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Efficient palladium-catalyzed synthesis of substituted indoles employing a new (silanyloxyphenyl)phosphine ligand†

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The new and easily prepared OTips-DalPhos ligand (L1) offers broad substrate scope at relatively low loadings in the palladium-catalyzed C–N cross-coupling/cyclization of *o*-alkynylhalo(hetero)arenes with primary amines, affording indoles and related heterocyclic derivatives in high yield.

In addition to being among the most ubiquitous heterocycles in nature, the indole framework represents a privileged sub-structure in the design of pharmaceutical agents, owing to the ability of such derivatives to bind to a diversity of receptors with high affinity.[1] Despite the numerous "classical" methods of preparing indoles, the need for efficient synthetic protocols that enable the selective assembly of functionalized indoles under relatively mild conditions has inspired the examination of metal-catalyzed methodologies, most notably those employing palladium.[2] The application of palladium catalysis has revolutionized indole synthesis, and several novel disconnection strategies have been established, including (but not restricted to) those starting from *o*-alkynylanilines or *o*-haloanilines, and their derivatives.[2] A complementary yet less well-explored pathway to the indole core structure involving palladium-catalyzed amine arylation using *ortho*-alkynylhaloarene synthons (pre-formed or prepared *in situ*), followed by base-mediated cyclization of the resultant 2-aminophenylacetylene,[3] was pioneered by Ackermann.[4] This modular C–N cross-coupling/cyclization cascade is conceptually attractive in terms of diversifying the indole framework, in that substituted alkynyl moieties can be installed easily by use of Sonogashira coupling protocols, and the substitution at nitrogen can be varied by the choice of primary amine coupling partner. Following a brief catalyst optimization campaign, Ackermann and co-workers[4] identified $Pd(OAc)_2$/IPr·HCl (5 mol% each; IPr·HCl = 1,3-bis(2,6-di-isopropylphenyl)imidazolium chloride; 105–120 °C) as being optimal when using *o*-alkynylhaloarenes in combination with a range of primary amine reagents. However, some limitations exist with regard to the demonstrated substrate scope in these[4] and some closely related[5] reports; neither the successful utilization of challenging substrates such as methylamine[6] nor synthons featuring heterocycles attached to the alkynyl terminus was documented,[7] and the use of *o*-alkynylhalo(hetero)arene substrates is limited to two examples from the Ackermann group,[4d] in which 4-azaindoles are formed using sterically demanding amine reaction partners.

As part of our ongoing research efforts directed toward the design and application of modular ancillary ligands for use in metal-catalyzed transformations,[8] we became interested in utilizing such synthetically useful cascade C–N cross-coupling/cyclization processes as a challenging testing ground for new ligand design. In particular, we became interested in identifying a catalyst system that could offer broad scope in such transformations in accommodating both large and small amine coupling partners, as well as a diversity of *o*-alkynylhalo(hetero)arene substrates including those featuring heterocyclic functionality, at relatively low catalyst loading (< 5 mol% Pd/L). We report herein on the new and easily prepared DalPhos[8b] ligand variant, OTips-DalPhos (**L1**), which exhibits this desired reactivity profile.

Encouraged by the utility in palladium-catalyzed C–N and C–C cross-coupling chemistry of our Mor-DalPhos ligand,[6f,8b,9] which features an *ortho*-di(1-adamantyl)phosphino ($P(1\text{-Ad})_2$) group appended to an *N*-phenylmorpholine core, we sought to develop DalPhos variants featuring alternative heteroatom pairings, including phosphorus and oxygen.[10] In seeking modular and expedient synthetic protocols, the silylation of phenols was particularly attractive given the ease of Si–O bond formation, the commercial availability of structurally diverse R_3SiCl synthons, and the well-documented chemical behaviour of aryl silylethers. Our initial explorations have focussed on the triisopropylsilyl derivative, owing to the anticipated stability of the Ar-O–Si(*i*Pr)$_3$ motif. Treatment of *ortho*-bromophenol with iPr_3SiCl in the presence of imidazole afforded the known triisopropylsilyl ether, which was converted to **L1** *via* palladium-catalyzed P–C bond formation employing $(1\text{-Ad})_2PH$ in 77% overall yield (Scheme 1†). In contrast to related dialkylarylphosphines featuring small *ortho*-alkyl ether substituents,[11] only a single rotamer of **L1** is observable in solution (^1H, ^{13}C, and ^{31}P NMR). Presumably this rotamer corresponds to the solid state structure (Fig. 1†), where the triisopropylsilyl moiety is distal to the adamantyl groups.[12] This orientation would appear to

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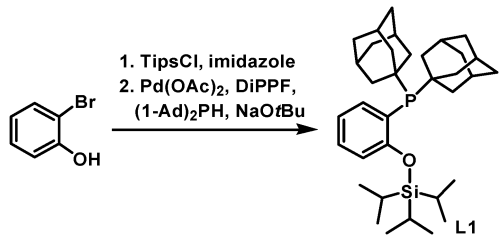

Scheme 1 Synthesis of OTips-DalPhos (**L1**).

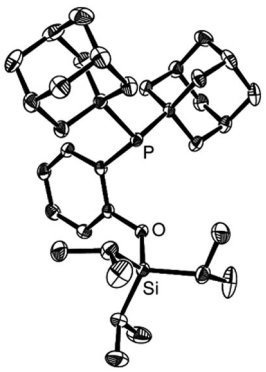

Fig. 1 ORTEP diagram for **L1** shown with 50% ellipsoids and with hydrogen atoms omitted for clarity. Selected interatomic distances (Å): P-Caryl, 1.8460(13); O-Caryl, 1.3726(16); Si–O, 1.6716(10).

enable the binding of both phosphorus and oxygen to palladium as needed during catalysis.

In a preliminary effort to assess the ability of Pd/**L1** (2.5 mol% each) catalyst mixtures to furnish indoles *via* C–N cross-coupling/cyclization processes, the reaction of 1-bromo-2-(phenylethynyl)-benzene with structurally diverse primary amines was surveyed (Fig. 2).[13] Our choice of palladium precursor was based on the success of the [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos catalyst system,[9] and for comparison parallel reactions were conducted with the *para*-isomer of OTips-DalPhos (**L1′**), as well as DavePhos (**L2**), IPr (**L3**) and Mor-DalPhos (**L4**). These comparator ligands were selected in order to explore both the influence of the ligand connectivity (**L1** *vs.* **L1′**) and choice of *ortho*-heteroatomic fragment (**L1** *vs.* **L4**[9]), as well as to benchmark the observed catalytic performance of **L1** against prominent ligands that

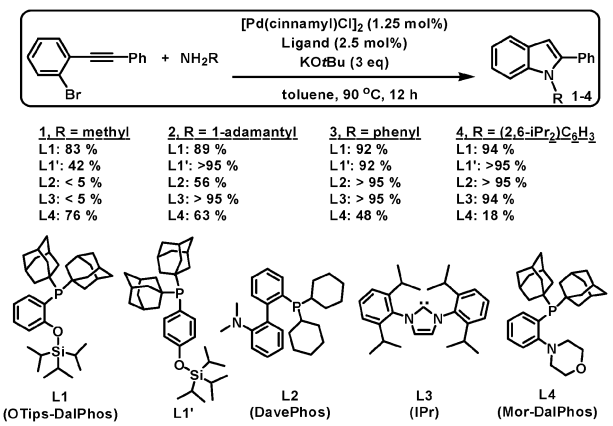

Fig. 2 Ligand screen for the Pd-catalyzed synthesis of 2-phenylindoles from 1-bromo-2-(phenylethynyl)benzene. Isolated yield for **L1**, otherwise yields are given on the basis of calibrated GC data (see ESI†).

have proven useful in the synthesis and functionalization of indoles (**L2**[14] and **L3**[4]). Among the ligands surveyed, only **L1** afforded each of the four target indoles (**1–4**) in high yield under the test conditions employed. The use of $MeNH_2$ served to differentiate **L1** from each of **L1′**, **L2** and **L3** (in addition to the poor performance of **L2** with 1-AdNH_2). In contrast, while **L4** performed reasonably well in combination with $MeNH_2$ (76%), the yields obtained with the other substrates (18–63%) were markedly inferior to those obtained using **L1**.

Having established **L1** as an effective ligand for the desired C–N cross-coupling/cyclization processes, the scope in the amine and *o*-alkynylhalo(hetero)arene reaction partners was explored further (Fig. 3). In building upon the results featured in Fig. 2, 1-bromo-2-(phenylethynyl)benzene, as well as the chloro derivative,

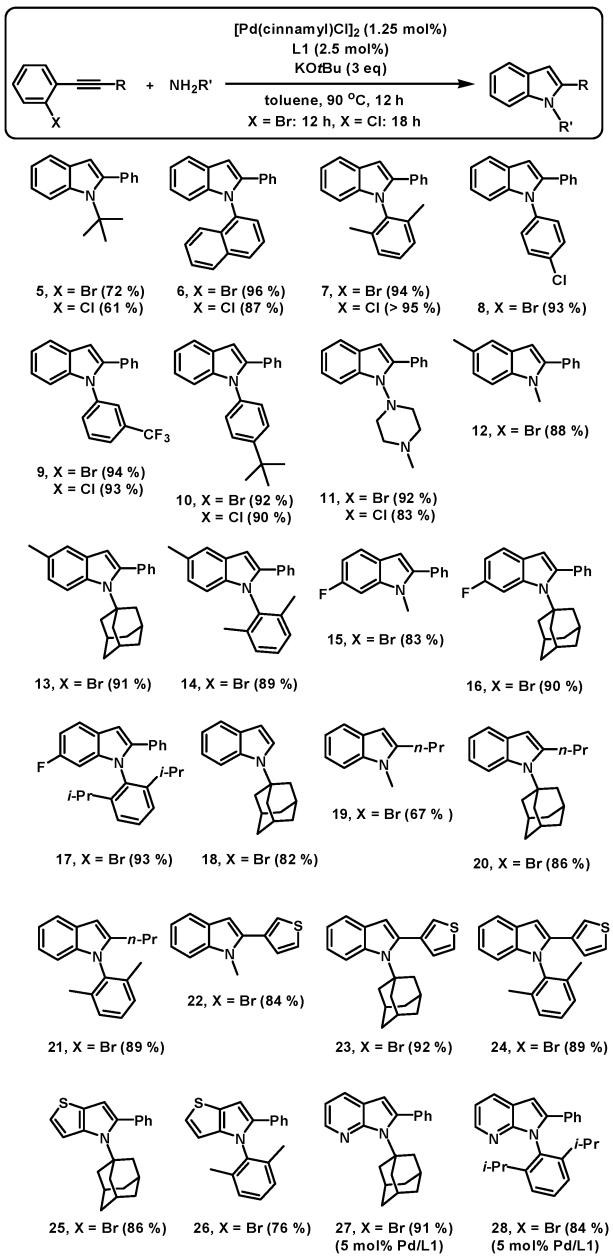

Fig. 3 Scope of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyzed cross-coupling of primary amines with 2-alkynylhaloarenes. Isolated yields for X = Br; for X = Cl, yield determined on the basis of calibrated GC data (see ESI†).

proved to be suitable substrates in combination with a range of amine coupling partners, providing the target indoles derived from tBuNH$_2$ (**5**), various hindered and unhindered aryl amines including those featuring electron-donating and electron-withdrawing substituents (**6–10**), and for the first time, *N*-methylpiperazine (**11**) in 61–96% yield. The use of a methylated variant of 1-bromo-2-(phenylethynyl)benzene was also tolerated, affording the corresponding indoles derived from MeNH$_2$ (88%, **12**), 1-AdNH$_2$ (91%, **13**), and (2,6-Me$_2$C$_6$H$_3$)NH$_2$ (89%, **14**) in high isolated yield. A fluorine-containing *o*-alkynylbromoarene substrate also worked well with the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system, enabling the isolation of indoles derived from MeNH$_2$ (83%, **15**), 1-AdNH$_2$ (90%, **16**), and DippNH$_2$ (Dipp = (2,6-iPr$_2$)C$_6$H$_3$; 93%, **17**) in excellent yield.

The use of *o*-alkynylbromoarene substrates featuring substitution on the alkynyl terminus other than phenyl was also successful. In the case of the reaction of 1-bromo-2-(trimethylsilylethynyl)-benzene with 1-AdNH$_2$, concurrent desilylation was observed, thereby providing access to the corresponding parent indole featuring a hydrogen at the C2 position (**18**, 82%). Alternatively, the use of 1-bromo-2-(propylethynyl)benzene afforded cleanly the corresponding indoles derived from MeNH$_2$ (67%, **19**), 1-AdNH$_2$ (86%, **20**), and (2,6-Me$_2$C$_6$H$_3$)NH$_2$ (89%, **21**).

Having succeeded in applying the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system to the synthesis of indoles featuring primarily hydrocarbon substituents, we turned our attention to substrates featuring heterocyclic moieties. Despite the relevance of hetero-functionalized indoles in medicinal chemistry, scant attention has been paid thus far to the synthesis of such species *via* palladium-catalyzed C–N cross-coupling/cyclization protocols. Gratifyingly, the incorporation of a thiophen-3-yl fragment onto the alkynyl terminus was well tolerated, affording *N*-substituted indoles featuring a C2-thiophen-3-yl substituent (84–92%, **22–24**). Furthermore, the synthesis of thienopyrroles and 7-azaindoles was achieved for the first time by use of palladium-catalyzed C–N cross-coupling/cyclization methods, thereby enabling the isolation of these ring-fused polyheterocyclic compounds in high yield (76–91%, **25–28**).

In summary, the catalytic utility of the new and easily prepared DalPhos ligand variant, OTips-DalPhos (**L1**) was established through an investigation of the palladium-catalyzed cascade C–N cross-coupling/cyclization of *o*-alkynylhalo(hetero)arene substrates with primary amines. At relatively low loadings, the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system offers remarkably broad scope in the amine reaction partner, enabling the use of small (*e.g.* MeNH$_2$) and large (*e.g.* 1-AdNH$_2$) alkylamines, various hindered and unhindered aryl amines including those featuring electron-donating and electron-withdrawing substituents, as well as *N*-methylpiperazine. Significant structural variation within the *o*-alkynylhalo(hetero)arene substrates was also well-tolerated, leading to indoles featuring alkyl, aryl, and heteroaryl substitution at the C2 position, as well as to substituted thienopyrroles and 7-azaindoles. To the best of our knowledge, this represents the most extensive and varied substrate scope to be demonstrated thus far in the literature for this class of transformations (11 amines, 8 *o*-alkynylhalo(hetero)arenes, 28 examples in total). Encouraged by the desirable performance of **L1** in this catalytic application, we are currently probing the applicability of **L1** and related ligands more broadly in addressing challenges in metal-catalyzed chemical synthesis. We will report on the results of these studies in due course.

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