphere (70 psi) in an autoclave at 50 °C for 24 h. The reaction mixture was filtered through Celite, which was then washed with MeOH (2× 10 mL). The filtrate was concentrated under vacuum to give a brown viscous residue. The residue was treated with satd. aq. Na_2CO_3 (5 mL), and the mixture was extracted with EtOAc (3× 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give virtually pure preclamol **25** (38 mg, quant.) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.3 Hz, 3 H), 1.50–1.60 (m, 3 H), 1.70–1.84 (m, 2 H), 1.93–2.04 (m, 3 H), 2.28–2.34 (m, 1 H), 2.37–2.43 (m, 1 H), 2.84–2.89 (m, 1 H), 3.05 (d, J = 11.5 Hz, 1 H), 3.16 (d, J = 11.2 Hz, 1 H), 6.70–6.76 (m, 3 H), 7.18 (t, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.0, 19.0, 25.3, 30.2, 42.9, 53.9, 61.26, 61.3, 114.4, 115.0, 116.9, 129.9, 145.5, 157.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3663, 3326, 3011, 2935, 2876, 1599, 1586, 1455, 1378, 1284, 1161, 1098, 1080, 997, 961, 858, 699, 667 cm^{-1}. HRMS (ESI–TOF): calcd. for $[C_{14}H_{21}NO + H]^+$ 220.1696; found 220.1688.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of all prepared compounds

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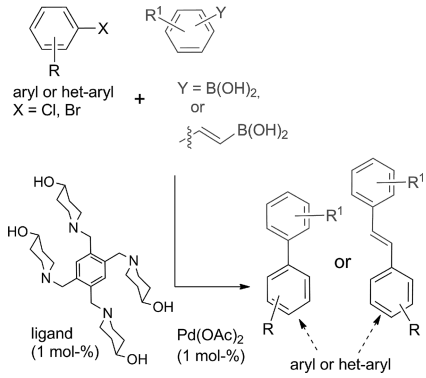
A domino aza-Cope/aza-Prins cascade enabled the synthesis of a new class of 4-hydroxypiperidine-appended mono-, bis-, tris-, and tetrakis-unimolecular compounds that served as efficient ligands to catalyze Suzuki–Miyaura cross-coupling reactions under aerobic conditions. Various biaryls, terphenyls, and heterocyclic biphenyls were obtained in good to excellent yields.



Keywords: Homogeneous catalysis / Palladium / Ligand design / Cross-coupling / Biaryls / Nitrogen heterocycles

