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Rational and Predictable Chemoselective Synthesis of Oligoamines via Buchwald–Hartwig Amination of (Hetero)Aryl Chlorides Employing Mor-DalPhos

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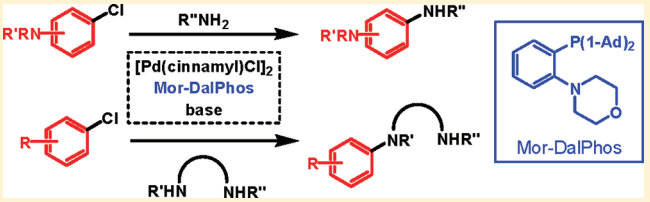
Supporting Information

ABSTRACT: We report a diverse demonstration of synthetically useful chemoselectivity in the synthesis of di-, tri-, and tetraamines (62 examples) by use of Buchwald–Hartwig amination employing a single catalyst system ([Pd(cinnamyl)Cl]$_2$/**L1**; **L1** = *N*-(2-(di(1-adamantyl)phosphino)phenyl)morpholine, Mor-DalPhos). Competition reactions established the following relative preference of this catalyst system for amine coupling partners: linear primary alkylamines and imines > unhindered electron-rich primary anilines, primary hydrazones, *N*,*N*-dialkylhydrazines, and cyclic primary alkylamines > unhindered electron-deficient primary anilines, α-branched acyclic primary alkylamines, hindered electron-rich primary anilines ≫ cyclic and acyclic secondary dialkylamines, secondary alkyl/aryl and diarylamines, α,α-branched primary alkylamines, and primary amides. The new isomeric ligand *N*-(4-(di(1-adamantyl)phosphino)phenyl)morpholine (*p*-Mor-DalPhos, **L2**) was prepared in 63% yield and was crystallographically characterized; the [Pd(cinnamyl)Cl]$_2$/**L2** catalyst system exhibited divergent reactivity. Application of the reactivity trends established for [Pd(cinnamyl)Cl]$_2$/**L1** toward the chemoselective synthesis of di-, tri-, and tetraamines was achieved. Preferential arylation was observed at the primary alkylamine position within 2-(4-aminophenyl)ethylamine with [Pd(cinnamyl)Cl]$_2$/**L1** and 4-chlorotoluene (affording **5a**); the alternative regioisomer (**5a′**) was obtained when using [Pd(cinnamyl)Cl]$_2$/**L2**. These observations are in keeping with coordination chemistry studies, whereby binding of 2-(4-aminophenyl)ethylamine to the in situ generated [(**L1**)Pd(*p*-tolyl)]$^+$ fragment occurred via the primary amine moiety, affording the crystallographically characterized adduct [(**L1**)Pd(*p*-tolyl)(NH$_2$CH$_2$CH$_2$(4-C$_6$H$_4$NH$_2$)]$^+$OTf$^-$ (**7**) in 72% yield.



INTRODUCTION

The palladium-catalyzed cross-coupling of (hetero)aryl (pseudo)halides and N–H containing substrates (i.e., Buchwald–Hartwig amination) has emerged as an effective methodology for the construction of (hetero)arylamines that is employed broadly in both academic and industrial settings.[1] Following the establishment of such cross-coupling protocols independently by Buchwald[2] and Hartwig[3] in 1995, significant research effort has been directed toward evaluating how modifying various reaction parameters,[4] including the choice of solvent, base, palladium precursor, and most notably the ancillary coligand, influences the outcome of the cross-coupling reaction. Consequently, several highly effective classes of catalysts for Buchwald–Hartwig amination have emerged that offer broad substrate scope and excellent functional group tolerance at relatively low catalyst loadings, including for the cross-coupling of less expensive and more abundant, but less reactive, (hetero)aryl chloride substrates.[1,5] Despite such progress, a number of significant challenges remain in Buchwald–Hartwig amination chemistry, including the establishment of catalysts for which predictably high yield and chemoselectivity has been achieved across a range of structurally diverse substrates featuring two or more competitive and chemically distinct N–H reactive functional groups.[6] The development of such chemoselective processes would further enhance the utility of Buchwald–Hartwig amination as a synthetic tool in the construction of structurally complex oligoamine targets, such as those commonly encountered in the synthesis of pharmaceuticals, natural products, and other nitrogenous materials, by offering more streamlined chemical pathways that circumvent the need for wasteful nitrogen protection/deprotection steps.

Despite the significant attention that has been given to the application of Buchwald–Hartwig amination protocols in organic synthesis and the resulting proliferation of task-specific ligands for targeted substrate classes,[1b,c] reports documenting chemoselective variants of Buchwald–Hartwig aminations involving the preferential arylation of one amine fragment in the presence of multiple chemically distinct competitor amine functionalities are relatively few.[7−15] Moreover, a number of important limitations exist with regard to many of the

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chemoselective Buchwald–Hartwig synthetic protocols that have been reported thus far in the literature, including: limited demonstrated substrate scope for a given Pd/L catalyst system; the use of substrates where the statistical bias of amine functional groups can be viewed as contributing directly to the observed product ratio; low (<50%) isolated yields of isomeric monoarylation and diarylation product mixtures; and/or the incompatibility of inexpensive and abundant (hetero)aryl chloride substrates.

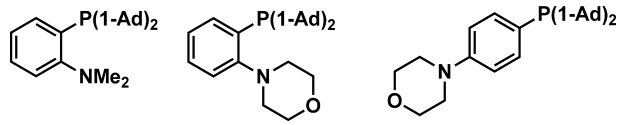
To date, the most extensive investigations of chemoselective amine arylation have been published by the Buchwald group, using five variants of their biarylphosphine ligands (Cy-XPhos, *t*Bu-XPhos, SPhos, BrettPhos, and RuPhos).[11−14] In 2003, Buchwald and co-workers demonstrated that Pd/XPhos precatalyst mixtures and substituted aryl bromides could be employed for the chemoselective arylation of primary aniline fragments within diamines containing primary amide, indole, and primary alkylamino competitor functionalities, affording monoarylated products in synthetically useful yields (5 examples, 2 mol % Pd and 5 mol % Cy-XPhos, 74%–96%, 5:1–25:1 selectivity).[11a] In a further demonstration of chemoselectivity, secondary amides derived from (pseudo)-haloanilines (X = Cl, Br, OTs), halo(hetero)aryl primary amides, 3-bromoaniline, and halogenated heterocycles featuring competitor N–H functionalities were aminated by using nitrogen coupling partners that included anilines, primary alkyl amines, linear and cyclic secondary alkylamines, as well as amino-functionalized heterocyclic substrates (20 examples, 2–5 mol % Pd and 4–10 mol % Cy-XPhos or *t*Bu-XPhos depending on the substrate, 57%–99%).[11] These results establish the following qualitative chemoselectivity hierarchy for Pd/XPhos-catalyzed amination: anilines ≫ primary and secondary (di)alkylamines >2-aminoheteroaromatics > primary amides ≈ NH-heterocycles.[11]

In a subsequent report employing competition experiments between pairs of monoamine substrates, Buchwald and co-workers[12] examined the origins of chemoselectivity in Pd/SPhos-catalyzed amine arylations by evaluating the competitive role of amine binding and acidity in intermediates of the type (SPhos)Pd(Ph)Cl(amine). Among isosteric aliphatic amines, amine acidity rather than the relative binding affinity was found to be the dominant factor in determining chemoselectivity; these observations suggest that such aminations occur under Curtin–Hammett control, whereby product formation arising from the more acidic yet less favorably bound amine competitor substrate is observed. Conversely, binding affinity was found to be the primary determinant in the arylation of isosteric anilines, and such processes appear not to be under Curtin–Hammett control. These observations indicate that the origin of chemoselectivity in amine arylations employing Pd/SPhos-based catalysts cannot be rationalized on the basis of steric effects alone. Indeed, these competition studies establish the following heirarchical reactivity preference for the Pd/SPhos system for the amination of chlorobenzene: anilines ≫ cyclic secondary dialkylamines > small primary alkylamines > acyclic secondary dialkylamines > sterically demanding primary alkylamines. Unfortunately, the application of these competitive reactivity trends toward the rational, chemoselective arylation of oligoamines has yet to be reported. In 2008, a report by Buchwald and co-workers[13] focusing on the application of Pd/BrettPhos precatalysts contained two examples in which amine arylation employing chlorobenzene occurred preferentially at the primary alkylamine fragment within diamine substrates featuring either a secondary arylalkylamine or cyclic secondary dialkylamine competitor fragment, and a third example whereby a primary aniline group was selectively arylated in the presence of a diarylamine functionality (3 examples, 1 mol % Pd and 2 mol % BrettPhos, 84%–92%). Most recently, Buchwald and co-workers[14] demonstrated the utility of Pd/BrettPhos and Pd/RuPhos precatalysts in enabling the arylation of primary and secondary amine coupling partners, respectively, employing halogenated (X = Cl, Br) NH-heterocycles.[15]

Notwithstanding the collective insights derived from the reports published thus far involving the use of monodentate and bidentate ligand frameworks of varying efficacy,[7−15] the establishment of predictive and complementary chemoselective models, each based on a single Pd/L catalyst system, and the demonstrated application of such reactivity models with synthetically useful scope, remains an important goal in the quest to expand the utility and implementation of Buchwald–Hartwig amination chemistry.

In this context, we recently initiated a research program that exploits phenylene P,N-ligands as useful alternatives to more commonly employed phosphine and bis(phosphine) ancillary ligands in metal-catalyzed C–N and C–C bond-forming reactions.[16] Building on our initial discovery that Me-DalPhos (Chart 1) is a broadly useful ligand for the Buchwald–Hartwig

Chart 1



Me-DalPhos Mor-DalPhos (**L1**) *p*-Mor-DalPhos (**L2**)

amination of aryl chlorides,[16a] we have subsequently demonstrated that Mor-DalPhos (**L1**) offers excellent performance in the Pd-catalyzed monoarylation of ammonia,[16b] hydrazine,[16c] and acetone.[16e] Given the remarkable preference exhibited by the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system for the selective monoarylation of ammonia or hydrazine when employing aryl chloride substrates bearing competitor primary amine (aryl and alkyl) or secondary amine (cyclic and acyclic dialkyl, alkyl/aryl, and diaryl) functionalities,[16b,c] we turned our attention to exploring more broadly the utility of **L1** in the chemoselective synthesis of oligoamines employing Buchwald–Hartwig amination protocols. We report herein on the results of these studies, including the development of a predictive chemoselectivity model for the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system, and the broad application of this reactivity model in the chemoselective synthesis of a structurally diverse series of di-, tri-, and tetraamine target compounds.

RESULTS AND DISCUSSION

Competition Experiments. In an effort to establish a qualitative reactivity hierarchy for the $[Pd(cinnamyl)Cl]_2$/**L1** catalyzed amine arylation under standard conditions that could be applied rationally to the chemoselective synthesis of oligoamines, competition experiments employing 4-chlorotoluene and various pairings of monoamine substrates were conducted.[17] So as to place these results in context and to gain an appreciation of the importance of *ortho*-disposed phosphorus and nitrogen donors in **L1** on the observed chemoselectivity, parallel competition experiments were conducted

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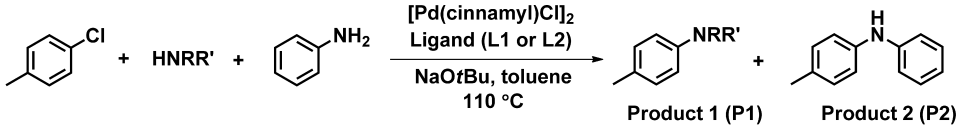
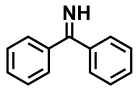
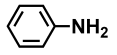
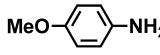
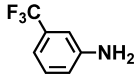
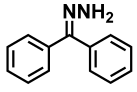
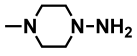
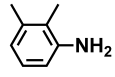
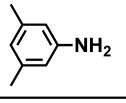
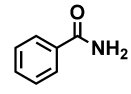
Table 1. Amine Arylation Competition Studies Employing Mor-DalPhos (L1) and *p*-Mor-DalPhos (L2)[a]



Entry	HNRR'	P1 : P2 L1	P1 : P2 L2	Entry	HNRR'	P1 : P2 L1	P1 : P2 L2	Entry	HNRR'	P1 : P2 L1	P1 : P2 L2
1	octylamine	5.1:1	1:12	7	$CyNH_2$	1.4:1	1:20	13		<1:50	1:8.0
2		4.7:1	1:9.3	8		-	-	14		<1:50	<1:50
3[b]		2.1:1	1.6:1	9[b]		1:1.6	1.4:1	15	$tBuNH_2$	<1:50	<1:50
4		2.0:1	1:1.1	10		1:1.9	1:43	16	$(hex)_2NH$	<1:50	<1:50
5[c]		1.7:1	1:5.0	11		1:3.1	1:2.4	17	Ph_2NH	<1:50	<1:50
6		1.4:1	1.2:1	12		1:22	1:12	18[c,d]		<1:50	<1:50

[a]Conditions: 0.25 mol % Pd, ArCl/amine/aniline/NaOtBu = 1:1.2:1.2:1.4, Pd/L = 1:2, [ArCl] = 0.5 M, 12−48 h (reaction times not optimized). All reactions >99% conversion based on consumption of ArCl determined by use of GC analysis. Product ratios determined by use of GC analysis. Selected data (*entry*, pK_a(ammonium) in water): *1*, 10.65; *3*, 5.29; *6*, 4.74; *7*, 10.64; *8*, 4.58; *9*, 3.49; *10*, 10.56; *11*, 4.70; *12*, 11.22; *13*, 8.36; *15*, 10.55. [b]0.5 mol % Pd. [c]1 mol % Pd. [d]2.4 equiv of NaOtBu used.

with the isomeric ligand *p*-Mor-DalPhos (**L2**; Chart 1). The new ligand **L2** was prepared in 63% isolated yield via the Pd-catalyzed cross-coupling of di(1-adamantyl)phosphine with 4-(4-bromophenyl)morpholine and was structurally characterized, including by use of single-crystal X-ray diffraction techniques (Figure S1 and Table S1[18]).

The results of the competition experiments employing $[Pd(cinnamyl)Cl]_2$/L (L = **L1** or **L2**) precatalyst mixtures in combination with limiting 4-chlorotoluene, aniline (as the reference competitor), and a diverse series of competitor amine substrates spanning a wide range of steric and electronic characteristics (including pK_a) are collected in Table 1. On the basis of these competition data, the following qualitative chemoselectivity hierarchy emerges for the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system employing 4-chlorotoluene: linear primary alkylamines and imines > unhindered electron-rich primary anilines, primary hydrazones, *N,N*-dialkylhydrazines, and cyclic primary alkylamines > unhindered electron-deficient primary anilines, α-branched acyclic primary alkylamines, hindered electron-rich primary anilines ≫ cyclic and acyclic secondary dialkylamines, secondary alkyl/aryl and diarylamines, α,α-branched primary alkylamines, and primary amides.[19] This chemoselectivity trend is divergent from that of the $[Pd(cinnamyl)Cl]_2$/**L2** catalyst system (i.e., primary anilines > linear primary alkylamines, imines, cyclic secondary dialkylamines, and *N,N*-dialkylhydrazines ≫ branched primary alkylamines, secondary acyclic dialkyl, alkyl/aryl and diarylamines, and primary amides), as well as previously reported catalysts employing XPhos or SPhos (vide supra).[11,12] This trend establishes amine sterics as being the primary determining factor with regard to uptake by the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system, with small nucleophilic amines being preferred substrates; these observations are entirely consistent with the demonstrated propensity of $[Pd(cinnamyl)Cl]_2$/**L1** to promote the monoarylation of both ammonia and hydrazine[16b,c] and confirms the need for *ortho*-disposed pnictogen donors (as in **L1**) in order to achieve such selectivity.

In considering the traditionally accepted Buchwald−Hartwig amination mechanism involving aryl halide oxidative addition, amine binding, deprotonation, and C−N reductive elimination, chemoselectivity can be envisioned to arise from the amine binding and/or deprotonation steps of the catalytic cycle.[20,21] The striking difference in competitiveness observed for unhindered and hindered primary amine substrates featuring closely matched pK_a(ammonium) values (e.g., entries 1, 7, 10, and 15) and the observation that within a series of isostructural anilines (e.g., entries 3, 6, 8, and 9) the substrate featuring the largest pK_a(ammonium) value proved to be the most competitive suggest that the chemoselectivity exhibited by the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system can likely be attributed to the amine binding step (rather than deprotonation) of the catalytic cycle. This concept is further supported by the observation that while the conjugate acid of piperidine and morpholine differ in acidity by 3 orders of magnitude, both perform rather poorly when in competition with aniline, with the difference in chemoselectivity observed for piperidine (entry 12) and morpholine (entry 13) being relatively small in comparison to the other competition results. We view the unique chemoselectivity exhibited by $[Pd(cinnamyl)Cl]_2$/**L1** (versus XPhos, SPhos, and **L2**) as being attributable to the chelating ability of **L1**.

Application of Chemoselectivity Model to the Synthesis of Di-, Tri-, and Tetraamines. Having established a qualitative chemoselectivity model for the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system, we sought to rationally apply such reactivity trends toward the chemoselective synthesis of di-, tri-, and

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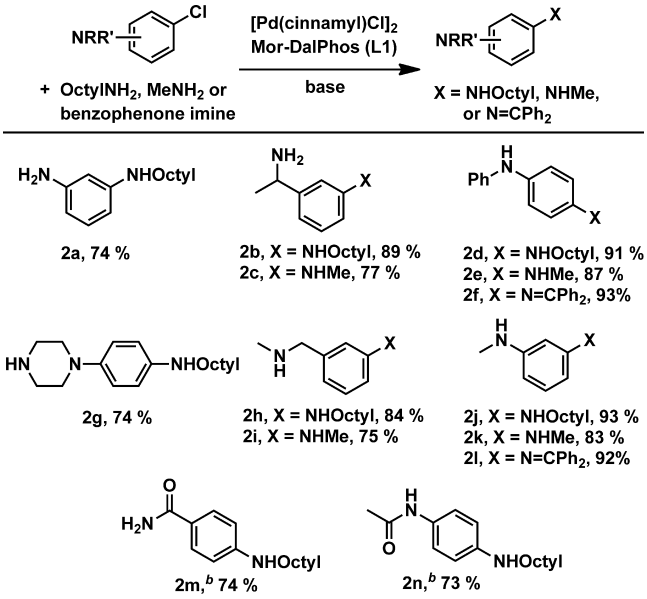
tetraamines by use of two complementary synthetic strategies: the amination of aminoaryl chloride substrates (Tables 2–4) and the arylation of diamines (Table 5). Achieving high levels of chemoselectivity when employing the former synthetic strategy requires that the external amine coupling partner react preferentially relative to the competitor amine fragment that is bound to the aryl chloride substrate, while the latter requires the preferential arylation of one amine fragment in the presence of a chemically distinct competitor amine functionality. In both cases, diarylation represents an unwanted side-reaction that can be challenging to circumvent.[10]

Having established linear primary alkylamines and imines as the substrates of choice when using the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system, the chemoselective cross-coupling of octylamine, methylamine, or benzophenone imine with aminoaryl chlorides was examined (Table 2); the successful utilization of

Table 2. Chemoselective Amination of Aminoaryl Chlorides Employing Octylamine, Methylamine, or Benzophenone Imine[a]

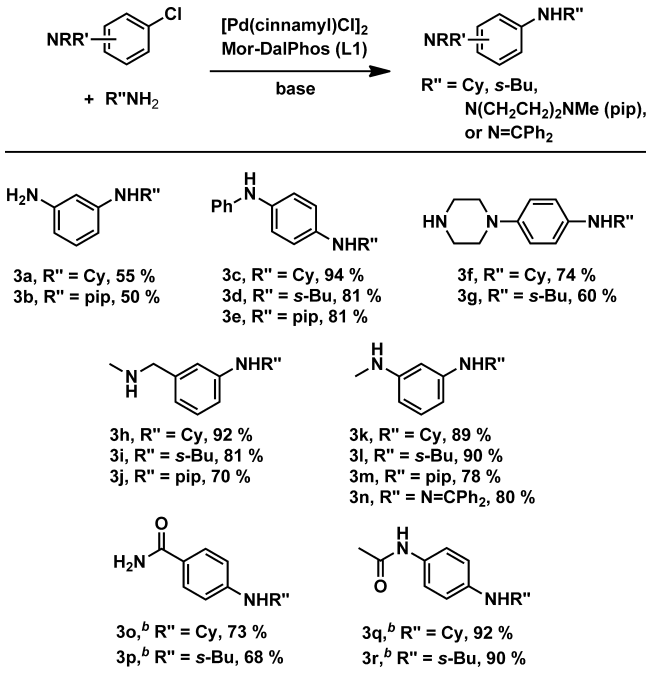


[a]Octylamine and benzophenone imine reactions: ArCl/amine/NaOtBu = 1:1.1:1.4, 1 mol % Pd, Pd/**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. Methylamine reactions: ArCl/amine/NaOtBu = 1:4:1.4, 2 mol % Pd, Pd/**L1** = 1:2, THF/toluene (1:1, resulting from use of commercial 2.0 M stock solutions of methylamine in THF), 85 °C, [ArCl] = 0.25 M. [b]ArCl/amine/LiHMDS = 1:1.1:1.2, 8 mol % NaOtBu (for use in catalyst activation), 2 mol % Pd, Pd/**L1** = 1:2, 1,4-dioxane, 65 °C. All reactions on 0.5 mmol scale with reaction times of 12–48 h (unoptimized); yields are of isolated material.

methylamine in this chemistry is noteworthy, given the challenges associated with the efficient monoarylation of this small nucleophilic amine in Buchwald–Hartwig amination chemistry.[13,16a,22] In keeping with the reactivity heirarchy outlined in Table 1, octylamine, methylamine, or benzophenone imine could be employed in the amination of a diversity of aryl chloride substrates bearing competitor α-branched primary alkylamine, primary arylamine, or secondary amine (cyclic and acyclic dialkyl, alkyl/aryl, and diaryl) functionalities, providing the target di- or triamines in high isolated yield (74–93%). Furthermore, the appropriate selection of base enabled the chemoselective amination of aryl chlorides featuring primary and secondary amides, thereby confirming the tolerance of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system to such functional groups.

The relative success of 1-amino-4-methylpiperazine and benzophenone hydrazone, as well as the α-branched primary amines cyclohexylamine and *sec*-butylamine, in our preliminary competition experiments (Table 1) was reflected in the chemoselective amination of aminoaryl chloride substrates employing the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system (Table

Table 3. Chemoselective Amination of Aminoaryl Chlorides Employing α-Branched Primary Alkylamines, 1-Amino-4-methylpiperazine, or Benzophenone Hydrazone[a]



[a]Conditions: ArCl/amine/NaOtBu = 1:1.1:1.4, 1 mol % Pd, Pd/**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. [b]ArCl/amine/LiHMDS = 1:1.1:1.2, 8 mol % NaOtBu (for use in catalyst activation), 2 mol % Pd, Pd/**L1** = 1:2, 1,4-dioxane, 65 °C. All reactions on 0.5 mmol scale with reaction times of 12–48 h (unoptimized); yields are of isolated material.

3). Whereas cross-coupling reactions employing octylamine in combination with 3-chloroaniline afforded the desired octylamine-derived product (**2a**) in 74% isolated yield (vide supra), diminished levels of chemoselectivity were achieved when either cyclohexylamine or 1-amino-4-methylpiperazine was employed as a coupling partner under analogous conditions (**3a**, 55%; **3b**, 50%). These results are in keeping with the chemoselectivity ranking established for the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system (Table 1), whereby primary anilines proved to be competitive with 1-amino-4-methylpiperazine and the aforementioned α-branched primary amines but inferior to the linear primary alkylamine octylamine. Also consistent with the chemoselectivity trends noted for [Pd(cinnamyl)Cl]$_2$/**L1** is the observation that generally high isolated yields of the target di-, tri-, and tetraamines (60–94%) were achieved when 1-amino-4-methylpiperazine, benzophenone hydrazone, cyclohexylamine, or *sec*-butylamine was used in combination with aryl chloride substrates featuring various secondary amine (cyclic and acyclic dialkyl, alkyl/aryl, and diaryl) competitor moieties. Under appropriate conditions, cyclohexylamine and

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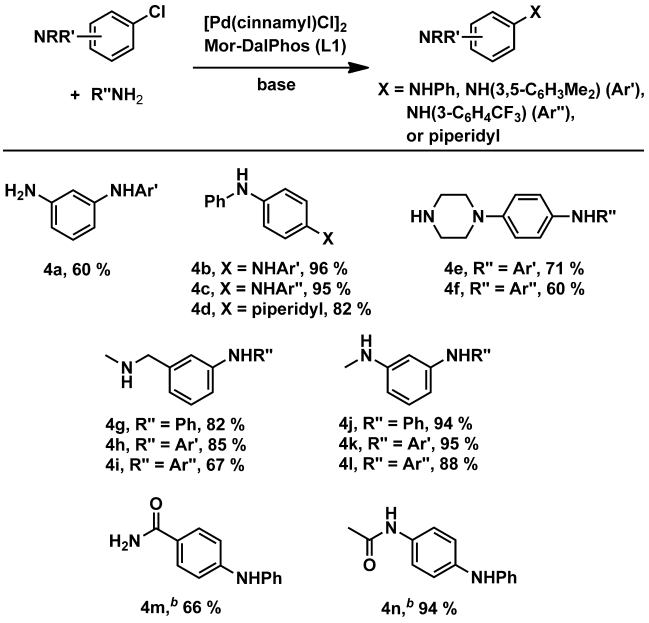
sec-butylamine each proved to be a suitable reaction partner for the chemoselective synthesis of phenylene-bridged diamines featuring an α-branched primary amine and either a primary or secondary amide (**3o**−**3r**, 68−92%).

To complete our investigation of the chemoselective amination of aminoaryl chloride substrates employing the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system, we turned our attention to the use of primary aniline substrates (Table 4). In keeping with the view that the chemoselectivity exhibited by the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system is associated with the amine binding step of the catalytic cycle, 3,5-dimethylaniline proved to be a modestly more favorable amine coupling partner relative to the amino fragment in the relatively electron-poor 3-chloroaniline, resulting in 60% isolated yield of the 3,5-dimethylaniline-derived species **4a**. In expanding this reactivity survey to include electron-rich, electron-neutral, and electron-poor anilines in combination with alternative aminoaryl chloride substrates featuring a diversity of appended secondary amine or primary/secondary amide functional groups, good-to-excellent isolated yields (60−96%) of the corresponding primary aniline-derived cross-coupling products were obtained, as predicted for the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system on the basis of the reactivity trends delineated in the competition studies (Table 1). Also in keeping with the reactivity hierarchy featured in Table 1 is the observation that whereas preferential uptake of piperidine leading to **4d** occurred in amination reactions employing *N*-(4-chlorophenyl)aniline, the use of *tert*-butylamine or dihexylamine under similar conditions failed to generate appreciable quantities of the desired cross-coupling product.

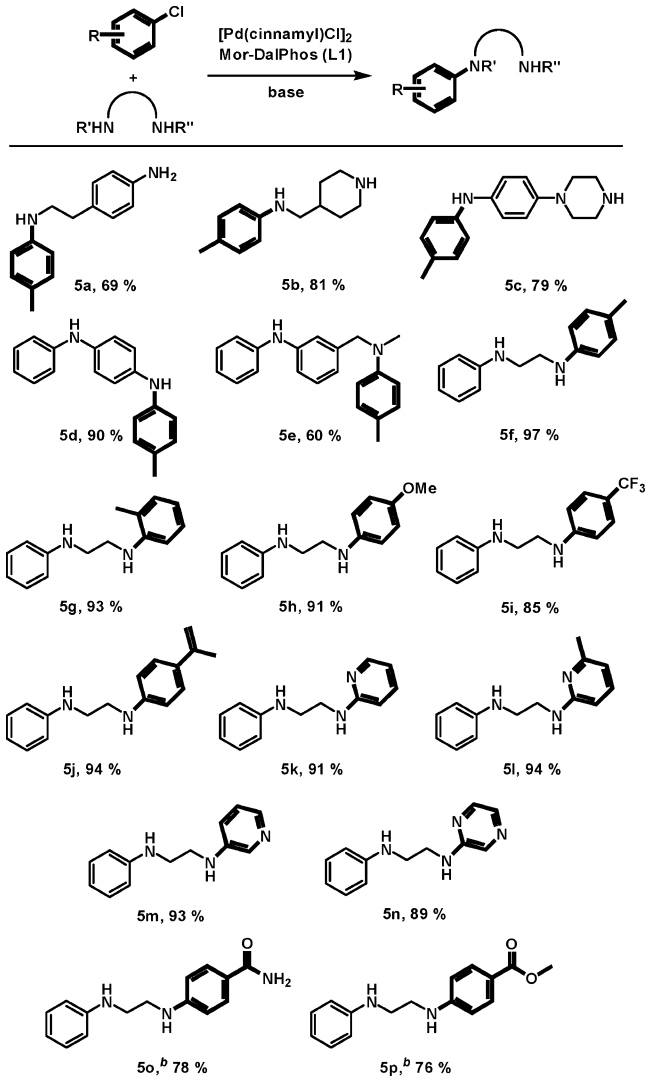
Table 4. Chemoselective Amination of Aminoaryl Chlorides Employing Anilines or Piperidine[a]



[a]Conditions: ArCl/amine/NaOtBu = 1:1.1:1.4, 1 mol % Pd, Pd/**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. [b]ArCl/amine/LiHMDS = 1:1.1:1.2, 8 mol % NaOtBu (for use in catalyst activation), 2 mol % Pd, Pd/**L1** = 1:2, 1,4-dioxane, 65 °C. All reactions on 0.5 mmol scale with reaction times of 12−48 h (unoptimized); yields are of isolated material.

As outlined previously, the high-yielding and chemoselective arylation of substrates featuring two or more chemically distinct and potentially competitive N−H functional groups is not well-documented; the substrate scope featured in such reports is often limited to a very small collection of diamine reactants, with the use of readily available (hetero)aryl chlorides receiving scant attention. Gratifyingly, **L1** can be successfully applied in such Pd-catalyzed synthetic applications with good substrate scope (Table 5). In keeping with the preference of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system for the monoarylation of primary alkylamine fragments even when using unhindered aryl chloride substrates, the preferential amination of 4-chlorotoluene occurred at the primary alkylamine locale within substrates featuring potentially competitive primary aniline, cyclic dialkylamine, and acyclic secondary alkyl/arylamines, thereby affording **5a** (69%), **5b** (81%), and **5f** (97%)

Table 5. Chemoselective Arylation of Diamines with (Hetero)aryl Chlorides[a]



[a]Conditions: ArCl/amine/NaOtBu = 1:1.1:1.4, 1 mol % Pd, Pd/**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. [b]ArCl/amine/LiHMDS = 1:1.1:1.2, 8 mol % NaOtBu (for use in catalyst activation), 5 mol % Pd at 65 °C (**5o**) or 2 mol % Pd at 110 °C (**5p**), Pd/**L1** = 1:2, 1,4-dioxane (**5o**) or toluene (**5p**). All reactions on 0.5 mmol scale with reaction times of 12−48 h (unoptimized); yields are of isolated material.

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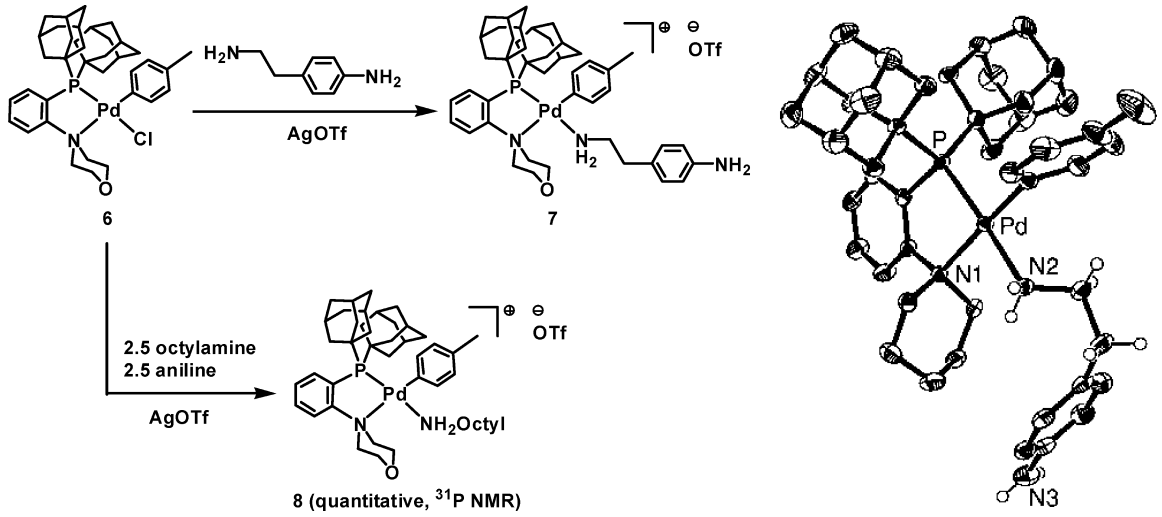
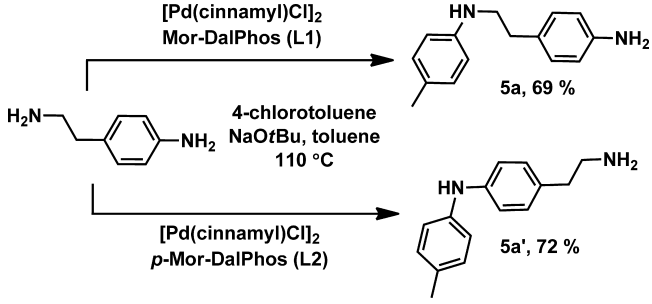


Figure 1. Competitive binding of primary alkylamines to the [(Mor-DalPhos)Pd(*p*-tolyl)]$^+$ fragment affording **7** and **8**. The crystallographically determined structure of **7**·CH_2Cl_2 shown with 50% ellipsoids; selected hydrogen atoms, the dichloromethane solvate, and the triflate counteranion have been omitted for clarity. Selected interatomic distances (Å): Pd–P, 2.2625(5); Pd–N1, 2.2265(15); Pd-Caryl, 2.0068(19); Pd–N2, 2.1629(15).

respectively. Under analogous conditions, and consistent with the reactivity trends delineated in Table 1, primary aniline moieties were also selectively monoarylated in the presence of cyclic dialkylamine or diarylamine functional groups, giving **5c** (79%) and **5d** (90%), while the arylation of an acyclic dialkylamine moiety was achieved in the presence of a diarylamine competitor fragment (**5e**, 60%). Scope in the (hetero)aryl chloride reaction partner also proved to be quite broad as evidenced by representative reactions employing N^1-phenyl-ethane-1,2-diamine, whereby selective monoarylation at the primary amine locale occurred when using a range of hindered and unhindered (hetero)aryl chloride substrates, including those featuring electron-donating or electron-withdrawing substituents, unsaturated functionalities, and base-sensitive substituents (**5f**–**5p**, 76–97%).

The chemoselectivity preference displayed by the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system can be attributed to the amine binding step of the catalytic cycle, whereby small basic amines represent preferred substrates (vide supra). This reactivity trend is manifested in the arylation experiments featured in Table 5 including the formation of **5a**, whereby preferential monoarylation is observed at the primary alkylamine locale despite the greater acidity of the competitor primary aniline fragment within the 2-(4-aminophenyl)-ethylamine reactant. In an effort to establish the binding preference of 2-(4-aminophenyl)ethylamine to a (Mor-DalPhos)Pd(II) species, the 4-chlorotoluene C–Cl oxidative addition complex **6** was treated with silver triflate in the presence of this diamine (Figure 1). Monitoring of the reaction by use of ^{31}P NMR methods confirmed the consumption of **6** along with the clean formation of a single phosphorus-containing product (**7**), which was subsequently isolated in 72% yield as an analytically pure solid and structurally characterized. The crystallographic characterization of **7** (Figure 1 and Table S1[18]) confirms the formation of a square planar, cationic (κ^2-*P*,*N*-**L1**)Pd(II) species in which the alkylamino substituent of the diamine is coordinated to palladium. The preferential binding in solution of a primary alkylamine in the presence of potentially competitive primary arylamine was further confirmed through a competition study in which a mixture of **6** and 2.5 equivalents each of octylamine and aniline was treated with silver triflate ($CDCl_3$, room temperature, 1 h); whereas independent syntheses confirmed the viability of both potential [(Mor-DalPhos)Pd(*p*-tolyl)NH_2R]$^+$OTf$^-$ products of this reaction (**8**, R = octyl; **9**, R = phenyl), only **8** was observed (^{31}P NMR) in this competition scenario. The lack of reactivity observed between **6** and either 2-(4-aminophenyl)ethylamine, octylamine, or aniline (^{1}H and ^{31}P NMR) in the absence of base suggests that cationic species analogous to **7**-**9** arising from chloride displacement by the amine are unlikely to represent important catalytic intermediates in Buchwald–Hartwig amination chemistry when employing **L1**. Nonetheless, the preferential binding of the diamine alkylamino fragment in **7**, and the observation that the use of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system results in chemoselective monoarylation at the alkylamino locale to afford **5a**, provide indirect (although not definitive) support for the view that this process is not operating under Curtin-Hammett control. While efforts to compare the coordination chemistry of **L2** with that of **L1** have thus far not yielded informative results, orthogonal chemoselectivity giving rise to **5a′** (72%) was observed when employing the [Pd(cinnamyl)Cl]$_2$/**L2** catalyst system in the monoarylation of 2-(4-aminophenyl)ethylamine with 4-chlorotoluene (Scheme 1).[23]

Scheme 1. Divergent Chemoselectivity for the Arylation of 2-(4-Aminophenyl)ethylamine Employing L1 and L2



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SUMMARY AND CONCLUSIONS

The results presented herein establish [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos (**L1**)[16f] as being an effective catalyst system for the chemoselective synthesis of a structurally diverse set of di-, tri-, and tetraamine compounds in synthetically useful yields by use of Buchwald−Hartwig amination protocols; indeed, this study represents the most extensive compilation of such reactivity to be reported thus far in the literature. Despite the distinct preference of [Pd(cinnamyl)Cl]$_2$/**L1** for unhindered nucleophilic amine reaction partners, this catalyst system has proven useful in the chemoselective arylation of a series of alternative amine functionalities (e.g., linear and α-branched primary alkylamines, imines, primary hydrazones, *N*,*N*-dialkylhydrazines, substituted anilines, and piperidine), while tolerating the presence of a range of potential competitor amine fragments as well as varied substitution within the (hetero)aryl chloride reactant partner. Comparative reactivity studies involving the new isomeric ligand *p*-Mor-DalPhos (**L2**) confirmed that the *ortho*-disposition of phosphorus and nitrogen donors is the key to achieving the distinct chemoselectivity behavior that is observed when employing **L1**. Furthermore, the reactivity profile exhibited by [Pd(cinnamyl)Cl]$_2$/**L1** suggests that the chemoselectivity enabled by use of this catalyst system is attained in the amine binding step of the catalytic cycle, whereby amine sterics represent the key parameter in determining preferential substrate uptake. We view the proven reactivity model that has been established herein for the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system as representing a useful contribution toward addressing the challenge of enabling the more widespread application of Buchwald−Hartwig amination protocols in the selective monoarylation of high-value oligoamine target molecules, thereby circumventing problematic nitrogen protecting-group chemistry. Our progress toward identifying new and efficient DalPhos ligand variants that offer increasingly high levels of chemoselectivity in amine monoarylation reactions, including systems that are complementary to Mor-DalPhos (**L1**), will be disclosed in future reports.

EXPERIMENTAL SECTION

General Considerations. All reactions were set up inside a dinitrogen-filled, inert atmosphere glovebox, while the organic products of the catalytic reactions were isolated following workup by using standard benchtop conditions. Toluene and dichloromethane used in the glovebox were deoxygenated by sparging with dinitrogen followed by passage through a double column solvent purification system equipped either with one alumina-packed column and one column packed with copper-Q5 reactant (toluene), or two alumina-packed columns (dichloromethane and diethyl ether). 1,4-Dioxane and diethyl ether were dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. Deuterated solvents used for the characterization of organic reaction products were used as received, while the $CDCl_3$ used in the characterization of **L2** and **7**−**9** was degassed by using three repeated freeze−pump−thaw cycles and stored over 4 Å molecular sieves for 24 h prior to use within the glovebox. Mor-DalPhos (**L1**),[16b] (Mor-DalPhos)Pd(*p*-tolyl)Cl,[16b] [Pd(cinnamyl)Cl]$_2$,[24] di(1-adamantyl)-phosphine,[25] 4-(4-bromophenyl)morpholine,[26] 1-(4-chlorophenyl)-piperazine,[27] and 4-chloro-*N*-phenylaniline[28] were prepared according to literature procedures. All methylamine cross-coupling reactions were conducted by using purchased 2.0 M $MeNH_2$ solutions in THF. Prepared and purchased solid reagents were evacuated under reduced pressure for 24 h prior to use and were stored in an inert atmosphere glovebox. All other reagents, solvents (including those used on the benchtop), and materials were used as received from commercial sources. Flash column chromatography was performed on silica gel (SiliaFlash P60, Silicycle). GC data were obtained on an instrument equipped with a SGE BP-5 30 m, 0.25 mm i.d. column. In the case of the competition experiments (Table 1), conversions are given on the basis of the consumption of the aryl chloride as determined by use of GC methods; otherwise, stated yields correspond to isolated products. Unless otherwise stated, ^{1}H, ^{13}C, and ^{31}P NMR characterization data were collected at 300 K on an 11.7 T spectrometer operating at 500.1, 125.8, and 202.5 MHz (respectively) with chemical shifts reported in parts per million downfield of $SiMe_4$ (for ^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (for ^{31}P). Where required, structural elucidation was enabled through analysis of ^{1}H−^{1}H COSY, ^{1}H−^{13}C HSQC, ^{1}H−^{13}C HMBC, and ^{1}H−^{1}H NOESY data. In some cases, quaternary carbons could not be observed despite prolonged acquisition times.

Representative Catalytic Procedure (Synthesis of 4a). In an inert atmosphere glovebox, [Pd(cinnamyl)Cl]$_2$ (1 mol % Pd, from a toluene stock solution) and Mor-DalPhos (**L1**, 2 mol %) were combined, along with sufficient toluene so as to create a 0.5 M solution of the aryl chloride in the final reaction solution. This mixture was added to a vial containing a stir bar and NaOtBu (67 mg, 0.70 mmol). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. 3-Chloroaniline (53 uL, 0.50 mmol) and (3,5-dimethylphenyl)amine (69 uL, 0.55 mmol) were added via microlitre syringe. The reaction was heated at 110 °C for 16 h (unoptimized) and the consumption of the aryl chloride was confirmed by use of GC methods. The reaction mixture was then cooled, opened to air, filtered through a layer of neutral alumina and the alumina was then washed with dichloromethane (15 mL). Following removal of solvent from the combined eluent, the crude product was purified via column chromatography on silica (4:1 hex/EtOAc), affording N^1-(3,5-dimethylphenyl)benzene-1,3-diamine (**4a**) as a brown oil in 60% isolated yield (64 mg, 0.30 mmol). ^{1}H NMR ($CDCl_3$): δ 7.06 (t, 1H, J = 8 Hz, ArH), 6.72 (s, 2H, ArH), 6.60 (s, 1H, ArH), 6.48 (m, 1H, ArH), 6.41 (t, 1H, J = 2 Hz), 6.27 (m, 1H, ArH), 5.55 (br s, 1H, NH), 3.62 (br s, 2H, NH_2), 2.29 (s, 6H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.8, 144.8, 143.3, 139.3, 130.4, 123.2, 116.4, 108.7, 108.2, 104.4, 21.7. HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{17}N_2$: 213.1386, found 213.1378.

***N*-(4-(Di(1-adamantyl)phosphino)phenyl)morpholine (*p*-Mor-DalPhos) (L2).** Using a method analogous to that described for the synthesis of Mor-DalPhos,[16b] within a glovebox $Pd(OAc)_2$ (3 mol %) and DiPPF (1,1′-bis(diisopropylphosphino)ferrocene; Pd/L ≈ 1:1.2) were combined in a vial containing a magnetic stir bar and 3 mL of toluene, and stirred magnetically for 10 min. This solution was then added to a vial containing di(1-adamantyl)phosphine (124 mg, 0.41 mmol) and NaOtBu (48 mg, 0.50 mmol), followed by the addition of *N*-(4-bromophenyl)morpholine (104 mg, 0.43 mmol). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The mixture was heated at 110 °C under the influence of magnetic stirring and the consumption of the phosphine was monitored periodically by use of ^{31}P NMR techniques. After 18 h, the reaction mixture was then cooled and filtered through a plug of alumina, which was then washed with CH_2Cl_2. The combined eluant was collected and the solvent was removed in vacuo, followed by washing of the solid with Et_2O to afford **L2** as an off-white solid in 63% yield (122 mg, 0.26 mmol). ^{1}H NMR ($CDCl_3$): δ 7.53 (br m, 2H, ArH), 6.85 (d, 2H, J = 6.5 Hz, ArH), 3.86 (app. t, 4H, J = 4.5 Hz, CH_2), 3.21 (app. t, 4H, J = 4.5 Hz, CH_2), 1.96−1.86 (m, 18H, Ad), 1.66 (s, 12H, Ad). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 151.5 (ArC), 123.8 (d, J_{PC} = 16.4 Hz, ArC), 114.2 (ArC), 67.2 (CH_2), 48.7 (CH_2), 41.9 (d, J_{PC} = 11.3 Hz, Ad), 37.3−36.6 (m, Ad), 29.1 (d, J_{PC} = 14.2 Hz, Ad). ^{31}P NMR ($CDCl_3$): δ 38.8. HRMS (ESI/[M + H]$^+$) calcd for $C_{30}H_{43}N_1O_1P_1$: 464.3077, found 464.3090. Crystals suitable for X-ray diffraction were grown by vapor diffusion of diethyl ether into a concentrated solution of **L2** in CH_2Cl_2 at −30 °C. Broadening of the aryl ^{1}H NMR resonances arising due to apparent restricted rotation about aryl-P bond is observed at 300 K (500 MHz); such dynamic processes also likely account for the observation of fewer than expected aryl resonances in the accompanying ^{13}C{^{1}H} NMR

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spectrum. Such dynamic behavior is not manifested in the ^{1}H and ^{13}C resonances of the morpholino group, possibly due to rapid rotation about the aryl-N linkage with concomitant inversion at nitrogen. Support for restricted rotation about the aryl-P linkage was obtained from variable-temperature ^{1}H NMR data (250 MHz, 223−328 K), whereby initially broad aryl resonances (223 K) were observed to sharpen to an apparent triplet (7.54 ppm) and doublet (6.84 ppm) upon warming to 328 K ($\Delta G^{\ddagger}_{288}$ = 14.1 kcal/mol). ^{1}H NMR ($CDCl_3$, 250 MHz, 328 K): δ 7.54 (app. t, 2H, J = 7.7 Hz, ArH), 6.85 (d, 2H, J = 8.5 Hz, ArH), 3.85 (app. t, 4H, J = 5 Hz, CH_2), 3.22 (app. t, 4H, J = 4 Hz, CH_2), 1.96−1.84 (m, 18H, Ad), 1.68 (s, 12H, Ad).

Preparation of N^1-Octylbenzene-1,3-diamine (2a). The general procedure was followed, with 3-chloroaniline (53 uL, 0.50 mmol) and H_2NOctyl (91 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (4:1 hex/EtOAc) and isolated as a brown oil in 74% yield (82 mg, 0.37 mmol). ^{1}H NMR ($CDCl_3$): δ 6.95 (t, 1H, J = 8 Hz, ArH), 6.06 (m 2H, ArH), 5.96 (s, 1H, ArH), 3.53 (br s, 3H, NH), 3.06 (t, 2H, J = 7.5 Hz, NCH_2), 1.58 (m, 2H, CH_2), 1.41−1.29 (m, 10 H, octyl), 1.29 (t, 3H, J = 6.5 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 150.1, 147.8, 130.4, 104.9, 104.3, 99.6, 44.3, 32.2, 29.9, 29.8, 29.6, 27.5, 22.9, 14.4. HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{25}N_2$: 221.2012, found 221.1995.

Preparation of 3-(1-Aminoethyl)-*N*-octylaniline (2b). The general procedure was followed, with 4-chloro-α-methylbenzylamine (70 uL, 0.50 mmol) and H_2NOctyl (90 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (DCM − 100:10:1 DCM/MeOH/NH_4OH) and isolated as dark yellow oil in 89% yield (112 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.15 (d, 2H, J = 8.5 Hz, ArH), 6.58 (m, 2H, ArH), 4.02 (quart., 1H, J = 7 Hz, CH), 3.08 (t, 2H, J = 7 Hz, CH_2), 2.39 (br s, 2H, NH), 1.63−1.57 (m, 2H, CH_2N), 1.39−1.28 (m, 13 H, octyl), 0.90 (t, 3H, J = 7 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.9, 135.8, 127.0, 112.9, 51.1, 44.4, 32.1, 29.9, 29.7, 29.6, 27.5, 25.4, 23.0, 14.4. HRMS (ESI/[M + H]$^+$) calcd for $C_{16}H_{29}N_2$: 249.2325, found 249.2322.

Preparation of 3-(1-Aminoethyl)-*N*-methylaniline (2c). The general procedure was followed, with 4-chloro-α-methylbenzylamine (70 uL, 0.50 mmol) and methylamine (2 mmol from a 2 M stock solution in THF) added via a microlitre syringe. The reaction was allowed to proceed for 48 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (100:10:1 DCM/MeOH/NH_4OH) and isolated as yellow oil in 77% yield (58 mg, 0.39 mmol). ^{1}H NMR ($CDCl_3$): δ 7.19−7.16 (m, 2H, ArH), 6.61−6.58 (m, 2H, ArH), 4.03 (quart., 1H, J = 6.5 Hz, CH), 2.83 (s, 3H, CH_3), 1.81 (br s, 2H, NH), 1.36 (d, 3H, J = 6.5 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.6, 136.7, 126.9, 112.8, 51.1, 31.2, 25.8. HRMS (ESI/[M + Na]$^+$) calcd for $C_9H_{14}N_2$Na: 173.1049, found 173.1053.

Preparation of N^1-Octyl-N^4-phenylbenzene-1,4-diamine (2d). The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox, H_2NOctyl (91 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a white solid in 91% yield (134 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.19 (t, 2H, J = 8 Hz, ArH), 7.05−7.01 (m, 2H, ArH), 6.83−6.78 (m, 3H, ArH), 6.78 (m, 1H, ArH), 6.64−6.56 (m, 2H, ArH), 5.37 (br s, 1H, NH), 3.09 (br s, 1H, NH), 1.63 (quint, 2H, J = 7.5 Hz, NCH_2), 1.44−1.27 (m, 12H, CH_2), 0.90 (t, 3H, 7 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 145.1, 132.8, 129.5, 124.3, 119.0, 115.0, 114.8, 114.0, 44.9, 32.2, 29.9, 29.8, 29.6, 27.5, 23.0, 14.4. HRMS (ESI/[M + H]$^+$) calcd for $C_{20}H_{29}N_2$: 297.2325, found 297.2351.

Preparation of N^1-Methyl-N^4-phenylbenzene-1,4-diamine (2e). The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and methylamine (2 mmol from a 2 M stock solution in THF) added via a microlitre syringe. The reaction was allowed to proceed for 48 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as an orange-brown solid in 87% yield (86 mg, 0.44 mmol). ^{1}H NMR (MeOD): δ 7.13 (t, 2H, J = 8.5 Hz, ArH), 7.00 (d, 2H, J = 8.5 Hz, ArH), 6.87 (d, 2H, J = 8 Hz, ArH), 6.72−6.66 (m, 3H, ArH), 4.91 (s, 3H, CH_3), 2.78 (br s, 2H, NH). ^{13}C{^{1}H} NMR (MeOD): δ 147.6, 136.1, 130.8, 124.5, 120.1, 116.7, 115.9, 32.5. HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{15}N_2$: 199.1230, found 199.1224.

Preparation of N^1-(Diphenylmethylene)-N^4-phenylbenzene-1,4-diamine (2f). The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) and benzopheneone imine (100 mg, 0.55 mmol) weighed out in the glovebox. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as an orange oil in 93% yield (162 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.77−7.75 (m, 2H, ArH), 7.47 (tt, 1H, J = 7 Hz, J = 1.5 Hz, ArH), 7.43−7.39 (m, 2H, ArH), 7.35−7.29 (m, 3H, ArH), 7.25−7.2 (m, 2H, ArH), 7.19−7.15 (m, 2H, ArH), 6.97−6.94 (m, 2H, ArH), 6.91−6.89 (m, 3H, ArH), 6.71−6.68 (m, 2H, ArH), 5.57 (br s, 1H, NH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 168.0, 145.5, 144.1, 140.3, 138.9, 137.0, 130.9, 129.9, 129.6, 129.5, 128.8, 128.5, 128.4, 123.0, 120.6, 119.2, 117.6. HRMS (ESI/[M + H]$^+$) calcd for $C_{25}H_{21}N_2$: 349.1699, found 349.1706.

Preparation of *N*-Octyl-4-(piperazin-1-yl)aniline (2g). The general procedure was followed, with 1-(4-chlorophenyl)piperazine (98 mg, 0.50 mmol) weighed in the glovebox and H_2NOctyl (91 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM/MeOH/NH_4OH) and isolated as an off-white solid in 74% yield (107 mg, 0.37 mmol). ^{1}H NMR ($CDCl_3$): δ 6.86−6.83 (m, 2H, ArH), 6.60−6.57 (m, 2H, ArH), 3.07−2.99 (m, 10 H, CH_2), 2.67 (br s, 2H, NH), 1.60 (m, 2H, CH_2), 1.41−1.25 (m, 11H, CH_2), 0.88 (t, 3H, J = 7 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 144.3, 143.5, 119.3, 114.1, 52.7, 46.6, 45.1, 32.2, 30.0, 29.8, 29.6, 27.5, 23.0, 14.5. HRMS (ESI/[M + H]$^+$) calcd for $C_{18}H_{32}N_3$: 290.2591, found 290.2584.

Preparation of 3-((Methylamino)methyl)-*N*-octylaniline (2h). The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 uL, 0.50 mmol) and H_2NOctyl (91 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 20 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (80:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow oil in 84% yield (104 mg, 0.42 mmol). ^{1}H NMR ($CDCl_3$): δ 7.12 (t, 1H, J = 8 Hz, ArH), 6.62 (d, 1H, J = 7.5 Hz, ArH), 6.58 (t, 1H, J = 1.5 Hz, ArH), 6.49 (m, 1H, ArH), 3.68 (s, 2H, NCH_2), 3.10 (t, J = 7 Hz, CH_2), 2.45 (s, 1H, CH_3), 1.59 (m, 2H, CH_2), 1.40−1.26 (m, 10H, CH_2), 0.89 (t, 3H, J = 7 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 149.1, 141.3, 129.6, 117.3, 112.8, 111.7, 56.6, 44.3, 36.3, 32.2, 29.9, 29.8, 29.6, 27.5, 23.0, 14.5. HRMS (ESI/[M + H]$^+$) calcd for $C_{16}H_{29}N_2$: 249.2325, found 249.2329.

Preparation of *N*-Methyl-3-((methylamino)methyl)aniline (2i). The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 uL, 0.50 mmol) and methylamine (2 mmol

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from a 2 M stock solution in THF) added via a microlitre syringe. The reaction was allowed to proceed for 24 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM/MeOH/NH_4OH) and isolated as an orange oil in 75% yield (56 mg, 0.38 mmol). ^1H NMR ($CDCl_3$): δ 7.14 (t, 1H, J = 7.5 Hz, ArH), 6.65 (d, 1H, J = 7.5 Hz, ArH), 6.60 (s, 1H, ArH), 6.51 (dd, 1H, J = 8 Hz, J = 2 Hz, ArH), 3.69 (s, 2H, CH_2), 2.82 (s, 3H, CH_3), 2.48 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 149.9, 129.6, 117.6, 112.6, 111.6, 56.4, 36.1, 31.1. HRMS (ESI/$[M + H]^+$) calcd for $C_9H_{15}N_2$: 151.1230, found 151.1236.

Preparation of N^1-Methyl-N^3-octylbenzene-1,3-diamine (2j). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) and $H_2NOctyl$ (91 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM/MeOH/NH_4OH) and isolated as an off-white solid in 93% yield (109 mg, 0.47 mmol). ^1H NMR ($CDCl_3$): δ 6.99 (t, 1H, J = 8 Hz, ArH), 6.05−6.02 (m, 2H, ArH), 5.89 (t, 1H, J = 2 Hz, ArH), 3.66 (br s, 2H, NH), 3.09 (t, 2H, J = 7 Hz, CH_2), 2.81 (s, 3H, CH_3), 1.60 (m, 2H, CH_2), 1.40−1.26 (m, 10H, CH_2), 0.89 (t, 3H, J = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 149.9, 130.3, 103.3, 102.9, 97.2, 44.5, 32.2, 31.2, 29.9, 29.8, 29.6, 27.5, 23.0, 14.5. HRMS (ESI/$[M + H]^+$) calcd for $C_{15}H_{27}N_2$: 235.2169, found 235.2169.

Preparation of N^1,N^3-Dimethylbenzene-1,3-diamine (2k). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) and methylamine (2 mmol from a 2 M stock solution in THF) added via a microlitre syringe. The reaction was allowed to proceed for 21 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a dark orange oil in 83% yield (57 mg, 0.42 mmol). ^1H NMR ($CDCl_3$): δ 7.01 (t, 1H, J = 8 Hz, ArH), 6.05 (dd, 2H, J = 8 Hz, J = 2 Hz, ArH), 5.91 (t, 1H, J = 2 Hz, ArH), 2.82 (s, 6H, CH_3).$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 130.2, 102.9, 96.8, 31.2. HRMS (ESI/$[M + H]^+$) calcd for $C_8H_{13}N_2$: 137.1073, found 137.1079.

Preparation of N^1-(Diphenylmethylene)-N^3-methylbenzene-1,3-diamine (2l). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) added by a microlitre syringe and benzopheneone imine (100 mg, 0.55 mmol) weighed in the glovebox. The reaction was allowed to proceed for 48 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow oil in 92% yield (132 mg, 0.46 mmol). ^1H NMR ($CDCl_3$): δ 7.76−7.74 (m, 2H, ArH), 7.45 (m, 1H, ArH), 7.42−7.39 (m, 2H, ArH), 7.28−7.26 (m, 3H, ArH), 7.18−7.16 (m, 2H, ArH), 6.93 (t, 1H, J = 8 Hz, ArH), 6.21 (ddd, 1H, J = 8 Hz, J = 2 Hz, J = 1 Hz, ArH), 6.09 (t, 1H, J = 2 Hz, ArH), 6.05 (ddd, 1H, J = 8 Hz, J = 2 Hz, J = 1 Hz, ArH), 3.60 (br s, 1H, NH), 2.71 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 168.0, 152.6, 150.0, 140.2, 136.8, 130.9, 129.8, 129.6, 129.4, 128.8, 128.5, 128.1, 110.4, 108.4, 105.4, 31.0. HRMS (ESI/$[M + H]^+$) calcd for $C_{20}H_{19}N_2$ 287.1543, found 287.1552.

Preparation of 4-(Octylamino)benzamide (2m). The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) weighed out in the glovebox and $H_2NOctyl$ (91 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 48 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as a white solid in 74% yield (92 mg, 0.37 mmol). ^1H NMR (MeOD): δ 7.71−7.68 (m, 2H, ArH), 6.63−6.59 (m, 2H, ArH), 4.91 (br s, NH), 3.15 (t, 2H, J = 7.5 Hz, CH_2), 1.65 (m, 2H, CH_2), 1.46−1.35 (m, 10H, CH_2), 0.93 (t, 3H, J = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR (MeOD): δ 173.8, 154.8, 131.4, 121.7, 113.0, 44.9, 33.9, 31.5, 31.3, 31.1, 29.1, 24.6, 15.3. HRMS (ESI/$[M + H]^+$) calcd for $C_{15}H_{25}N_2O$: 249.1961, found 249.1966.

Preparation of *N*-(4-(Octylamino)phenyl)acetamide (2n).[29] The general procedure was followed, *N*-(4-chlorophenyl)acetamide (84 mg, 0.50 mmol) weighed out in the glovebox and $H_2NOctyl$ (91 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as an off-white solid in 73% yield (96 mg, 0.37 mmol). ^1H NMR (MeOD): δ 7.26 (d, 2H, J = 9 Hz, ArH), 6.62 (d, 2H, J = 8.5 Hz, ArH), 4.91 (br s, 3H, NH), 3.06 (t, 2H, J = 7 Hz, CH_2), 2.09 (s, 3H, CH_3), 1.62 (m, 2H, CH_2), 1.44−1.33 (m, 10H, CH_2), 0.93 (t, 3H, J = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR (MeOD): δ 172.1, 148.5, 130.3, 124.2, 114.9, 46.2, 33.9, 31.5, 31.3, 31.2, 29.2, 24.6, 24.3, 15.3. HRMS (ESI/$[M + H]^+$) calcd for $C_{16}H_{27}N_2O$: 263.2118, found 263.2115.

Preparation of N^1-Cyclohexylbenzene-1,3-diamine (3a). The general procedure was followed, with 3-chloroaniline (53 uL, 0.50 mmol) and cyclohexylamine (63 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 14 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (8:1−5:1 hex/EtOAc) and isolated as a dark brown solid in 55% yield (52 mg, 0.28 mmol). ^1H NMR ($CDCl_3$): δ 6.94 (t, 1H, J = 8 Hz, ArH), 6.07−6.04 (m, 2H, ArH), 5.97 (t, 1H, J = 2 Hz, ArH), 3.5 (br s, 2H, NH), 3.20 (m, 1H, CH), 2.28−2.03 (m, 2H, Cy), 1.78−1.73 (m, 2H, Cy), 1.65 (m, 1H, Cy), 1.39−1.09 (m, 5H, Cy). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.8, 147.8, 130.4, 104.8, 100.1, 52.0, 33.9, 26.3, 25.3. HRMS (ESI/$[M + H]^+$) calcd for $C_{12}H_{19}N_2$: 191.1543, found 191.1543.

Preparation of N^1-(4-Methylpiperazin-1-yl)benzene-1,3-diamine (3b). The general procedure was followed, with 3-chloroaniline (53 μL, 0.50 mmol) and 1-amino-4-methylpiperazine (66 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of the solvent, the product was purified using column chromatography on silica (200:10:1−70:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow solid in 50% yield (52 mg, 0.25 mmol). ^1H NMR ($CDCl_3$): δ 6.96 (t, 1H, J = 7.5 Hz, ArH) 6.34 (t, 1H, J = 2 Hz, ArH), 6.25 (m, 1H, ArH), 6.14 (m, 1H, ArH), 4.29 (br s, 1H, NH), 3.59 (br s, 1H, NH), 2.88−2.40 (br m, 8 H, CH_2), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.9, 147.9, 130.3, 107.1, 104.8, 100.6, 56.0, 55.4, 46.1. HRMS (ESI/$[M + H]^+$) calcd for $C_{11}H_{19}N_4$: 207.1604, found 207.1603.

Preparation of N^1-Cyclohexyl-N^4-phenylbenzene-1,4-diamine (3c). The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and cyclohexylamine (63 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as a dark yellow solid in 94% yield (125 mg, 0.47 mmol). ^1H NMR ($CDCl_3$): δ 7.19−7.16 (m, 2H, ArH), 6.99 (d, 2H, J = 8.5, ArH), 6.82 (d, 2H, J = 8 Hz, ArH), 6.77 (t, 1H, J = 7 Hz, ArH), 6.58 (d, 2H, J = 8.5 Hz, ArH), 5.37 (br s, 1H, NH), 3.41 (br s, 1H, NH), 3.22 (m, 1H, Cy), 2.09−2.06 (m, 2H, Cy), 1.80−1.75 (m, 2H, Cy), 1.66 (m, 1H, Cy), 1.42−1.34 (m, 2H, Cy), 1.33−1.45 (m, 3H, Cy). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.7, 144.1, 132.4, 129.5, 124.4, 118.9, 115.0, 114.5, 52.6, 33.9, 26.3, 25.4. HRMS (ESI/$[M + H]^+$) calcd for $C_{18}H_{23}N_2$: 267.1856, found 267.1849.

Preparation of N^1-*sec*-Butyl-N^4-phenylbenzene-1,4-diamine (3d). The general procedure was followed, with 4-chloro-*N*-phenyl-

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aniline (102 mg, 0.50 mmol) weighed out in the glovebox and $sBuNH_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 16 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of the solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a brown oil in 81% yield (97 mg, 0.41 mmol). ^1H NMR (MeOD): δ 7.13 (t, 2H, *J* = 8 Hz, ArH), 6.97 (d, 2H, *J* = 8 Hz, ArH), 6.87 (d, 2H, *J* = 8 Hz, ArH), 6.72−6.68 (m, 3H, ArH), 4.91 (s, 2H, NH), 1.65 (m, 1H, CH), 1.45 (m, 1H, CH), 1.17 (d, 3H, *J* = 6 Hz, CH_3), 0.99 (t, 3H, *J* = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR (MeOD): δ 135.8, 130.8, 124.5, 120.1, 117.2, 116.7, 52.9, 31.2, 20.9, 11.7. HRMS (ESI/$[M + H]^+$) calcd for $C_{16}H_{21}N_2$: 241.1699, found 241.1701.

Preparation of N^1-(4-Methylpiperazin-1-yl)-N^4-phenylbenzene-1,4-diamine (3e). The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and 1-amino-4-methylpiperazine (66 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of the solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow solid in 81% yield (115 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.21−7.18 (m, 2H, ArH), 7.02−7.01 (m, 2H, ArH), 6.89−6.87 (m, 4H, ArH), 6.79 (m, 1H, ArH), 5.47 (br s, 1H, NH), 4.28 (br s, 1H, NH), 2.78−2.47 (m, 8H, CH_2), 2.34 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.0, 143.4, 135.0, 129.6, 123.1, 119.3, 115.5, 115.2, 56.0, 55.4, 46.1. HRMS (ESI/$[M-H]^+$) calcd for $C_{17}H_{21}N_4$: 281.1761, found 281.1772.

Preparation of *N*-Cyclohexyl-4-(piperazin-1-yl)aniline (3f). The general procedure was followed, with 1-(4-chlorophenyl)-piperazine (98 mg, 0.50 mmol) weighed out in the glovebox and cyclohexylamine (63 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (100:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow solid in 74% yield (96 mg, 0.35 mmol). ^1H NMR ($CDCl_3$): δ 6.84−6.81 (m, 2H, ArH), 6.58−6.55 (m, 2H, ArH), 3.17 (m, 1H, CH), 3.05−2.99 (m, 8H, NCH_2), 2.50−2.26 (br s, 2H, NH), 2.05−2.02 (m, 2H, Cy), 1.76−1.72 (m, 2H, Cy), 1.63 (m, 1H, Cy), 1.39−1.35 (m, 2H, Cy), 1.25−1.07 (m, 3H, Cy). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.9, 142.4, 119.4, 114.7, 52.8, 52.4, 46.4, 34.0, 26.3, 25.4. HRMS (ESI/$[M + H]^+$) calcd for $C_{16}H_{26}N_3$: 260.2121, found 260.2112.

Preparation of *N*-*sec*-Butyl-4-(piperazin-1-yl)aniline (3g). The general procedure was followed, with 1-(4-chlorophenyl)-piperazine (98 mg, 0.50 mmol) weighed out in the glovebox and $sBuNH_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow solid in 60% yield (70 mg, 0.30 mmol. ^1H NMR ($CDCl_3$): δ 6.84 (d, 2H, *J* = 8.5 Hz, ArH), 6.55 (d, 2H, J = 8.5 Hz, ArH), 3.31 (m, 1H, CH), 3.09−3.02 (m, 8H, CH_2), 2.87 (br s, 2H, NH), 1.57 (m, 1H, CH), 1.46 (m, 1H, CH), 1.25 (m, 1H, CH), 1.15 (d, 3H, *J* = 6.5 Hz, CH_3), 0.94 (t, 3H, *J* = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.9, 142.7, 119.4, 114.6, 52.4, 50.8, 46.4, 30.0, 20.7, 10.7. HRMS (ESI/$[M + H]^+$) calcd for $C_{14}H_{24}N_3$: 234.1965, found 234.1966.

Preparation of *N*-Cyclohexyl-3-((methylamino)methyl)-aniline (3h). The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 uL, 0.50 mmol) and cyclohexylamine (63 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 16 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (80:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow oil in 92% yield (100 mg, 0.46 mmol). ^1H NMR ($CDCl_3$): δ 7.10 (t, 1H, *J* = 8 Hz, ArH), 6.59 (d, 1H, *J* = 7.5 Hz, ArH), 6.56 (br s, 1H, ArH), 6.49 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz, ArH), 3.66 (s, 2H, NCH_2), 3.27 (m, 1H, CH), 2.45 (s, 3H, CH_3), 2.06−2.03 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 1.64 (m, 1H, CH), 1.38−1.13 (m, 5H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.9, 141.2, 129.6, 117.1, 113.2, 112.1, 56.5, 51.2, 36.2, 33.8, 26.2, 25.3. HRMS (ESI/$[M + H]^+$) calcd for $C_{14}H_{23}N_2$: 219.1856, found 219.1853.

Preparation of *N*-*sec*-Butyl-3-((methylamino)methyl)aniline (3i). The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 uL, 0.50 mmol) and $sBuNH_2$ (56 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 16 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (40:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow oil in 81% yield (78 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.11 (t, 1H, *J* = 7.5 Hz, ArH), 6.59 (d, 1H, *J* = 7.5 Hz, ArH), 6.56 (s, 1H, ArH), 6.47 (dd, 1H, *J* = 7.5 Hz, *J* = 2 Hz, ArH), 3.67 (s, 2H, CH_2), 3.41 (m, 1H, CH), 2.45 (s, 3H, CH_3), 4.37 (br s, 1H, NH), 1.57 (m, 1H, CH), 1.47 (m, 1H, CH), 1.15 (d, *J* = 6 Hz, 3H, CH_3), 0.94 (t, 3H, *J* = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.2, 141.3, 129.6, 117.0, 113.3, 112.0, 56.5, 50.0 36.2, 30.0, 20.6, 10.7. HRMS (ESI/$[M + H]^+$) calcd for $C_{12}H_{21}N_2$: 193.1699, found 193.1701.

Preparation of 4-Methyl-*N*-(3-((methylamino)methyl)-phenyl)piperazin-1-amine (3j). The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and 1-amino-4-methylpiperazine (66 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of the solvent, the product was purified using column chromatography on silica (30:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow oil in 70% yield (83 mg, 0.35 mmol). ^1H NMR ($CDCl_3$): δ 7.14 (t, 1H, *J* = 7.5 Hz, ArH), 6.84 (s, 1H, ArH), 6.79 (d, 1H, *J* = 8 Hz, ArH), 6.72 (d, 1H, *J* = 7.5 Hz, ArH), 4.37 (br s, 1H, NH), 3.67 (s, 2H, CH_2), 2.97−2.54 (m, 8H, CH_2), 2.46 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.05 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.9, 141.2, 129.5, 119.7, 113.6, 112.7, 56.4, 56.0, 55.4, 46.1, 36.2. HRMS (ESI/$[M + H]^+$) calcd for $C_{13}H_{23}N_4$: 235.1917, found 235.1908.

Preparation of N^1-Cyclohexyl-N^3-methylbenzene-1,3-diamine (3k). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) and cyclohexylamine (63 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as an orange oil in 89% yield (91 mg, 0.45 mmol). ^1H NMR ($CDCl_3$): δ 7.01 (t, 1H, *J* = 8 Hz, ArH), 6.05−6.01 (m, 2H, ArH), 5.89 (t, 1H, *J* = 2 Hz, ArH), 3.55 (br s, 2H, NH), 3.27 (m, 1H, CH), 2.29 (s, 3H, CH_3), 2.10 −2.08 (m, 2H, CH_2), 1.81−1.76 (m, 2H, CH_2), 1.67 (m, 1H, CH), 1.41−1.35 (m, 2H, CH_2), 1.29−1.16 (m, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.9, 148.9, 130.3, 103.4, 102.5, 97.5, 52.0, 39.9, 31.1, 26.3, 25.4. HRMS (ESI/$[M + H]^+$) calcd for $C_{13}H_{21}N_2$: 205.1699, found 205.1702.

Preparation of N^1-*sec*-Butyl-N^3-methylbenzene-1,3-diamine (3l). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) and $sBuNH_2$ (56 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a brown oil in 90% yield (80 mg, 0.45 mmol). ^1H NMR ($CDCl_3$): δ 6.99 (t, 1H, *J* = 8 Hz, ArH), 6.00 (dt, 2H, *J* = 8 Hz, *J* = 2.5 Hz, ArH), 5.87 (t, 1H, *J* = 2.5 Hz, ArH), 3.49 (br s, 2H, NH), 3.39 (m,

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1H, CH), 2.82 (s, 3H, CH_3), 1.60 (m, 1H, CH), 1.47 (m, 1H, CH), 1.17 (d, 3H, J = 6.5 Hz, CH_3), 0.96 (t, 3H, J = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.9, 149.2, 130.2, 103.4, 102.4, 97.4, 50.1, 31.1, 30.1, 20.7, 10.7. HRMS (ESI/[M + H]$^+$) calcd for $C_{11}H_{19}N_2$: 179.1543, found 179.1540.

Preparation of N^1-Methyl-N^3-(4-methylpiperazin-1-yl)-benzene-1,3-diamine (3m). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and 1-amino-4-methylpiperazine (66 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (100:10:1−50:10:1 DCM/MeOH/NH_4OH) and isolated as a dark red oil in 78% yield (86 mg, 0.39 mmol). ^1H NMR ($CDCl_3$): δ 7.02−6.98 (m, 1H, ArH), 6.25−6.23 (m, 2H, ArH), 6.10−6.08 (m, 1H, ArH), 4.30 (br s, 1H, NH), 2.80 (s, 3H, CH_3), 2.74−2.36 (m, 8H, CH_2), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 148.8, 130.1, 104.6, 103.6, 97.9, 55.9, 55.4, 46.1, 31.1. HRMS (ESI/[M + H]$^+$) calcd for $C_{12}H_{21}N_4$: 221.1761, found 221.1752.

Preparation of 3-(2-(Diphenylmethylene)hydrazinyl)-*N*-methylaniline (3n). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) added by a microlitre syringe and benzopheneone hydrazone (108 mg, 0.55 mmol) weighed out in the glovebox. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a dark red oil in 80% yield (121 mg, 0.40 mmol). ^1H NMR ($CDCl_3$): δ 7.63−7.59 (m, 4H, ArH), 7.55 (m, 1H, ArH), 7.59 (br s, 1H, ArH), 7.38−7.29 (m, 4H, ArH), 7.08 (t, 1H, J = 8 Hz, ArH), 6.5 (t, 1H, J = 2 Hz, ArH), 6.39 (ddd, 1H, J = 8 Hz, J = 2 Hz, J = 1 Hz, ArH), 6.18 (ddd, 1H, J = 8 Hz, J = 2 Hz, J = 1 Hz, ArH), 2.86 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 145.9, 143.9, 138.8, 133.2, 130.2, 129.9, 129.5, 129.5, 128.5, 128.2, 126.7, 105.3, 102.8, 97.0, 31.1. HRMS (ESI/[M + H]$^+$) calcd for $C_{20}H_{20}N_3$: 302.1652, found 302.1642.

Preparation of 4-(Cyclohexylamino)benzamide (3o).[30] The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) weighed out in the glovebox and cyclohexylamine (63 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as an off-white solid in 73% yield (80 mg, 0.37 mmol). ^1H NMR (MeOD): δ 7.65 (m, 2H, ArH), 6.59 (m, 2H, ArH), 3.33 (m, 1H, CH), 2.09−2.07 (m, 2H, Cy), 1.82−1.79 (m, 2H, Cy), 1.69 (m, 1H, Cy), 1.47−1.19 (m, 5 H, Cy). $^{13}C\{^1H\}$ NMR (MeOD): δ 169.3, 151.1, 129.7, 121.1, 112.2, 51.8, 33.6, 26.3, 25.5. HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{19}N_2O$: 219.1492, found 219.1497.

Preparation of 4-(*sec*-Butylamino)benzamide (3p). The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) weighed out in the glovebox and sBuNH$_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow solid in 68% yield (65 mg, 0.34 mmol). ^1H NMR (MeOD): δ 7.68 (m, 2H, ArH), 6.61 (m, 2H, ArH), 4.91 (br s, 3H, NH), 3.48 (m, 1H, CH), 1.64 (m, 1H, CH), 1.55 (m, 1H, CH), 1.20 (d, 3H, J = 6 Hz, CH_3), 0.99 (t, 3H, J = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR (MeOD): δ 173.8, 154.2, 131.4, 121.4, 113.3, 51.3, 31.3, 21.1, 11.7. HRMS (ESI/[M + H]$^+$) calcd for $C_{11}H_{17}N_2O$:193.1335, found 193.1340.

Preparation of *N*-(4-(Cyclohexylamino)phenyl)acetamide (3q). The general procedure was followed, *N*-(4-chlorophenyl)-acetamide (84 mg, 0.50 mmol) weighed out in the glovebox and cyclohexylamine (63 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as a brown solid in 92% yield (106 mg, 0.46 mmol). ^1H NMR (MeOD): δ 7.25 (m, 2H, ArH), 6.64 (m, 2H, ArH), 4.91 (br s, 3H, NH), 3.21 (m, 1H, CH), 2.09 (s, 3H, CH_3), 2.05−1.93 (m, 2H, Cy), 1.82−1.78 (m, 2H, Cy), 1.69 (m, 1H, Cy), 1.43−1.17 (m, 5H, Cy). $^{13}C\{^1H\}$ NMR (MeOD): δ 172.1, 147.2, 130.4, 124.2, 115.9, 54.4, 35.1, 27.9, 27.1, 24.3. HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{21}N_2O$: 233.1648, found 233.1644.

Preparation of *N*-(4-(*sec*-Butylamino)phenyl)acetamide (3r). The general procedure was followed, with *N*-(4-chlorophenyl)-acetamide (84 mg, 0.50 mmol) weighed out in the glovebox and sBuNH$_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow oil in 90% yield (93 mg, 0.45 mmol). ^1H NMR (MeOD): δ 7.24 (m, 2H, ArH), 6.61 (m, 2H, ArH), 4.91 (br s, 2H, NH), 3.37 (m, 1H, CH), 2.09 (s, 3H, CH_3), 1.62 (m, 1H, CH), 1.47 (m, 1H, CH), 1.16 (d, 3H, J = 6 Hz, CH_3), 0.97 (t, 3H, J = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR (MeOD): δ 172.1, 147.8, 130.0, 124.3, 115.5, 52.2, 31.2, 24.3, 21.1, 11.7. HRMS (ESI/[M + H]$^+$) calcd for $C_{12}H_{19}N_2O$: 207.1492, found 207.1497.

Preparation of N^1-(3,5-Dimethylphenyl)benzene-1,3-diamine (4a). Full details of the preparation of this compound are provided as the Representative Catalytic Procedure.

Preparation of N^1-(3,5-Dimethylphenyl)-N^4-phenylbenzene-1,4-diamine (4b). The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and 3,5-dimethylaniline (69 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 16 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow solid in 96% yield (138 mg, 0.48 mmol). ^1H NMR (MeOD): δ 7.19−7.17 (m, 2H, ArH), 7.06−7.03 (m, 4H, ArH), 6.99 (dd, 2H, J = 8.5 Hz, J = 1 Hz, ArH), 6.77 (t, 1H, J = 7.5 Hz, ArH), 6.63 (s, 2H, ArH), 6.46 (s, 1H, ArH), 4.91 (s, 2H, NH), 2.23 (s, 6H, ArH). $^{13}C\{^1H\}$ NMR (MeOD): δ 147.7, 147.4, 140.5, 139.9, 139.3, 130.9, 122.8, 122.4, 122.3, 120.9, 117.6, 115.8, 22.5. HRMS (ESI/[M + H]$^+$) calcd for $C_{20}H_{21}N_2$: 289.1699, found 289.1685.

Preparation of N^1-Phenyl-N^4-(3-(trifluoromethyl)phenyl)-benzene-1,4-diamine (4c). The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and 3-CF_3-aniline (68 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow solid in 95% yield (156 mg, 0.48 mmol). ^1H NMR (MeOD): δ 7.30 (t, 1H, J = 8 Hz, ArH), 7.22−7.19 (m, 2H, ArH), 7.16−7.13 (m, 2H, ArH), 7.12−7.07 (m, 4H, ArH), 7.05−7.03 (m, 2H, ArH), 6.96 (d, 1H, J = 7.5 Hz, ArH), 6.80 (tt, 1 H, J = 7.5 Hz, J = 1 Hz, ArH), 4.92 (br s, 2H, NH). $^{13}C\{^1H\}$ NMR (MeOD): δ 148.9, 146.9, 141.1, 137.4, 133.3 (quart., J_{CF} = 31.5 Hz), 131.7, 130.9, 123.9, 121.5, 121.3, 119.7 (quart., J_{CF} = 171.2 Hz), 119.6, 118.2, 116.1 (m), 112.6 (m). HRMS (ESI/[M + H]$^+$) calcd for $C_{19}H_{16}F_3N_2$: 329.1260, found 329.1265.

Preparation of *N*-Phenyl-4-(piperidin-1-yl)aniline (4d). The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and piperidine (54 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 46 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with

dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as a brown solid in 82% yield (104 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.22−7.19 (m, 2H, ArH), 7.05 (d, 2H, J = 9 Hz, ArH), 6.92 (d, 4H, J = 8 Hz, ArH), 6.82 (t, 1H, J = 7 Hz, ArH), 5.48 (br s, 1H, NH), 3.10 (s, 4H, CH_2), 1.76−1.71 (m, 4H, CH_2), 1.59−1.55 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.5, 145.6, 135.2, 129.6, 122.1, 119.7, 118.4, 115.9, 51.9, 26.4, 24.6. HRMS (ESI/[M + H]$^+$) calcd for $C_{17}H_{21}N_2$: 253.1699, found 253.1705.

Preparation of 3,5-Dimethyl-*N*-(4-(piperazin-1-yl)phenyl)-aniline (4e). The general procedure was followed, with 1-(4-chlorophenyl)piperazine (98 mg, 0.50 mmol) weighed out in the glovebox and 3,5-Me-aniline (69 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (100:15:1.5 DCM/MeOH/NH_4OH) and isolated as an orange oil in 71% yield (100 mg, 0.36 mmol). ^1H NMR ($CDCl_3$): δ 7.05 (m, 2H, ArH), 6.90 (m, 2H, ArH), 6.57 (s, 2H, ArH), 6.50 (s, 1H, ArH), 5.45 (br s, 1H, NH), 3.11−3.03 (m, 8H, CH_2), 2.25 (s, 6H, CH_3), 1.82 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.6, 145.3, 139.2, 135.9, 121.9, 121.7, 117.8, 113.9, 51.6, 46.5, 21.7. HRMS (ESI/[M + H]$^+$) calcd for $C_{18}H_{24}N_3$: 282.1965, found 282.1962.

Preparation of *N*-(4-(Piperazin-1-yl)phenyl)-3-(trifluoromethyl)aniline (4f). The general procedure was followed, with 1-(4-chlorophenyl)piperazine (98 mg, 0.50 mmol) weighed out in the glovebox and 3-trifluoromethylaniline (68 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (100:15:1.5 DCM/MeOH/NH_4OH) and isolated as a yellow solid in 60% yield (96 mg, 0.30 mmol. ^1H NMR ($CDCl_3$): δ 7.27 (t, 1H, J = 8 Hz, ArH), 7.10−7.06 (m, 3H, ArH), 7.03−6.99 (m, 2H, ArH), 6.94−6.91 (m, 2H, ArH), 5.68 (br s, 1H, NH), 3.13−3.04 (m, 8 H, CH_2), 1.95 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): 148.7, 146.3, 134.0, 131.9 (quart., J_{CF} = 31 Hz), 130.0, 124.5 (quart., J_{CF} = 273 Hz), 123.2, 118.2, 117.8, 115.7 (m), 111.5 (m), 51.2, 46.5. HRMS (ESI/[M + H]$^+$) calcd for $C_{17}H_{19}F_3N_3$: 322.1526, found 322.1528.

Preparation of 3-((Methylamino)methyl)-*N*-phenylaniline (4g). The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 uL, 0.50 mmol) and aniline (50 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (80:10:1 DCM/MeOH/NH_4OH) and isolated as a white solid in 82% yield (86 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.29−7.25 (m, 2H, ArH), 7.22 (t, 1H, J = 8 Hz, ArH), 7.09−7.07 (m, 2H, ArH), 7.02 (m, 1H, ArH), 6.99 (d of d of d, 1H, J = 8 Hz, J = 2.5 Hz, J = 1 Hz, ArH), 6.93 (t of t, 1H, J = 7.5 Hz, J = 1 Hz, ArH), 6.88 (m, 1H, ArH), 5.77 (br s, 1H, NH), 3.71 (s, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.69 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.6, 143.4, 141.7, 129.7, 121.3, 121.1, 118.2, 117.8, 116.5, 56.3, 36.3. HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{17}N_2$: 213.1386 Found: 213.1381.

Preparation of 3,5-Dimethyl-*N*-(3-((methylamino)methyl)-phenyl)aniline (4h). The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 uL, 0.50 mmol) and 3,5-Me-aniline (69 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM/MeOH/NH_4OH) and isolated as an off-white solid in 85% yield (102 mg, 0.43 mmol). ^1H NMR ($CDCl_3$): δ 7.23 (t, 1H, J = 7.5 Hz, ArH), 7.02−6.99 (m, 2H, ArH), 6.87 (d, 1H, J = 7.5 Hz, ArH), 6.72 (s, 2H, ArH), 6.62 (s, 1H, ArH), 5.74 (br s, 1H, NH), 3.72 (s, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.29 (s, 6H, CH_3), 2.07 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.8, 143.3, 141.4, 139.3, 129.6, 123.2, 120.8, 117.9, 116.5, 116.1, 56.1, 36.1, 21.7. HRMS (ESI/[M + H]$^+$) calcd for $C_{16}H_{21}N_2$: 241.1699 Found: 241.1700.

Preparation of 3-((Methylamino)methyl)-*N*-(3-(trifluoromethyl)phenyl)aniline (4i). The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 uL, 0.50 mmol) and 3-CF_3-aniline (68 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM/MeOH/NH_4OH) and isolated as an off-white solid in 67% yield (94 mg, 0.34 mmol). ^1H NMR ($CDCl_3$): δ 7.34 (t, 1H, J = 8 Hz, ArH), 7.28 (t, 2H, J = 8 Hz, ArH), 7.19 (m, 1H, ArH), 7.13 (d, 1H, J = 8 Hz, ArH), 7.07 (s, 1H, ArH), 7.04 (dd, 1H, J = 8 Hz, J = 1.5 Hz, ArH), 6.97 (d, 1H, J = 8 Hz, ArH), 5.95 (br s, 1H, NH), 3.74 (s, 2H, CH_2), 2.48 (s, 3H, CH_3), 2.02 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 144.3, 142.4, 141.8, 132.0 (quart., J_{CF} = 32.7 Hz), 130.2, 129.9, 124.4 (quart., J_{CF} = 276.8 Hz), 122.4, 120.2, 119.1, 117.7, 117.2 (m), 113.6 (m), 56.1, 36.2. HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{16}F_3N_2$: 281.1260, found 281.1258.

Preparation of N^1-Methyl-N^3-phenylbenzene-1,3-diamine (4j). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) and aniline (50 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as an orange oil in 94% yield (93 mg, 0.47 mmol). ^1H NMR ($CDCl_3$): δ 7.32−7.29 (m, 2H, ArH), 7.15−7.12 (m, 3H, ArH), 6.96 (t, 1H, J = 7 Hz, ArH), 6.50 (m, 1H, ArH), 6.39 (t, 1H, J = 2.5 Hz), 6.28 (m, 1H, ArH), 5.70 (br s, 1H, NH), 3.61 (br s, 1H, NH), 2.86 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.7, 144.5, 143.6, 130.3, 129.6, 121.0, 118.3, 107.6, 106.1, 101.9, 31.1. HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{15}N_2$: 199.1230, found 199.1225.

Preparation of N^1-(3,5-Dimethylphenyl)-N^3-methylbenzene-1,3-diamine (4k). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) and 3,5-Me-aniline (69 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 12 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM/MeOH/NH_4OH) and isolated as an orange oil in 95% yield (107 mg, 0.48 mmol). ^1H NMR ($CDCl_3$): δ 7.11 (t, 1H, J = 8 Hz, ArH), 6.75 (s, 2H, ArH), 6.61 (s, 1H, ArH), 6.47 (m, 1H, ArH), 6.36 (t, 1H, J = 2 Hz, ArH), 6.25 (m, 1H, ArH), 2.83 (s, 3H, CH_3), 2.30 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.6, 144.6, 143.5, 139.2, 130.3, 122.9, 116.1, 107.7, 105.9, 102.1, 31.1, 21.7. HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{19}N_2$: 227.1543, found 227.1541.

Preparation of N^1-Methyl-N^3-(3-(trifluoromethyl)phenyl)-benzene-1,3-diamine (4l). The general procedure was followed, with 3-chloro-*N*-methylaniline (61 uL, 0.50 mmol) and 3-CF_3-aniline (68 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (DCM − 1000:10:1 DCM/MeOH/NH_4OH) and isolated as a dark orange oil in 88% yield (118 mg, 0.44 mmol). ^1H NMR ($CDCl_3$): δ 7.33 (t, 1H, J = 8 Hz, ArH), 7.29 (s, 1H, ArH), 7.29 (dd, 1H, J = 8 Hz, J = 2 Hz, ArH), 7.14−7.10 (m, 2H, ArH), 6.47 (ddd, 1H, J = 8 Hz, J = 2 Hz, J = 1 Hz, ArH), 6.37 (t, 1H, J = 2 Hz, ArH), 6.31 (ddd, 1H, J = 8 Hz, J = 2 Hz, J = 1 Hz, ArH), 5.78 (br s, 1H, NH), 2.83 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.7, 144.5, 143.2, 131.9 (quart., J_{CF} = 32.7 Hz), 130.6, 130.1, 124.5 (quart., J_{CF} = 272.9 Hz), 120.3, 116.9 (m), 113.7 (m), 108.6, 107.5, 103.0, 31.1. HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{14}F_3N_2$: 267.1104, found 267.1120.

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Preparation of 4-(Phenylamino)benzamide (4m). The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) weighed out in the glovebox and aniline (50 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as an off-white solid in 66% yield (70 mg, 0.33 mmol). ^1H NMR (MeOD): δ 7.79−7.76 (m, 2H, ArH), 7.33−7.29 (m, 2H, ArH), 7.21−7.18 (m, 2H, ArH), 7.09−7.06 (m, 2H, ArH), 6.99 (t of t, 1H, J = 8 Hz, J = 1 Hz, ArH), 4.92 (br s, 3H, NH). $^{13}C\{^1H\}$ NMR (MeOD): δ 173.2, 150.4, 144.1, 131.3, 131.1, 125.2, 123.9, 121.5, 116.3. HRMS (ESI/$[M + Na]^+$) calcd for $C_{13}H_{12}N_2NaO$: 235.0842, found 235.0843.

Preparation of *N*-(4-(Phenylamino)phenyl)acetamide (4n)..[31] The general procedure was followed, with *N*-(4-chlorophenyl)-acetamide (84 mg, 0.50 mmol) weighed in the glovebox and aniline (50 uL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as an off-white solid in 94% yield (106 mg, 0.47 mmol). ^1H NMR ($CDCl_3$): δ 7.39−7.37 (m, 2H, ArH), 7.25−7.23 (m, 2H, ArH), 7.05−7.00 (m, 4H, ArH), 6.90 (t, 1H, J = 7.5 Hz, ArH), 5.67 (br s, 1H, NH), 2.16 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 168.5, 143.8, 139.9, 131.9, 129.7, 122.0, 121.0, 119.3, 117.5, 24.8. HRMS (ESI/$[M + Na]^+$) calcd for $C_{14}H_{14}N_2NaO$: 249.0998, found 249.1001.

Preparation of *N*-(4-Aminophenethyl)-4-methylaniline (5a). The general procedure was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) and 2-(4-aminophenyl)ethylamine (79 μL, 0.60 mmol) added via a microlitre syringe The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (4:3 hex/EtOAc) and isolated as a sticky, orange solid in 69% yield (78 mg, 0.35 mmol). ^1H NMR ($CDCl_3$): δ 7.05−7.00 (m, 4H, ArH), 6.68−6.65 (m, 2H, ArH), 6.58−6.55 (m, 2H, ArH), 3.56 (br s, 3H, NH), 3.34 (t, 2H, J = 7 Hz, CH_2), 2.82 (t, 2H, J = 7 Hz, CH_2), 2.27 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.2, 145.1, 130.0, 129.9, 129.5, 126.9, 115.7, 113.6, 45.9, 34.9, 20.7. HRMS (ESI/$[M + H]^+$) calcd for $C_{15}H_{19}N_2$: 227.1543, found 227.1525.

Preparation of 4-(2-Aminoethyl)-*N*-*p*-tolylaniline (5a′). The general procedure was followed, with *p*-Mor-DalPhos (**L2**) employed as the ligand (2 mol % Pd, 4 mol % **L2**), with 4-chlorotoluene (58 μL, 0.50 mmol) and 2-(4-aminophenyl)ethylamine (79 μL, 0.60 mmol) added via a microlitre syringe The reaction was allowed to proceed for 48 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (500:10:1 DCM/MeOH/NH_4OH) and isolated as an orange solid in 72% yield (81 mg, 0.36 mmol). ^1H NMR ($CDCl_3$): δ 7.08 (m, 4H, ArH), 6.98 (m, 4H, ArH), 5.69 (br s, 1H, NH) 2.94 (t, 2H, J = 7 Hz, CH_2), 2.69 (t, 2H, J = 7 Hz, CH_2), 2.31 (s, 3H, CH_3), 1.45 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 142.3, 141.0, 132.0, 130.7, 130.1, 129.9, 118.6, 117.7, 44.0, 39.5, 20.9. HRMS (ESI/$[M + H]^+$) calcd for $C_{15}H_{19}N_2$ 227.1543, found 227.1545.

Preparation of 4-Methyl-*N*-(piperidin-4-ylmethyl)aniline (5b). The general procedure was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) and 4-(aminomethyl)-piperidine (72 μL, 0.60 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the solid was washed with pentane (3 × 5 mL) and dried in vacuo to obtain the pure product as an off-white solid in 81% yield (83 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 6.99−6.97 (m, 2H, ArH), 6.53−6.51 (m, 2H, ArH), 3.59 (br s, 1H, NH), 3.09 (d of t, 2H, J = 12 Hz, J = 3 Hz, CH_2), 2.98 (d, 2H, J = 6.5 Hz, CH_2), 2.59 (d of t, 2H, J = 2 Hz, J = 2.5 Hz, CH_2), 2.23 (s, 3H, CH_3), 1.80−1.75 (m, 2H, CH_2), 1.70 (m, 1H, CH), 1.52 (br s, 1H, NH), 1.18 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.5, 130.0, 126.6, 113.1, 51.0, 46.8, 36.5, 32.0, 20.7. HRMS (ESI/$[M + H]^+$) calcd for $C_{13}H_{21}N_2$: 205.1699, found 205.1703.

Preparation of 4-Methyl-*N*-(4-(piperazin-1-yl)phenyl)aniline (5c). The general procedure was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) added via a microlitre syringe and *N*-(4-amino-phenyl)-piperazine (106 mg, 0.60 mmol) weighed out in the glovebox for convenience. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (9:1 DCM:MeOH) and isolated as an orange solid in 79% yield (105 mg, 0.40 mmol). ^1H NMR ($CDCl_3$): δ 7.05−6.99 (m, 4 H, ArH), 6.90−6.86 (m, 4H, ArH), 5.47 (br s, 1H, NH), 3.09−3.03 (m, 8H, CH_2), 2.28 (s, 3H, CH_3), 1.92 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.2, 142.5, 136.7, 130.0, 129.5, 120.7, 118.0, 116.9, 57.7, 46.5, 20.9. HRMS (ESI/$[M + H]^+$) calcd for $C_{17}H_{22}N_3$: 268.1808, found 268.1793.

Preparation of N^1-Phenyl-N^4-*p*-tolylbenzene-1,4-diamine (5d). The general procedure was followed, with 4-chlorotuluene (58 μL, 0.50 mmol) added via a microlitre syringe and *N*-phenyl-1,4-phenylene-diamine (111 mg, 0.60 mmol) weighed out in the glovebox for convenience. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (4:1 hex/EtOAc) and isolated as a pale orange solid in 90% yield (122 mg, 0.45 mmol). ^1H NMR ($CDCl_3$): δ 7.25 (t, 2H, J = 7.5 Hz, ArH), 7.09−6.94 (m, 10 H, ArH), 6.87 (t, 1 H, J = 7 Hz, ArH), 5.54 (br s, H, NH), 5.49 (br s, 1H, NH), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 145.1, 141.9, 138.6, 136.7, 130.2, 129.6, 121.7, 120.0, 117.7, 116.3, 20.9. HRMS (ESI/$[M]^+$) calcd for $C_{19}H_{18}N_2$: 274. 1465, found 274.1454.

Preparation of *N*,4-Dimethyl-*N*-(3-(phenylamino)benzyl)-aniline (5e). The general procedure was followed, with 4-chlorotoluene (58 μL, 0.5 mmol) added via a microlitre syringe and 3-((methylamino)methyl)-*N*-phenylaniline (111 mg, 0.53 mmol) weighed out in the glovebox for convenience. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (DCM) and isolated as a yellow solid in 60% yield (91 mg, 0.30 mmol). ^1H NMR ($CDCl_3$): δ 7.28−7.21 (m, 3 H, ArH), 7.08−7.03 (m, 4H, ArH), 6.99 (d of d, 1H, J = 8 Hz, J = 1.5 Hz, ArH), 6.96−6.93 (m, 2H, ArH), 6.83 (d, 1H, J = 8 Hz, ArH), 6.72−6.71 (m, 2H, ArH), 5.71 (br s, 1H, NH), 4.48 (s, 2H, CH_2), 3.01 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.0, 143.6, 143.3, 141.0, 130.0, 129.8, 129.6, 126.1, 121.2, 119.7, 118.0, 116.3, 116.1, 113.1, 57.3, 39.1, 20.6. HRMS (ESI/$[M + H]^+$) calcd for $C_{21}H_{23}N_2$: 303.1856, found 303.1849.

Preparation of N^1-Phenyl-N^2-p-tolylethane-1,2-diamine (5f). The general procedure was followed, with 4-chlorotoluene (58 μL, 0.5 mmol) and 4-(aminomethyl)-piperidine (72 μL, 0.60 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the resulting solid was washed with pentane (3 × 5 mL) and dried in vacuo to obtain the pure product as an off-white solid in 97% yield (110 mg, 0.49 mmol). ^1H NMR ($CDCl_3$): δ 7.22−7.18 (m, 2 H, ArH), 7.03−7.00 (m, 2 H, ArH), 6.73 (t of t, 1H, J = 7 Hz, J = 1 Hz, ArH), 6.67−6.65 (m, 2H, ArH), 6.61−6.58 (m, 2H, ArH), 3.39 (s, 4H, CH_2), 2.26 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.3, 146.1, 130.2, 129.7, 127.4, 118.1, 113.6, 113.4, 44.0, 43.7, 20.7. HRMS (ESI/$[M + H]^+$) calcd for $C_{15}H_{19}N_2$: 227.1543, found 227.1535.

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Preparation of N^1-Phenyl-N^2-*o*-tolylethane-1,2-diamine (5g). The general procedure was followed, with 2-chlorotoluene (58 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a brown solid in 93% yield (105 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.23−7.19 (m, 2H, ArH), 7.15 (m, 1H, ArH), 7.08 (d, 1H, *J* = 7 Hz, ArH), 6.76 (m, 1H, ArH), 6.72−6.68 (m, 4H, ArH), 3.98 (br s, 2H, NH), 3.46 (s, 4H, CH_2), 2.13 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.2, 146.1, 130.6, 129.7, 127.5, 122.9, 118.4, 117.4, 113.5, 110.4, 43.7, 43.6, 17.9. HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{19}N_2$: 227.1543, found 227.1539.

Preparation of N^1-(4-Methoxyphenyl)-N^2-phenylethane-1,2-diamine (5h). The general procedure was followed, with 4-chloroanisole (61 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (DCM) and isolated as a brown solid in 91% yield (110 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.24−7.20 (m, 2H, ArH), 6.84−6.81 (m, 2H, ArH), 6.76 (t, 1H, *J* = 7.5 Hz, ArH), 6.68−6.63 (m, 4H, ArH), 3.78 (s, 3H, CH_3), 3.40−3.34 (m, 4 H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 152.7, 148.4, 142.5, 129.6, 118.0, 115.2, 114.7, 113.3, 56.1, 44.6, 43.7. HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{19}N_2O$: 243.1492, found 243.1482.

Preparation of N^1-Phenyl-N^2-(4-(trifluoromethyl)phenyl)-ethane-1,2-diamine (5i). The general procedure was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of silica and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a yellow oil in 85% yield (119 mg, 0.42 mmol). ^{1}H NMR ($CDCl_3$): δ 7.43 (d, 2H, *J* = 8.5 Hz, ArH), 7.24−7.21 (m, 2H, ArH), 6.78 (t, 1H, *J* = 7 Hz, ArH), 6.69−6.64 (m, 4H, ArH), 4.25 (br s, 1H, NH), 3.79 (br s, 1H, NH), 3.43 (s, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 148.1, 129.8, 127.0, 125.2 (quart., J_{C-F} = 270.5 Hz), 119.2 (quart., J_{C-F} = 32.7 Hz), 118.4, 113.4, 112.4, 43.4, 43.1. HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{16}F_3N_2$: 281.1260, found 281.1266.

Preparation of N^1-Phenyl-N^2-(4-(prop-1-en-2-yl)phenyl)-ethane-1,2-diamine (5j). The general procedure was followed, with 4-chloro-α-methylstyrene (60 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of silica and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a brown solid in 94% yield (119 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, *J* = 8.5 Hz, ArH), 7.27 (t, 2H, *J* = 8 Hz, ArH), 6.82 (t, 1H, *J* = 7 Hz, ArH), 6.69 (m, 4H, ArH), 5.35 (s, 1H, CH), 5.01 (s, 1H, CH), 3.95−3.88 (m, NH), 3.42 (s, 4H, CH_2), 2.19 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.2, 147.7, 142.9, 130.9, 129.6, 126.8, 118.1, 113.3, 112.9, 109.4, 43.5, 43.3, 22.1. HRMS (ESI/[M + H]$^+$) calcd for $C_{17}H_{21}N_2$: 253.1699, found 253.1688.

Preparation of N^1-Phenyl-N^2-(pyridin-2-yl)ethane-1,2-diamine (5k). The general procedure was followed, with 2-chloropyridine (47 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a yellow oil 91% yield (97 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 8.11 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.21−7.16 (m, 2H, ArH), 6.72 (m, 1H, ArH), 6.63 (m, 2H, ArH), 6.59 (m, 1H, ArH), 6.40 (m, 1H, ArH), 4.76 (br s, 1H, NH), 4.17 (br s, 1H, NH), 3.59 (t, 2 H, *J* = 6 Hz, CH_2), 3.38 (t, 2H, *J* = 6 Hz, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 159.0, 148.4, 148.3, 137.7, 129.6, 117.8, 113.5, 113.2, 107.9, 44.2, 41.6. HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{16}N_3$: 214.1339, found 214.1342.

Preparation of N^1-(6-Methylpyridin-2-yl)-N^2-phenylethane-1,2-diamine (5l).[32] The general procedure was followed, with 2-chloro-6-methylpyridine (56 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a dark yellow oil in 94% yield (106 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.33 (t, 1H, *J* = 7 Hz, ArH), 7.22−7.18 (m, 2H, ArH), 6.73 (m, 1H, ArH), 6.65−6.63 (m, 2H, ArH), 6.49 (d, 1H, *J* = 7.5 Hz), 6.22 (d, 1H, *J* = 8 Hz, ArH), 4.77 (br s, 1H, NH), 4.38 (br s, 1H, NH), 3.55 (m, 2H, CH_2), 3.36 (m, 2H, CH_2), 2.43 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 158.7, 157.1, 148.4, 138.1, 129.5, 117.6, 113.1, 112.7, 104.0, 44.4, 41.7, 24.6. HRMS (ESI/[M + H]$^+$) calcd for $C_{14}H_{18}N_3$: 228.1495, found 228.1487.

Preparation of N^1-Phenyl-N^2-(pyridin-3-yl)ethane-1,2-diamine (5m). The general procedure was followed, with 3-chloropyridine (47 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as a dark yellow oil in 93% yield (99 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 1H, J = 8 Hz, ArH), 7.97 (dd, 1H, *J* = 4.5 Hz, *J* = 1 Hz, ArH), 7.22−7.18 (m, 2H, ArH), 7.08 (ddd, 1H, *J* = 8 Hz, *J* = 4.5 Hz, *J* = 0.5 Hz, ArH), 6.90 (ddd, 1H, *J* = 8.5 Hz, *J* = 3 Hz, *J* = 1.5 Hz, ArH), 6.75 (m, 1H, ArH), 6.67−6.64 (m, 2H, ArH), 4.09 (br s, 1H, NH), 3.42−3.38 (m, 4 H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.1, 144.4, 139.3, 136.4, 129.7, 124.1, 119.1, 118.3, 113.3, 43.4, 43.13. HRMS (ESI/[M + H]$^+$) calcd for $C_{13}H_{16}N_3$: 214.1339, found 214.1338.

Preparation of N^1-Phenyl-N^2-(pyrazin-2-yl)ethane-1,2-diamine (5n). The general procedure was followed, with 2-chloropyrazine (45 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as a yellow oil in 89% yield (96 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 1H, ArH), 7.85 (s, 1H, ArH), 7.79 (d, 1H, *J* = 2.5 Hz, ArH), 7.18 (t, 2H, *J* = 2.5 Hz, ArH), 6.72 (t, 1H, *J* = 8.5 Hz, ArH), 6.62 (d, 2H, *J* = 7.5 Hz, ArH), 5.09 (br s, 1H, NH), 4.07 (br s, 1H, NH), 3.60 (m, 2H, CH_2), 3.38 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 154.9, 148.2, 142.0, 133.0, 129.6, 117.9, 113.1, 43.8, 40.9. HRMS (ESI/[M + H]$^+$) calcd for $C_{12}H_{15}N_4$: 215.1291, found 215.1294.

Preparation of 4-(2-(Phenylamino)ethylamino)benzamide (5o). The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 40 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Removal of the solvent afforded the product as a white solid in 78% yield (100 mg, 0.39 mmol). ^{1}H NMR (MeOD): δ 7.72−7.70 (m, 2H, ArH), 7.16−7.12 (m, 2H, ArH), 6.71−6.66 (m, 5H, ArH), 4.92 (br s, NH), 3.41−3.35 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (MeOD): δ 173.7, 154.5, 150.8, 131.4, 130.9, 122.3, 119.1, 114.9, 113.2, 44.8, 44.2. HRMS (ESI/[M + H]$^+$) calcd for $C_{15}H_{18}N_3O$: 256.1444, found 256.1440.

Preparation of Methyl 4-(2-(Phenylamino)ethylamino)-benzoate (5p). The general procedure was followed, methyl 4-chlorobenzoate (85 mg, 0.50 mmol) weighed out in the glovebox and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the

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mixture, the product was purified using column chromatography on silica (200:10:1 DCM/MeOH/NH_4OH) and isolated as a brown oil in 76% yield (103 mg, 0.38 mmol). ^1H NMR ($CDCl_3$): δ 7.87 (d, 2H, J = 9 Hz, ArH), 7.22−7.16 (m, 2H, ArH), 6.76 (t, 1H, J = 7 Hz, ArH), 6.65 (d, 2H, J = 8 Hz), 6.58 (d, 2H, J = 8.5 Hz), 3.85 (s, 3H, CH_3), 3.45−3.42 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 167.6, 152.1, 148.1, 131.9, 129.7, 119.1, 118.4, 113.4, 112.0, 51.9, 43.4, 43.0. HRMS (ESI/$[M + H]^+$) calcd for $C_{16}H_{19}N_2O_2$: 271.1441, found 271.1451.

Synthesis of 7. To a vial containing a magnetic stir bar and (Mor-DalPhos)Pd(*p*-tolyl)Cl (174 mg, 0.25 mmol) in $CDCl_3$ (2 mL) were added 4-(2-aminoethyl)aniline (66 μL, 0.50 mmol) and AgOTf (192 mg, 0.275 mmol). The reaction mixture was stirred magnetically for 2 h at room temperature, over which time a white precipitate formed. ^{31}P NMR analysis of the crude reaction mixture indicated complete conversion of starting material to a single phosphorus-containing product. The reaction mixture was filtered through Celite, and the solvent removed under reduced pressure to afford **7** as an analytically pure brown solid (0.171 g, 0.181 mmol, 72%). Anal. Calcd for $C_{46}H_{61}F_3N_3O_4P_1S_1Pd_1$: C 58.36; H 6.50; N 4.44. Found: C 58.17; H 6.34; N 4.29. Crystals suitable for X-ray diffraction were grown by vapor diffusion of diethyl ether into a concentrated solution of **7** in CH_2Cl_2 at −30 °C. ^1H NMR ($CDCl_3$): δ 8.07 (dd, 1H, J = 8 Hz, J = 3 Hz, ArH), 7.81 (t, 1H, J = 6.5 Hz, ArH), 7.67 (t, 1H, J = 8 Hz, ArH), 7.45−7.41 (m, 3H, ArH), 6.89 (d, 2H, J = 7.5 Hz, ArH), 6.85 (d, 2H, J = 7.5 Hz, ArH), 6.59 (d, 2H, J = 8 Hz, ArH), 4.07−3.96 (m, 4H, CH_2), 3.82−3.79 (m, 2H, CH_2), 3.66 (br s, 2H, CH_2 or NH_2), 3.18−3.15 (m, 2H, CH_2), 3.05 (br s, 2H, CH_2 or NH_2), 2.54 (br s, 4H, CH_2 and/or NH_2), 2.27 (s, 3H, CH_3), 2.21 (m, 6H, Ad), 1.92 (m, 12H, Ad), 1.67 (s, 12H, Ad). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.2 (m, ArC), 145.4 (ArC), 139.7 (ArC), 137.5 (ArC), 136.3 (ArC), 133.8 (ArC), 130.0 (ArC), 128.9 (ArC), 127.3 (d, J_{PC} = 7.5 Hz, ArC), 126.9 (ArC), 126.2 (ArC), 126.0 (ArC), 119.9 (ArC), 115.9 (ArC), 62.0 (morpholino), 55.6 (morpholino), 44.6 (CH_2), 43.4 (d, J_{PC} = 15 Hz, Ad), 41.0 (Ad), 37.4 (CH_2), 36.4 (Ad), 28.7 (d, J_{PC} = 10 Hz, Ad), 21.0 (CH_3). ^{31}P NMR ($CDCl_3$): δ 62.3.

Synthesis of 8. A protocol similar to that used for the synthesis of **7** was employed, using (Mor-DalPhos)Pd(*p*-tolyl)Cl (100 mg, 0.14 mmol), $CDCl_3$ (3 mL), octylamine (48 μL, 0.29 mmol) and AgOTf (41 mg, 0.16 mmol). ^{31}P NMR analysis of the crude reaction mixture indicated complete conversion of **6** to **8**. The reaction mixture was filtered through Celite and the solvent removed under reduced pressure, followed by trituration of the resulting solid with pentane (3 × 2 mL) and diethyl ether (3 × 2 mL). The remaining material was dried in vacuo to afford **8** as an analytically pure brown solid (0.089 g, 0.095 mmol, 66%). Anal. Calcd for $C_{46}H_{68}F_3N_2O_4P_1S_1Pd_1$: C 58.81; H 7.30; N 2.98. Found: C 59.06; H 7.22; N 2.95. ^1H NMR ($CDCl_3$): δ 8.12 (dd, 1H, J = 8 Hz, J = 3 Hz, ArH), 7.83 (t, 1H, J = 6.5 Hz, ArH), 7.70 (t, 1H, J = 8 Hz, ArH), 7.47−7.42 (m, 3H, ArH), 6.90 (d, 2H, J = 7.5 Hz, ArH), 4.27−4.24 (m, 2H, CH_2), 4.13−4.07 (m, 4H, CH_2), 3.24 (m, 2H, CH_2), 3.06 (br s, 2H, octylamine), 2.34 (br s, 2H, octylamine), 2.25−2.22 (m, 9H, CH_3 and Ad), 1.99−1.94 (m, 12H, Ad), 1.68 (m, 12 H, Ad), 1.38−1.03 (m, 15H, octylamine). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 162.2 (ArC), 140.0 (ArC), 137.5 (ArC), 136.4 (ArC), 133.8 (d, J_{PC} = 7.5 Hz, ArC), 129.4 (d, J_{PC} = 13.8 Hz, ArC), 129.0 (ArC), 127.1 (m, ArC), 126.2 (d, J_{PC} = 28.9 Hz, ArC), 62.5 (morpholino), 55.9 (morpholino), 43.5 (d, J_{PC} = 15.1 Hz, Ad), 43.2 (CH_2), 41.0 (Ad), 36.4 (Ad), 32.4 (CH_2), 32.1 (CH_2), 29.4−29.3 (m, CH_2), 28.8 (d, J_{PC} = 10.1 Hz, Ad), 26.6 (CH_2), 22.9 (CH_2), 21.0 (CH_3), 14.4 (CH_3). ^{31}P NMR ($CDCl_3$): δ 62.2.

Synthesis of 9. A protocol directly analogous to that used for the synthesis of **8** was employed, using aniline (26 μL, 0.29 mmol) in place of octylamine. ^{31}P NMR analysis of the crude reaction mixture indicated complete conversion of **6** to **9**, and **9** was obtained as an analytically pure brown solid (0.083 g, 0.092 mmol, 64%). Anal. Calcd for $C_{44}H_{56}F_3N_2O_4P_1S_1Pd_1$: C 58.50; H 6.20; N 3.10. Found: C 58.54; H 6.17; N 3.02. ^1H NMR ($CDCl_3$): δ 8.20 (m, 1H, ArH), 7.83 (t, 1H, J = 7 Hz, ArH), 7.64 (t, 1H, J = 7.5 Hz), 7.44−7.39 (m, 4H, ArH), 7.15 (t, 1H, J = 8 Hz, ArH), 6.82 (d, 2H, J = 8 Hz, ArH), 6.77 (t, 1H, J = 7 Hz, ArH), 6.70 (d, 2H, J = 15 Hz, ArH), 5.01 (br s, 2H, NH_2), 4.06−3.99 (m, 4H, morpholino), 3.74 (br s, 2H, morpholino), 2.98 (br s, 2H, morpholino), 2.29−2.28 (m, 6 H, Ad), 2.22 (s, 3H, CH_3), 1.99−1.69 (m, 24 H, Ad). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.6 (ArC), 136.4 (ArC), 132.9 (ArC), 129.6 (ArC), 128.7 (ArC), 128.0 (ArC), 126.3 (ArC), 119.1 (ArC), 115.8 (ArC), 62.1 (morpholino), 55.2 (morpholino), 43.6 (d, J_{PC} = 16.4 Hz, Ad), 40.9 (Ad), 36.5 (Ad), 28.9 (d, J_{PC} = 10.1 Hz, Ad), 21.1 (CH_3). ^{31}P NMR ($CDCl_3$): δ 59.8.

Crystallographic Solution and Refinement Details for L2 and 7·CH_2Cl_2. Crystallographic data were obtained at 173(±2) K on a diffractometer using a graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation, employing a sample that was mounted in inert oil and transferred to a cold gas stream on the diffractometer. Gaussian integration (face-indexed) was employed as the absorption correction method. The structure of **L2** was solved by use of direct methods, while the structure of 7·CH_2Cl_2 was solved by use of a Patterson search/structure expansion. The structures were refined by use of full-matrix least-squares procedures (on F^2) with R_1 based on $F_o^2 \geq 2\sigma(F_o^2)$ and wR_2 based on $F_o^2 \geq -3\sigma(F_o^2)$. Anisotropic displacement parameters were employed for all the non-hydrogen atoms. Disorder involving the two CH_2−O carbon atoms as well as the nitrogen atom in **L2** was identified during the solution process; these atoms were each refined anisotropically over two positions employing an occupancy factor of 0.5. During the structure solution process for 7·CH_2Cl_2, one equivalent of dichloromethane was located in the asymmetric unit and refined anisotropically. Furthermore, disorder involving one of the adamantyl substituents was identified during the solution process for 7·CH_2Cl_2; these atoms were each refined anisotropically over two positions employing an occupancy factor ratio of 0.4:0.6. During the refinement, the P−C21A and P−C21B distances were constrained to be equal (within 0.03 Å), and the C21A−C22A, C21A−C26A, C21A−C27A, C21B−C22B, C21B−C26B, and C21B−C27B distances were constrained to be equal (within 0.03 Å) to a common refined value. For simplicity, only the major disorder components of **L2** and 7·CH_2Cl_2 are depicted and discussed in the text. All hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters based on the isotropic displacement parameter of the attached atom. Additional crystallographic information is provided in the Supporting Information, including the accompanying CIF file.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data (tabulated as well as in CIF format) and ^1H and ^{13}C NMR spectra of the cross-coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) See the Supporting Information for tabulated crystallographic solution and refinement data.
(19) Negligible changes in chemoselectivity were observed under analogous conditions on lowering the reaction temperature to 65 °C (using 1 mol % Pd) for selected representative entries (1, 3, and 13) featured in Table 1.
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(21) This assumes that the rate of amine exchange involving LPd(Ar)(NR_2) and HNR'_2 to give LPd(Ar)(NR'_2) and HNR_2 is slow relative to the rate of C–N reductive elimination.
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(23) (a) In monitoring by use of GC methods the time-dependent monoarylation of 2-(4-aminophenyl)ethylamine with 4-chlorotoluene employing $[Pd(cinnamyl)Cl]_2$/**L** (**L** = **L1** or **L2**) catalyst mixtures, clean monoarylation to afford **5a** (for **L1**) or **5a′** (for **L2**) is observed below 50% conversion, after which diarylation (not the formation of the alternative monoarylation regioisomer) becomes competitive. (b) Selectivity for an analogue of **5a′** (analogous to that achieved with **L2**) was observed by Buchwald and co-workers[11a] when employing Pd_2dba_3/Cy-XPhos catalyst mixtures in combination with bromo-3,5-dimethylbenzene (2 mol% Pd, 5 mol% Cy-XPhos, 87%).
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