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

Christopher B. Lavery,^a Robert McDonald^b and Mark Stradiotto^{*a}

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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 basemediated cyclization of the resultant 2-aminophenylacetylene,³ was pioneered by Ackermann.4 This modular C-N crosscoupling/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-workers⁴ identified Pd(OAc)₂/IPr·HCl (5 mol% each; IPr·HCl = 1,3bis(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 these⁴ and some closely related⁵ reports; neither the successful utilization of challenging substrates such as methylamine⁶ 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 crosscoupling/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,6,8b,9 which features an ortho-di(1-adamantyl)phosphino (P(1-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 silvlation of phenols was particularly attractive given the ease of Si-O bond formation. the commercial availability of structurally diverse R₃SiCl synthons, and the well-documented chemical behaviour of aryl silvlethers. Our initial explorations have focussed on the triisopropylsilyl derivative, owing to the anticipated stability of the Ar-O-Si(iPr)3 motif. Treatment of ortho-bromophenol with *i*Pr₃SiCl in the presence of imidazole afforded the known triisopropylsilyl ether, which was converted to L1 via palladiumcatalyzed P-C bond formation employing (1-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, ¹³C, and ³¹P 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

^a Department of Chemistry, Dalhousie University, 6274 Coburg Road, P.O. Box 15000, Halifax, Nova Scotia, Canada B3H 4R2. E-mail: mark.stradiotto@dal.ca; Fax: 1 902 494 1310;

Tel: 1 902 494 7190

^b X-Ray Crystallography Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

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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.* L4⁹), 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 MeNH₂ served to differentiate L1 from each of L1', L2 and L3 (in addition to the poor performance of L2 with 1-AdNH₂). In contrast, while L4 performed reasonably well in combination with MeNH₂ (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 *t*BuNH₂ (**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 MeNH₂ (88%, **12**), 1-AdNH₂ (91%, **13**), and (2,6-Me₂C₆H₃)NH₂ (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 MeNH₂ (83%, **15**), 1-AdNH₂ (90%, **16**), and DippNH₂ (Dipp = (2,6-*i*Pr₂)C₆H₃; 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-AdNH₂, 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 MeNH₂ (67%, **19**), 1-AdNH₂ (86%, **20**), and (2,6-Me₂C₆H₃)NH₂ (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.* MeNH₂) and large (*e.g.* 1-AdNH₂) 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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