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Simple Modular Synthetic Approaches to Asymmetric *NN′N″*, *NN′C*, or *NN′P*-Type Amido Pincer Ligands: Synthesis, Characterisation, and Preliminary Ligation Studies

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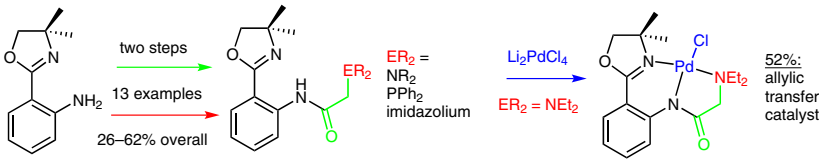

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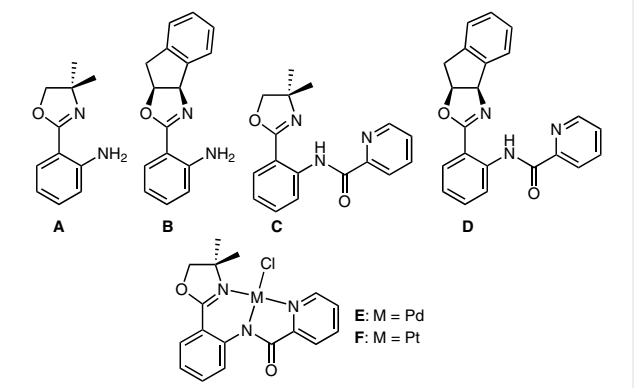
Abstract A simple modular approach is presented which has been directed towards the synthesis of potentially monoanionic *NN′N″*, *NN′C*, and *NN′P* pincer-type ligands. These pincers incorporate an amide functionality derived from the skeletal structure of readily available 2-(2-aminophenyl)-4,5-dioxooxazoles. All of the pincers are synthesized in moderate yields (up to 74%) and are characterised by nuclear magnetic spectroscopy (NMR), elemental analyses, and infrared (IR) spectroscopy. X-ray crystallography is also performed on the chiral and achiral alkyl halide precursors and on an oxide derivative of a pincer with a *NN′P*-atom donor set. A palladium derivative of one of the *NN′N″*-pincers is shown to be an active catalyst for the addition of an allyl group to various benzaldehydes using *n*-Bu_3Sn(allyl) as allyl source.

Key words pincer, oxazoline, ligands, palladium complex, allyl group transfer

Pincer ligands and the metal, metalloid, and main group complexes derived from them, are currently playing a major role in modern coordination chemistry, catalysis, materials science, and biologically directed chemical studies.[3] A pincer ligand typically consists of one or more formally anionic donor atoms and these are flanked by two other donor groups. The former being typically a *C*- or *N*-based fragment and the latter usually consisting of heteroatom donors with *P*, *N*, *S*, *Se*, in addition to carbene donors, being commonly employed.[4,5] Some time ago, we reported[6] on a new design of pincer ligand scaffold based on the independently useful organic framework derived from the 2-(2-aminophenyl)-4,5-dihydrooxazole skeleton (i.e., **A**/**B**, Scheme 1).[6,7] Amide bond formation via reaction of **A** with 2-picolinic acid yields the benchmark formally C_1 symmetric pincer precursor **C** (Scheme 1).

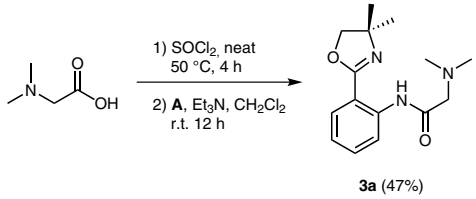


Scheme 1 Schematic representations of compounds **A**–**F**

A chiral analogue **D** was likewise described (Scheme 1) from precursor **B**.[6] Compound **C** and its chiral cousin were thereafter shown to produce pincer complexes of Pd or Pt (i.e., M) via N–H bond rupture and formation of an amido N–M bond resulting from the formal loss of H^+.[6,8,9] The κ^3-*N*,*N*′,*N*″ binding mode being completed by oxazoline[10–12] and pyridine *N*-base donation to M. These pincer complexes (i.e., **E** and **F**, Scheme 1) were thereafter shown to be not only useful pre-catalysts for C–C bond forming reactions,[6] but also as potential therapeutic agents in anti-cancer re-

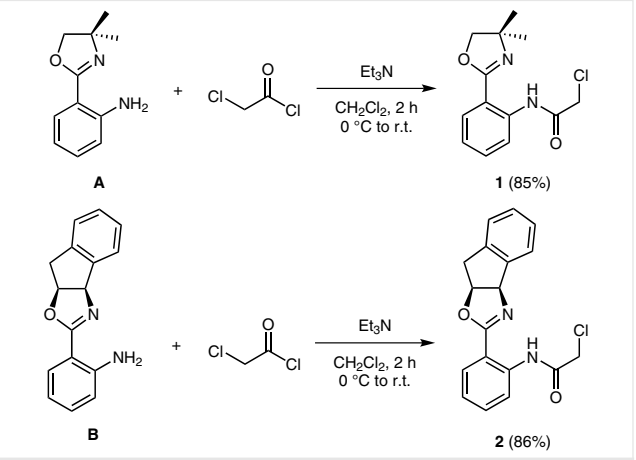
search.[8] For the organometallic chemist, lengthy and expensive syntheses of ligands is a serious bottleneck to the rapid expansion of libraries of compounds that are intended for later screening of catalytic potency. The desire to make such pincer systems in a simple, inexpensive, and more modular fashion is in line with our objectives to design such molecules for a whole range of applications in both chemical synthesis and chemical biology. Herein, we present our recent investigations into modular pincer ligand syntheses based on the synthetically readily obtainable compounds **A** and **B**. In addition, a pincer–Pd derivative of one of the materials is reported and tested for C–C bond forming process. In this regard, it is shown to be a useful catalyst in allylic group transfer chemistry.

Our earlier synthetic methodology used to generate **C** or **D** employed **A** or **B** in combination with picolinoyl chloride obtained in situ by treatment of picolinic acid (i.e., PA) with excess $SOCl_2$. Alternatively, amide bond formation could be facilitated with DCC/DMAP protocols using pure PA and **A**/**B**.[6] Our initial attempts to expand this series of ligands using this latter method proved ineffective when PA was replaced with *N*,*N*-dimethylglycine (i.e., DMG), likely due to the insolubility of this material in the relatively non-polar solvents previously employed. This situation can be attributed to the zwitterionic nature of this compound. Hence, the former (less environmentally benign, costly, and poorly atom-economic) method was chosen which does lead to the desired ω-tertiary amine compound **3a** (Equation 1) in reasonable yield (47%). Despite this success, we were concerned about the obvious necessity to use $SOCl_2$ in the presence of reagents containing more sensitive functional groups. In addition, several of our desired new ligand designs required currently unavailable or synthetically challenging R-COOH compounds. Therefore, this prompted us to pre-modify **A**/**B** to allow for simpler and less expensive modification of the ligand platform.



Equation 1 Synthetic route to compound **3a**

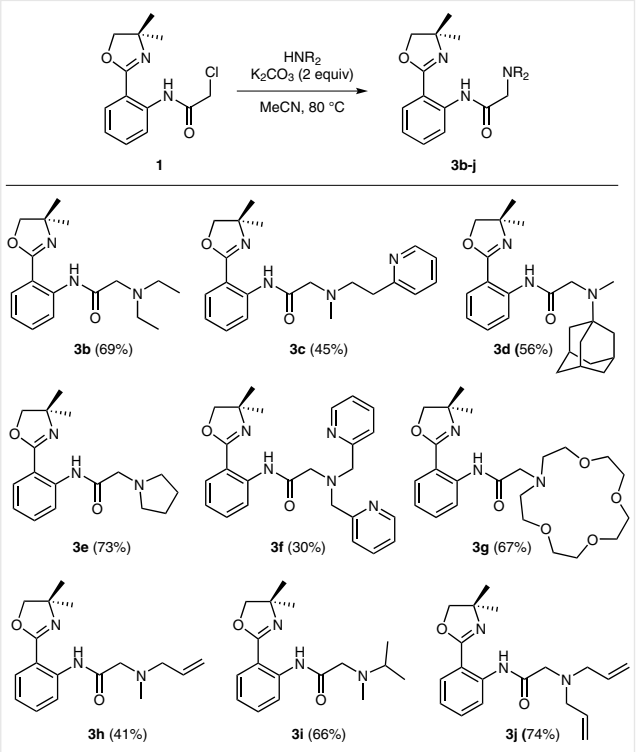
Thus, reaction of **A** or **B** with 2-chloroacetyl chloride leads to the isolation of our key ligand precursors **1** (Equation 2)[13] and its chiral congener **2** in excellent yields (85 and 86%, respectively). Both of these materials were further characterised in the solid-state by single crystal X-ray diffraction methods (see Supporting Information).



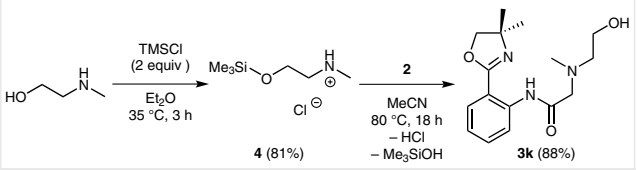
Equation 2 Synthetic route to compounds **1** and **2**

Nucleophilic attack at the chloromethyl group was thus investigated as a new stratagem with the intention to produce a library of ligands using simple and inexpensive secondary amine reagents. This concept was then tested and the desired ligand products **3b**–**j** were obtained (Scheme 2), as mildly hydroscopic materials, with *N*,*N*-diethylamine, 2-[2-(methylamino)ethyl]pyridine, *N*-methyladamantane-1-amine, pyrrolidine, di(2-picolyl)amine, 1-aza-15-crown-5, *N*-allyl-*N*-methylamine, *N*-isopropyl-*N*-methylamine, and *N*,*N*-diallylamine, respectively. The use of inexpensive K_2CO_3 was found to be a suitable base for this process when using MeCN as the reaction medium.[14] The isolated yields of these ligands range from 74 to 30% (Scheme 2) and all species gave satisfactory and otherwise unsurprising spectroscopic and elemental analyses data.[15] A diagnostic ^1H NMR signal can be used to confirm formation of the desired ligand; the N–H signal initially corresponding to the amide group of **1**/**2** (δ_H = 13.05 and 12.98, respectively) is shifted considerably downfield upon reaction (see the experimental procedures). Series **3b**–**j** was designed to offer ligands with a variety of steric profiles (cf. **3b** vs. **3d**), and/or *N*-basicity (cf. **3e** vs. **3j**) at the flanking NR_2 group; the presence of groups capable of secondary metal-bonding interactions (e.g., **3f**) have also been included. Compound **3k**, which contains a potential secondary binding group in the form of an ω-ethanol chain, required a two-step synthesis due to the necessity to protect the OH functionality (Scheme 3). Protective group removal occurs in situ under the base-free reaction conditions affording product **3k** directly.

The successful syntheses of **3b**–**k** by these simple methods prompted us to investigate if materials such as **1** could be used with other, non-*N*-based nucleophiles. In this regard, reaction of **1** with $KPPh_2$ following by recrystallisation in air gives the corresponding phosphane oxide material **3m**·oxide. This complex has also been characterised by single crystal X-ray diffraction as the isolated monohydrate



Scheme 2 The general reaction, schematic representations and yields of compounds **3b–j**



Scheme 3 The two-step synthetic route to ω-ethanol appended pincer **3k**

(Scheme 4; also see Supporting Information). The oxide free material can be observed spectroscopically (δ_P = –15.8 [$CDCl_3$]) before exposure to air and hence the phosphane should be amenable to reactions with metal fragments in situ.

Classical pincer ligands are characterised by the presence of *N*- or *P*-donor atoms.[3] In recent years however, there have been a variety of pincers reported which contain a potent metal-binding carbene fragment.[16] We therefore further investigated our synthetic protocols to form a carbene precursor derivative. Thus, reaction of pre-formed 1-benzyl-1*H*-imidazole with **3** under the base-free conditions readily yielded the desired carbene precursor **3l**, in the form of the HCl salt, in reasonable yield (57%, Figure 1).

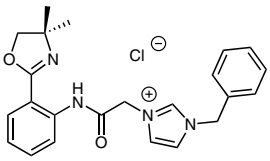


Figure 1 Schematic representation of carbene precursor **3l**

With the library of ligands in hand, it was thereafter prudent to clarify complexation with an example and indeed to test such material in catalysis. Our earlier work had demonstrated facile κ^3-*N*,*N*′,*N*″ binding of this class of pincers (i.e., LH) to a Pd metal centre via treatment with Li_2PdCl_4 in MeOH solution. This process results in net loss of HCl (de-protonation of the pincer) and 2 equivalents of LiCl, yielding the Pd(κ^3-*N*,*N*′,*N*″-L)Cl product (Scheme 1,**E**).[6] Pincer **3b** was chosen for testing in this regard due to its availability and favourable NMR characteristics. The reaction as detailed above proceeded smoothly to give Pd complex **5** (Figure 2) in reasonable yield (see experimental procedures).

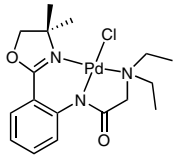
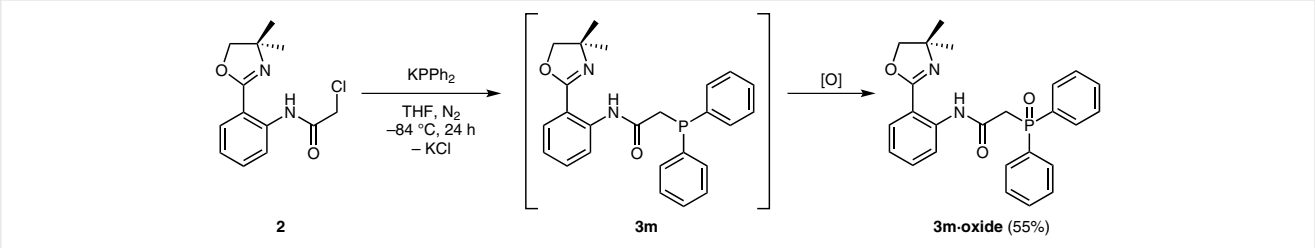


Figure 2 Schematic representation of Pd complex **5**

Szabó and co-workers have pioneered the use of pincer Pd complexes as catalysts in a variety of organic transformations,[4n] and notably in allyl group transfer reactions.[4n,17–19] In this regard, *PCP*-type pincers were found to be particu-



Scheme 4 The Synthetic route to **3m**·oxide

larly effective in the transfer of an allyl group from a tin precursor such as *n*-Bu_3Sn(allyl) (i.e., TBAT) to aldehydes to yield, after acidic work-up, homoallylic alcohols. Common side reactions, such as allylic homocoupling, are suppressed under these conditions.[20] Thus, complex **5** was tested for such chemistry using TBAT and aromatic aldehydes (Table 1) under typical protocols (see experimental procedures). As predicted from the assumed reaction mechanism,[19] EWGs are known to favour the overall process and indeed 4-nitrobenzaldehyde is converted quantitatively with 4-methoxybenzaldehyde displaying lower conversions. In Szabó's seminal study on such chemistry, it was noted that *NCN* (*N* = trialkyl or oxazoline *N*-donor) and *C′CC′* type pincers (*C′* = carbene donor) of Pd were notably poorer catalysts when compared with the *PCP* designs that were tested.[18,19] The data obtained here suggests that this particular class of *NN′N″* ligands are worthy for further studies as group transfer catalysts. Such work is currently a focus of our on-going research efforts in this area.

Table 1 Complex **5** Catalysed Allylation of Selected Benzaldehydes[a]

Entry	R[a]	Yield (%)[b]
1	NO_2	<99
2	NO_2	0[c]
3	OMe	76
4	OMe	0[c]
5	H	<99
6	H	0[c]

[a] General formula 4-R-C_6H_4-CHO (see experimental procedures).
[b] Yields determined by ^{1}H NMR spectroscopy.
[c] No **5** added.

The synthesis and characterisation of small library of potential *N,N′,N″* pincer ligands has been realised. The use of a key alkyl chloride derivative considerably widens the potential scope of this library and indeed examples of both *N,N′P* and *N,N′*-carbene pincer precursors have also been synthesised. A Pd chlorido complex of one of the *N,N′,N″* pincers has been made and it is shown to be an active catalysts for allyl group transfer chemistry. Future work based on these studies will include a further exploration of chiral pincers obtained from **2**, enantioselective catalytic screening, and the use of new pincers in bio-inorganic chemistry; these results will be reported in due course.

All reactions were carried out under an ambient atmosphere unless otherwise stated. All chemicals were purchased commercially and were used without further purification. Solvents used for reactions were supplied by an mBraun Solvent Purification System (SPS) or commercial suppliers, none of which were further purified. Compounds **A** and **B** were synthesized according to literature.[21,22] NMR experiments were recorded on a Bruker Avance II 400 using $CDCl_3$ at 400 MHz (^{1}H), 162 MHz (^{31}P), and 100 MHz (^{13}C) at r.t. In all spectra, chemical shifts were adjusted to the residual solvent peak (δ = 7.26 for the ^{1}H resonance frequency of $CHCl_3$ and δ = 77.16 for ^{13}C pertaining to the central resonance of $^{13}CDCl_3$). Melting points were determined using a Fisher Scientific melting point (mp) apparatus with a maximum temperature of 300 °C. The values provided for each mp are uncorrected. IR spectra were obtained on Perkin Elmer Spectrum One using KBr disks (for solid materials) and NaCl disks for compounds in the liquid/oil phase. SiliCycle TLC plates (thickness: 250 µm) were used for TLC characterisation; visualized under UV light. Some of the products (as specified) were purified by dry-column flash chromatography (DCFC). The general procedure included the sample being adsorbed onto the silica (~3 g) using a rotary evaporator. Then, a 100 mL sintered glass funnel was packed with clean silica (~12 g) and then topped with compound-adsorbed onto silica. Fractions were collected individually by applying vacuum. Each fraction consisted of total 25 mL of the solvent mixture; initially from hexanes (25 mL) and increasing the polarity by adding EtOAc (1 mL) with each consecutive fraction [e.g., fraction 2: hexanes (24 mL) and EtOAc (1 mL)].

2-(Dimethylamino)-*N*-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]acetamide (3a)

$SOCl_2$ (8.81 mL, 121 mmol) was added to *N,N*-dimethylglycine (0.50 g, 4.9 mmol) in a 50-mL round-bottomed flask. The orange-coloured mixture was heated to 50 °C and then stirred for 4 h (until any solids dissolved). Excess $SOCl_2$ was removed in vacuo from the clear, bright yellow solution resulting in the formation of a bright yellow coloured solid. Then, the solution of **A** (0.46 g, 2.4 mmol) and Et_3N (0.70 mL, 5.0 mmol) in CH_2Cl_2 (25.0 mL) was added to the mixture which was then stirred for 12 h at r.t. The dark orange coloured solution was then extracted with water (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and gravity filtered, resulting in a transparent brownish-orange coloured solution. After evaporation of the solvent, a beige-coloured solid was formed. The compound was purified by DCFC and the product was collected as a dark orange coloured hydroscopic wax from fractions 5 to 14 (0.34 g, 47% yield); R_f = 0.58 (hexanes–EtOAc, 4:1).

IR (KBr): 2969, 2779, 1677, 1645, 1581, 1532, 1447, 1291, 1208, 1053, 1044, 963, 877, 753, 689 cm^{-1}.

^{1}H NMR: δ = 1.40 (s, 6 H), 2.39 (s, 6 H), 3.16 (s, 2 H), 4.05 (s, 2 H), 7.07 (t, *J* = 8.0 Hz, 1 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.83 (dd, *J* = 8.0, 4.0 Hz, 1 H), 8.84 (d, *J* = 12.0 Hz, 1 H), 12.80 (s, 1 H).

^{13}C NMR: δ = 28.6, 46.0, 64.5, 68.1, 77.7, 114.1, 119.8, 122.3, 129.0, 132.2, 139.5, 161.1, 171.0.

Anal. Calcd for $C_{15}H_{21}N_3O_2$·0.25H_2O: C, 64.38; H, 7.74; N, 15.02. Found: C, 64.88; H, 7.66; N, 15.00.

2-Chloro-*N*-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]acetamide (1)

The solution of **A** (1.70 g, 8.94 mmol) and Et_3N (1.86 mL, 13.3 mmol) in CH_2Cl_2 (25 mL) in a round-bottomed flask was placed into an ice bath and stirred for 15 min. 2-Chloroacetyl chloride (0.78 mL, 9.8 mmol) was then added dropwise over 5 min to the stirred solution. Upon completion of the addition, the contents of the reaction vessel were stirred for 2 h at r.t. Over that period of time, the colour of the solution changed from yellow to orange and finally to deep red; a pale pink precipitate was also noted. After 2 h, the dark red solution was gravity filtered and the filtrate was left to evaporate overnight. Dark brown crystals formed and were washed with Et_2O (20 mL), resulting

in an orange solution and a black-coloured precipitate. The mixture was gravity filtered. The product was isolated as orange-coloured crystalline solid (2.02 g, 85% yield); mp 97–99 °C; R_f = 0.62 (hexanes–EtOAc, 4:1).

IR (KBr): 2953, 1675, 1639, 1609, 1589, 1535, 1450, 1355, 1303, 1057, 1046, 959, 776, 690 cm^{-1}.

^1H NMR: δ = 1.41 (s, 6 H), 4.07 (s, 2 H), 4.21 (s, 2 H), 7.13 (ddd, *J* = 1.2, 7.6, 8.0 Hz, 1 H), 7.47 (dddd, *J* = 0.4, 2.0, 7.6, 8.8 Hz, 1 H,), 7.85 (ddd, *J* = 0.4, 2.0, 8.0 Hz, 1 H), 8.74 (dd, *J* = 1.2, 8.8 Hz, 1 H), 13.05 (s, 1 H).

^{13}C NMR: δ = 28.6, 43.7, 68.2, 78.1, 114.5, 120.0, 123.3, 129.1, 132.4, 139.2, 161.6, 165.9.

Anal. Calcd for $C_{13}H_{15}N_2O_2Cl$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.40; H, 5.55; N, 10.44.

2-Chloro-*N*-{2-[(3a*R*,8a*S*)-3a,8a-dihydro-8*H*-indeno[1,2-*d*]oxazol-2-yl]phenyl}acetamide (2)

A solution of **B** (0.50 g, 2.0 mmol) and Et_3N (0.42 mL, 3.0 mmol) in CH_2Cl_2 (25 mL) in a round-bottomed flask was placed into an ice bath and stirred for 30 min. 2-Chloroacetyl chloride (0.17 mL, 2.2 mmol) was then added dropwise over 5 min to the stirring solution. Upon completion of the addition, the contents of the reaction vessel were stirred for 24 h at r.t. The colour of the solution changed from yellow to dark brown with white precipitate over the course of the reaction. The solution was gravity filtered. Hexanes (10 mL) and then Et_2O (5 mL) were used to precipitate the product out of CH_2Cl_2 solution. The product was isolated as a peachy coloured crystalline solid after filtration (0.56 g, 86% yield); R_f = 0.63 (hexanes–EtOAc, 4:1).

^1H NMR: δ = 1.41 (t, *J* = 7.6 Hz, 1 H), 3.35–3.45 (m, 1 H), 3.50–3.60 (m, 1 H), 4.25 (q, *J* = 14.8 Hz, 2 H), 5.47 (ddd, *J* = 8.4, 7.2, 2.0 Hz, 1 H), 5.86 (d, *J* = 8.0, 1 H), 7.13 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.25–7.35 (m, 2 H), 7.47 (ddd, *J* = 8.8, 7.6, 2.0 Hz, 1 H), 7.51–7.57 (m, 1 H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.72 (dd, *J* = 8.4, 0.8 Hz, 1 H), 12.98 (s, 1 H).

^{13}C NMR: δ = 39.8, 43.7, 76.5, 82.4, 114.2, 120.3, 123.4, 125.6, 125.8, 127.8, 129.0, 129.5, 132.8, 139.0, 139.7, 141.4, 163.8, 165.8.

Anal. Calcd for $C_{18}H_{15}N_2O_2Cl$: C, 66.16; H, 4.63; N, 8.57. Found: C, 65.88; H, 4.60; N, 8.50.

2-(Diethylamino)-*N*-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]acetamide (3b); Typical Procedure

Compound **1** (1.27 g, 4.78 mmol) was added to a stirred solution of K_2CO_3 (1.32 g, 9.55 mmol) and Et_2NH (1.00 mL, 9.55 mmol) in MeCN (30.0 mL) in a round-bottomed flask. The orange-coloured solution was then heated to reflux temperature (~80 °C). The reaction progress was monitored by TLC, and the reflux was stopped after 24 h. The mixture appeared dark brown with light brown precipitate. The mixture was allowed to cool to r.t., and then it was gravity filtered and the solution was left to evaporate to give a compound that appeared brown in colour and waxy in composition. The compound was purified by DCFC and the product was collected as a yellow-coloured oil from fractions 8 to 18 (1.1 g, 69% yield); R_f = 0.59 (hexanes–EtOAc, 4:1).

IR (NaCl): 2971, 1686, 1641, 1581, 1520, 1446, 1283, 1056, 1046, 773, 754 cm^{-1}.

^1H NMR: δ = 1.09 (t, *J* = 7.2 Hz, 6 H), 1.39 (s, 6 H), 2.67 (q, *J* = 7.2 Hz, 4 H), 3.24 (s, 2 H), 4.04 (s, 2 H), 7.06 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 1 H), 7.44 (dddd, *J* = 8.8, 7.2, 1.6, 0.4 Hz, 1 H), 7.85 (ddd, *J* = 8.0, 1.6, 0.4 Hz, 1 H), 8.88 (dd, *J* = 8.8, 1.2 Hz, 1 H), 12.64 (s, 1 H).

^{13}C NMR: δ = 12.1, 28.7, 49.3, 58.2, 68.4, 77.8, 114.3, 120.1, 122.4, 129.3, 132.2, 139.6, 161.1, 172.8.

Anal. Calcd for $C_{17}H_{25}N_3O_2$: C, 67.30; H, 8.31; N, 13.85. Found: C, 67.52; H, 8.20; N, 13.75.

N-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-2-{methyl[2-(pyridin-2-yl)ethyl]amino}acetamide (3c)

The compound was prepared similarly as for **3b** from 2-[2-(methylamino)ethyl]pyridine (0.50 mL, 3.6 mmol), **1** (0.48 g, 1.8 mmol), and K_2CO_3 (0.50 g, 3.6 mmol) in MeCN (10 mL) for 23 h. The compound was purified by DCFC and the product was collected as yellowish coloured powder from fractions 20 to 34 (0.30 g, 45% yield); R_f = 0.12 (hexanes–EtOAc, 3:2).

^1H NMR: δ = 1.38 (s, 6 H), 2.50 (s, 3 H), 2.95–3.10 (m, 4 H), 3.31 (s, 2 H), 4.02 (s, 2 H), 7.04–7.11 (m, 2 H), 7.14 (dt, *J* = 8.0, 0.8 Hz, 1 H), 7.44 (ddd, *J* = 8.8, 7.6, 1.6 Hz, 1 H), 7.54 (td, *J* = 7.6, 2.0 Hz, 1 H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.50 (ddd, *J* = 4.8, 2.0, 0.8 Hz, 1 H), 8.84 (dd, *J* = 8.4, 1.2 Hz, 1 H), 12.65 (s, 1 H).

^{13}C NMR: δ = 28.8, 35.9, 43.6, 58.1, 62.2, 68.3, 77.8, 114.3, 120.1, 121.4, 122.5, 123.3, 129.2, 132.3, 136.5, 139.6, 149.4, 160.0, 161.2, 171.2.

Anal. Calcd for $C_{21}H_{26}N_4O_2$: C, 68.83; H, 7.15; N, 15.29. Found: C, 68.56; H, 7.14; N, 15.23.

2-[Adamantan-1-yl(methyl)amino]-*N*-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]acetamide (3d)

The compound was prepared similarly as for **3b** from *N*-methyladamantane-1-amine (0.17 g, 1.0 mmol), **1** (0.24 g, 0.90 mmol), and K_2CO_3 (0.14 g, 1.0 mmol) in MeCN (20 mL) for 28 h. The compound was recrystallized (CH_2Cl_2 and hexanes) as yellow-coloured hydroscopic wax (0.20 g, 56% yield); R_f = 0.66 (hexanes–EtOAc, 4:1).

^1H NMR: δ = 1.42 (s, 6 H), 1.63 (q, *J* = 12.4 Hz, 6 H), 1.76 (d, *J* = 2.4 Hz, 6 H), 2.07–2.13 (br m, 3 H), 2.36 (s, 3 H), 3.31 (s, 2 H), 4.02, (s, 2 H), 7.06 (ddd, *J* = 8.0, 7.6, 0.8 Hz, 1 H), 7.44 (ddd, *J* = 8.8, 7.6, 1.6 Hz, 1 H), 7.88 (dd, *J* = 7.6, 1.2 Hz, 1 H), 8.86 (dd, *J* = 8.4, 0.8 Hz, 1 H), 12.24 (br s, 1 H).

^{13}C NMR: δ = 28.7, 29.6, 36.2, 36.8, 38.7, 54.4, 56.0, 68.6, 77.8, 114.6, 120.5, 122.5, 129.6, 132.2, 139.6, 161.2, 173.6.

Anal. Calcd for $C_{24}H_{33}N_3O_2{\cdot}0.5H_2O$: C, 71.25; H, 8.47; N, 10.39. Found: C, 71.01; H, 8.49; N, 10.39.

N-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-2-(pyrrolidin-1-yl)acetamide (3e)

The compound was prepared similarly as for **3b** from pyrrolidine (0.58 mL, 7.0 mmol), **1** (1.20 g, 4.50 mmol), and K_2CO_3 (1.24 g, 9.00 mmol) in MeCN (30 mL) for 7 h. The compound was recrystallized (CH_2Cl_2 and hexane) as a beige-coloured solid (0.62 g, 73% yield); mp 106–108 °C; R_f = 0.28 (hexanes–EtOAc, 4:1).

^1H NMR: δ = 1.39 (s, 6 H), 1.82–1.91 (m, 4 H), 2.68–2.76 (m, 4 H), 3.37 (s, 2 H), 4.04 (s, 2 H), 7.07 (ddd, *J* = 8.0, 7.6, 1.2 Hz, 1 H), 7.44 (dddd, *J* = 9.2, 7.2, 1.6, 0.4 Hz, 1 H), 7.84 (ddd, *J* = 8.0, 2.0, 0.4 Hz, 1 H), 8.83 (dd, *J* = 8.4, 0.8 Hz, 1 H), 12.47 (s, 1 H).

^{13}C NMR: δ = 24.5, 28.6, 54.7, 61.6, 68.3, 77.8, 114.3, 120.3, 122.5, 129.2, 132.3, 139.6, 161.3, 171.3.

Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.93; H, 7.66; N, 13.96.

2-[Bis(pyridin-2-ylmethyl)amino]-*N*-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]acetamide (3f)

The compound was prepared similarly as for **3b** from di(2-picolyl)amine (0.20 mL, 1.1 mmol), **1** (0.30 g, 1.1 mmol), and K_2CO_3 (0.31 g, 2.3 mmol) in MeCN (20 mL) for 24 h. The compound was purified by DCFC from fractions 29 to 38, then washed with Et_2O and collected as a white-coloured solid (0.14 g, 30% yield); R_f = 0.05 (hexanes–EtOAc, 1:1).

^{1}H NMR: δ = 1.40 (s, 6 H), 3.49 (s, 2 H), 4.08 (s, 2 H), 4.12 (s, 4 H), 7.10 (ddd, *J* = 8.0, 7.6, 1.2 Hz, 1 H), 7.18 (ddd, *J* = 6.8, 5.2, 2.4 Hz, 2 H), 7.45 (ddd, *J* = 8.8, 7.6, 2.0 Hz, 1 H), 7.61–7.72 (m, 4 H), 7.88 (dd, *J* = 8.0, 2.0 Hz, 1 H), 8.55 (dt, *J* = 6.0, 1.2 Hz, 2 H), 8.76 (dd, *J* = 8.4, 0.8 Hz, 1 H), 12.57 (s, 1 H).

^{13}C NMR: δ = 28.7, 57.9, 60.6, 68.3, 77.7, 114.1, 120.2, 122.2, 122.5, 123.6, 129.2, 132.3, 136.4, 139.4, 149.2, 157.9, 161.6, 170.6.

Anal. Calcd for $C_{25}H_{27}N_5O_2$: C, 69.91; H, 6.34; N, 16.31. Found: C, 69.88; H, 6.26; N, 16.13.

***N*-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-2-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)acetamide (3g)**

The compound was prepared similarly as for **3b** from 1-aza-15-crown-5 (0.22 g, 1.00 mmol), **1** (0.27 g, 1.0 mmol), and K_2CO_3 (0.28 g, 2.0 mmol) in MeCN (25 mL) for 17 h. The compound was dissolved in $CHCl_3$(30 mL) and extracted with H_2O (30 mL), and then brine (10 mL). The organic layer was dried ($MgSO_4$). Collected as yellow-coloured wax (0.30 g, 67% yield); R_f = 0.15 (hexanes–EtOAc, 1:1).

IR (KBr): 3089, 2867, 1683, 1636, 1582, 1520, 1446, 1355, 1284, 1127, 1057, 968, 934, 755 cm^{-1}.

^{1}H NMR: δ = 1.40 (s, 6 H), 3.04 (t, *J* = 6.0 Hz, 4 H), 3.48 (s, 2 H), 3.60–3.68 (m, 12 H), 3.72 (t, *J* = 6.0 Hz, 4 H), 4.03 (s, 2 H), 7.06 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 8.82 (d, *J* = 8.4 Hz, 1 H), 12.52 (br s, 1 H).

^{13}C NMR: δ = 28.7, 54.5, 60.0, 68.2, 69.4, 70.4, 70.5, 70.9, 77.6, 114.1, 120.0, 122.4, 129.2, 132.2, 139.5, 161.2, 171.8.

Anal. Calcd for $C_{23}H_{35}N_3O_6$: C, 61.45; H, 7.85; N, 9.35. Found: C, 61.38; H, 7.82; N, 9.52.

2-[Allyl(methyl)amino]-*N*-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]acetamide (3h)

The compound was prepared similarly as for **3b** from *N*-allyl-*N*-methylamine (0.30 mL, 3.1 mmol), **1** (0.80 g, 3.00 mmol), and K_2CO_3 (0.71 g, 5.1 mmol) in MeCN (30 mL) for 48 h. The compound was purified by DCFC and the product was collected as yellowish coloured oil from fractions 7 to 10 (0.37 g, 41% yield); R_f = 0.53 (hexanes–EtOAc, 4:1).

IR (KBr): 3083, 2971, 1683, 1643, 1582, 1520, 1447, 1354, 1293, 1209, 1056, 1046, 968, 926, 773, 754, 690 cm^{-1}.

^{1}H NMR: δ = 1.39 (s, 6 H), 2.38 (s, 3 H), 3.16 (dt, *J* = 6.8, 1.6 Hz, 2 H), 3.20 (s, 2 H), 4.03 (s, 2 H), 5.16 (ddt, *J* = 10.0, 2.0, 0.8 Hz, 1 H), 5.23 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.95 (ddt, *J* = 16.8, 10.4, 6.8 Hz, 1 H), 7.06 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 1 H), 7.43 (dddd, *J* = 9.2, 7.6, 2.0, 0.4 Hz, 1 H), 7.84 (ddd, *J* = 8.0, 1.6, 0.4 Hz, 1 H), 8.86 (dd, *J* = 8.4, 0.8 Hz, 1 H), 12.71 (s, 1 H).

^{13}C NMR: δ = 28.6, 43.7, 61.1, 61.4, 68.2, 77.7, 114.2, 118.4, 120.0, 122.4, 129.2, 132.2, 135.2, 139.6, 161.2, 171.4.

Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.96; H, 7.67; N, 13.73.

***N*-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-2-[isopropyl(methyl)amino]acetamide (3i)**

The compound was prepared similarly as for **3b** from *N*-isopropyl-*N*-methylamine (1.04 g, 10.0 mmol), **1** (2.67 g, 10.0 mmol), and K_2CO_3 (2.76 g, 20.0 mmol) in MeCN (50 mL) for 24 h. The compound was dissolved in CH_2Cl_2(30 mL) and extracted with H_2O (2 × 30 mL), and then brine (30 mL). The organic layer was dried ($MgSO_4$). The product was collected as orange-coloured oil (2.00 g, 66% yield); R_f = 0.14 (hexanes–EtOAc, 4:1).

^{1}H NMR: δ = 1.07 (d, *J* = 6.8 Hz, 6 H), 1.38 (s, 6 H), 2.35 (s, 3 H), 2.93 (septet, *J* = 6.8 Hz, 1 H), 3.17 (s, 2 H), 4.02 (s, 2 H), 7.05 (t, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 7.6 Hz, 1 H), 8.88 (d, *J* = 8.4 Hz, 1 H), 12.63 (br s, 1 H).

^{13}C NMR: δ = 18.2, 28.5, 40.2, 54.3, 57.1, 68.2, 77.6, 114.3, 120.0, 122.3, 129.2, 132.1, 139.5, 161.0, 172.5.

Anal. Calcd for $C_{17}H_{25}N_3O_2$: C, 67.30; H, 8.31; N, 13.85. Found: C, 67.18; H, 8.28; N, 13.96.

2-(Diallylamino)-*N*-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]acetamide (3j)

The compound was prepared similarly as for **3b** from *N*,*N*-diallylamine (0.43 mL, 3.5 mmol), **1** (0.80 g, 3.0 mmol), and K_2CO_3 (0.83 g, 6.0 mmol) in MeCN (25 mL). The compound was recrystallized (petroleum ether) as a orange-coloured hydroscopic wax (0.72 g, 74% yield); R_f = 0.67 (hexanes–EtOAc, 4:1).

^{1}H NMR: δ = 1.41 (s, 6 H), 3.24 (d, *J* = 6.8 Hz, 4 H), 3.27 (s, 2 H), 4.05 (s, 2 H), 5.15 (d, *J* = 10.4 Hz, 2 H), 5.21 (d, *J* = 17.2 Hz, 2 H), 5.97 (tdd, *J* = 6.8, 10.4, 17.2 Hz, 2 H), 7.07 (t, *J* = 8.0 Hz, 1 H), 7.44 (dt, *J* = 1.6, 8.8 Hz, 1 H), 7.86 (dd, *J* = 1.6, 8.0 Hz, 1 H), 8.86 (d, *J* = 8.8 Hz, 1 H), 12.61 (s, 1 H).

^{13}C NMR: δ = 28.6, 57.6, 58.5, 68.3, 77.6, 114.1, 118.6, 119.9, 122.3, 129.2, 132.2, 134.8, 139.5, 161.2, 171.8.

Anal. Calcd for $C_{19}H_{25}N_3O_2{\cdot}0.25H_2O$: C, 68.75; H, 7.74; N, 12.66. Found: C, 68.46; H, 7.64; N, 12.43.

***N*-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-2-[(2-hydroxyethyl)(methyl)amino]acetamide (3k)**

In a 50-mL three-neck round bottom flask, **4** (0.22, 1.20 mmol) and K_2CO_3 (0.21 g: 1.5 mmol) were dissolved in MeCN (15 mL) under an atmosphere of N_2 gas. The solution was stirred for 15 min. A solution of **1** (0.20 g, 0.75 mmol) in MeCN (10 mL) was then added and the mixture was stirred at reflux temperature (80 °C) for 18 h. After the reflux was complete, the solution was filtered and allowed to evaporate. The product was a light yellow coloured wax (0.20 g, 88% yield). A satisfactory N-elemental analysis could not be obtained, *vide infra*.

^{1}H NMR: δ = 1.40 (s, 6 H), 2.43 (s, 3 H), 2.66 (t, *J* = 4.8 Hz, 2 H), 3.24 (s, 2 H), 3.62 (t, *J* = 4.8 Hz, 2 H), 4.03 (s, 2 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.80 (dd, *J* = 8.0, 1.6 Hz, 1 H), 8.80 (d, *J* = 8.0 Hz, 1 H), 12.22 (br s, 1 H).

^{13}C NMR: δ = 28.5, 44.2, 59.2, 60.8, 62.8, 68.6, 77.9, 114.3, 120.0, 122.8, 129.6, 132.6, 139.1, 162.2, 170.7.

Anal. Calcd for $C_{16}H_{23}N_3O_3$: C, 62.93; H, 7.59; N, 13.76. Found: C, 62.56; H, 7.23; N, 12.06.[15]

1-Benzyl-1*H*-imidazole

K_2CO_3 (3.99 g, 28.8 mmol) and imidazole hydrochloride (1.00 g, 9.60 mmol) were dissolved in MeCN (30 mL) in a round-bottomed flask. Benzyl bromide (1.25 mL, 10.6 mmol) was added dropwise to the stirred solution at r.t. After 70 h, the solution was concentrated and

the materials re-dissolved in CH_2Cl_2 (i.e., CH_2Cl_2) and then extracted with H_2O (3 × 30 mL). The organic layer was then dried ($MgSO_4$). The product was collected as off-white coloured wax (0.63 g, 42% yield).

^{1}H NMR spectrum is consistent with that previously reported.[23]

1-Benzyl-3-(2-{[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]amino}-2-oxoethyl)-1*H*-imidazol-3-ium Chloride (3l)

A solution of **1** (0.40 g, 1.5 mmol) and 1-benzyl-1*H*-imidazole (*vide supra*) (0.19 g, 1.2 mmol) in THF/MeCN (15/3 mL) was heated to reflux temperature in a round-bottomed flask for 24 h. The solution was concentrated and then washed with Et_2O (10 mL total). The product was then collected as a yellow-coloured hydroscopic wax (0.29 g, 57% yield); R_f = 0.61 (hexanes–EtOAc, 4:1).

^{1}H NMR: δ = 1.43 (s, 6 H), 4.08 (s, 2 H), 5.50 (s, 2 H), 5.54 (s, 2 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.21 (br s, 1 H), 7.33–7.45 (m, 6 H), 7.47 (br s, 1 H), 7.84 (d, *J* = 7.6 Hz, 1 H), 8.44 (d, *J* = 8.4 Hz, 1 H), 10.71 (br s, 1 H), 12.96 (br s, 1 H).

^{13}C NMR: δ = 28.6, 52.3, 53.7, 68.2, 78.1, 114.0, 119.9, 120.8, 123.5, 123.6, 129.0, 129.2, 129.5, 129.6, 132.5, 132.6, 138.5, 139.1, 162.0, 162.6.

Anal. Calcd for $C_{23}H_{25}ClN_4O_2{\cdot}0.5H_2O$: C, 59.93; H, 6.34; N, 12.15. Found: C, 59.86; H, 6.27; N, 11.03.

***N*-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-2-(diphenylphosphoryl)acetamide (3m•oxide)**

Compound **1** (0.80 g, 3.0 mmol) was dissolved in dry THF (15 mL) in a round-bottomed flask and placed into an ice bath at –84 °C (EtOAc/liquid N_2). A 5.0 M $KPPh_2$ in THF solution (6.00 mL, 3.00 mmol) was added dropwise to the stirred solution. The solution was stirred for 24 h under N_2 at r.t., and then it was cannula transferred and the precipitate was discarded. The compound was recrystallized (in air, CH_2Cl_2/Et_2O) as a yellow-coloured waxy solid in the form of the phosphine oxide (0.69 g, 55% yield); R_f = (hexanes–EtOAc, 4:1).

^{1}H NMR: δ = 1.38 (s, 6 H), 3.56 (d, *J* = 15.6 Hz, 2 H), 4.03 (s, 2 H), 7.03 (td, *J* = 8.0, 1.2 Hz, 1 H), 7.34 (ddd, *J* = 8.8, 8.0, 1.6 Hz, 1 H), 7.40–7.53 (m, 6 H), 7.76 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.82–7.90 (m, 4 H), 8.45 (d, *J* = 8.4 Hz, 1 H), 12.43 (s, 1 H).

^{13}C NMR: δ = 28.7, 43.06 [d, $J(^{13}C\text{-}^{31}P)$ = 61.0 Hz], 68.0, 77.9, 113.7, 119.8, 122.8, 128.6, 128.7, 128.9, 131.3, 131.4, 131.5, 132.2 [d, $J(^{13}C\text{-}^{31}P)$ = 3.0 Hz], 132.3, 132.4, 139.3, 161.8, 162.7 [d, $J(^{13}C\text{-}^{31}P)$ = 5.0 Hz].

^{31}P NMR: δ = +28.5.

Anal. Calcd for $C_{25}H_{25}N_2O_3P{\cdot}2H_2O$: C, 64.09; H, 6.24; N, 5.98. Found: C, 64.70; H, 5.92; N, 5.75.

***N*-Methyl-2-(trimethylsiloxy)ethan-1-aminium Chloride (4)**[24]

To dry Et_2O (~30.0 mL) in a round-bottomed flask attached to a reflux condenser was added 2-(methylamino)ethanol (1.07 mL, 13.3 mmol) and the mixture was stirred for 5 min under an atmosphere of N_2. TMSCl (3.34 mL, 26.7 mmol) was then added dropwise to the flask. The mixture was then refluxed for 3 h. After reflux, volatiles were removed in vacuo yielding a white-coloured fluffy solid (1.98 g, 81% yield). Spectroscopic data are consistent with known values.[24]

^{1}H NMR: δ = 0.14 (s, 9 H), 2.74 (t, *J* = 5.2 Hz, 3 H), 3.08 (t, *J* = 5.2 Hz, 2 H), 3.93 (t, *J* = 5.2 Hz, 2 H), 9.43 (br s, 2 H).

^{13}C NMR: δ = –0.5, 33.3, 50.6, 57.7.

Pd(κ^3-*N*,*N*′,*N*″-L)Cl (Complex 5; LH = 3b)

A solution of **3b** (0.24 g, 0.79 mmol) in MeOH (5.0 mL) was cooled on an ice bath for 5 min. Subsequently, 0.079 M Li_2PdCl_4 in MeOH solution (10.0 mL, 0.79 mmol) was added dropwise over a period of a few minutes. The orange-coloured solution was then stirred at r.t. for 24 h. The solvent was removed in vacuo and the orange-coloured material thus obtained was re-dissolved in CH_2Cl_2 (5.0 mL) and then filtered through Celite. The product was then isolated as an orange-coloured hydroscopic solid following solvent evaporation; yield: 0.18 g (52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 6.96 (t, *J* = 7.6 Hz, 1 H), 4.21 (s, 2 H), 3.61 (s, 2 H), 3.23 (dq, *J* = 13.6, 6.8 Hz, 2 H), 2.43 (dq, *J* = 13.6, 6.8 Hz, 2 H), 1.73 (s, 6 H), 1.65 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 162.4, 144.7, 132.9, 129.4, 123.2, 121.6, 116.4, 81.6, 70.6, 63.6, 56.6, 27.9, 12.4.

Anal. Calcd for $C_{17}H_{24}ClN_3O_2Pd{\cdot}0.5H_2O$: C, 43.33; H, 5.77; N, 8.92. Found: C, 43.57; H, 5.47; N, 8.52.

Catalysis: Allylation of Aldehydes

Each respective aldehyde (0.15 mmol) and a 9.0 × 10^{-3} M THF solution of **5** (0.007 mmol, 5 mol%) were dissolved in THF (1.0 mL). Allyltributyltin (56 µL, 0.18 mmol) was added to the stirred solution at r.t. The reaction was thereafter stirred at 60 °C for 24 h. The solvent was removed in vacuo and the residual material was analysed by ^{1}H NMR spectroscopy.

X-ray Diffraction Studies

The single crystal X-ray diffraction study of compound **1** was carried out as described previously.[25] The diffraction study of compound **3m**·oxide was likewise carried out as reported[26] with the exception that CuKα radiation was used as the X-ray source. Raw diffraction data of compound **2** was supplied by the X-ray Crystallography Facility of the University of Zürich as part of the 2013 Zürich School of Crystallography. Further details, including checkcif files, can be found in the Supporting Information.

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Supporting Information

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(13) The use of the corresponding dibromo derivative, i.e., 2-bromoacetyl bromide, should be avoided as this leads to an inherently unstable bromo analogue of **1**.

(14) It should be noted that weakly nucleophilic secondary amines such as pyrrole and carbazole do not lead to the desired ligand product analogues. The reaction was also ineffective, leading to a number of unidentified materials, when i-Pr_2NH, Cy_2NH, or N-methylamino-substituted phenols were used as reactants. The use of O-benzyl protected 2-(methylamino)phenol likewise led to a number of undesired byproducts; hence, all of these above reagents were thereafter abandoned for this study.

(15) Despite repeated attempts, compound **3k** gave an unsatisfactory %N analysis, see experimental procedures.

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