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Design and Synthesis of Dialkylarylphosphine Urea Ligands and their Application in Palladium-Catalyzed Cross-Coupling Reactions

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Abstract

We describe herein the design and synthesis of a new class of dialkylarylphosphine ligands incorporating a Lewis-basic urea subunit. The ligand synthesis consisted of six linear steps and was enabled by the discovery of a new N-to-N alkyl migration reaction. This new series of dialkylarylphosphine urea ligands were applied in common palladium-catalyzed cross-coupling reactions for the formation of carbon-carbon and carbon-nitrogen bonds in moderate to high yields.

Keywords

dialkylarylphosphine; urea; palladium-catalyzed cross-coupling; N-to-N alkyl migration

Introduction

Metal-catalyzed cross-coupling reactions stand as one of the most powerful and practical reactions in the 21st century for carbon-carbon and carbon-heteroatom bond formation.[1–3] Among the many factors that have contributed to the widespread inclusion of metal-catalyzed cross-coupling reactions, the development of sophisticated phosphine ligands has played an essential role.[4] While traditional ligand scaffolds, such as triphenylphosphine, have been effective for the construction of general biaryl compounds, the construction

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Dedicated to Prof. *Scott E. Denmark* on the occasion of his 70th birthday

Conflict of Interest

The authors declare the following competing financial interest(s): The authors declare that they have filed a provisional patent on the design and synthesis of the dialkylarylphosphine urea ligands.

Supporting Information

The authors have cited additional references within the Supporting Information.[18–26] Deposition Numbers 2295144 (for **1**), 2295128 (for **2**), 2295129 (for **3**), 2295130 (for **4**), 2295134 (for **5**), 2295135 (for **6**), 2294848 (for **L1**), 2295136 (for **L2**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformations-zentrum Karlsruhe Access Structures service.

Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.202300244

of structurally complex ligands has enabled the preparation of highly functionalized lead compounds that would otherwise be difficult to access without the use of refined ligands (Figure 1A).[5,6] As such, the improvement and optimization of ligands continue to be of great importance to medicinal and process chemistry.

During the past few decades, the design and modification of ligand structural features has unearthed several classes of exemplary ligand platforms (*e.g.* Biaryl monophosphine[7] and JosiPhos[8] ligand series) that possess the unique ability to both stabilize catalytic intermediates and offer high reactivities – a required feature to obtain high yields under catalytic conditions (Figure 1B). Furthermore, due to the ease of structural variability the aforementioned ligand scaffolds can be easily tuned to promote the desired selectivity and reactivity of specific substrate classes *via* primary and/or secondary ligand interactions.[9,10] In this regard the incorporation of Lewis basic subunits has shown to play an essential role in achieving high reactivities, chemo- and enantio-selectivities[11,12] by directing the substrate to the metal center (Figure 1B). The growing understanding of the benefits associated with ligand structural modifications inspired us to develop and explore the catalytic efficiency of phosphine ligands incorporating urea functional groups within their framework (Figure 1C). Herein, we describe the development of dialkylarylphosphine urea ligands **L1** and **L2**, which were found to undergo Suzuki–Miyaura, Stille–Migita, Negishi, as well as Buchwald–Hartwig reactions. In addition, by employing a new N-to-N alkyl migration reaction a robust synthetic route was established to access this ligand class from readily available starting materials.

Results and Discussion

Rationality of Ligand Design

The overall synthetic route to access dialkylarylphosphine urea ligands **L1** and **L2** was strategically designed to have the addition of the dialkyl phosphine subunit to be the last step. In doing so, the arylurea fragment (after metalation) could be easily coupled with diverse R_2PCl electrophiles to generate analogs possessing distinct steric and electronic properties. For the fixed arylurea core **6**, 4-methyl-2-nitroaniline **1** was chosen as the starting nitroaniline, which allowed for each N-atom to be functionalized independently such that distinct alkyl groups could be incorporated within the urea subunit.

Construction of the Arylurea Core (6)

The synthesis of the arylurea core **6** began with an acid-catalyzed bromination of 4-methyl-2-nitroaniline **1** to give arylbromide intermediate **2** in 97% yield (Scheme 1). Following bromination, a reductive amination of aniline **2** with cyclohexanone afforded **3** in 77% yield. Due to the low nucleophilicity of **2**, the addition of trimethylsilyl trifluoromethanesulfonate (TMSOTf) proved necessary to push the equilibrium toward imine formation by consuming water. Next, the reduction of the arylnitro group of compound **3** was initially attempted using Pd/C in a hydrogen rich atmosphere; however, unwanted dehalogenation was observed. Therefore, a chemoselective reduction of the arylnitro group of **3** was conducted using tin(II) chloride dihydrate to afford intermediate **4**. Serendipitously, single-crystal X-ray diffraction analysis of **4** revealed that an unusual N-to-N cyclohexyl

migration had occurred from nitrogen-1 to the newly reduced nitrogen-2 in a 94:6 ratio of alkyl migration *vs.* nonmigration. The urea subunit was installed next by treating dianiline **4** with neat urea to afford **5** in 66% yield. Subsequent deprotonation of **5** followed by methylation with methyl iodide completed the arylurea fragment **6** in five synthetic steps with an overall yield of 49%.

Formation of the Aryl-P Bond through a Lithiation Capture Sequence

The final step in the ligand synthesis consisted of a lithium halogen exchange reaction using arylurea **6** and *t*-BuLi, followed by trapping with the desired dialkylphosphine chloride. Trapping of the intermediate aryllithium species using dicyclohexylphosphorous chloride (Cy_2PCl) afforded dialkylarylurea phosphine ligand **L1** in 60% yield. Similarly, using di-*tert*-butylphosphorus chloride (tBu_2PCl) provided phosphine-urea ligand **L2** in 47% yield. In general, the developed synthesis proved to be direct and robust to easily generate gram quantities of these dialkylarylphosphine urea ligands in only six steps. The dialkylarylphosphine urea ligands are stable to air and no apparent decomposition has been observed in a 20-month period.

Discovery of an N-to-N Alkyl Migration Reaction

It is interesting to speculate on the mechanism of the observed N-to-N alkyl migration reaction which likely proceeds through the formation of nitroso compound **3-INT**.[15] Rather than the usual tin chloride (II) coordination to the nitroso group, we suspect that it coordinates to the nearby aniline which facilitates the cyclohexyl migration to the electrophilic nitroso subunit (Scheme 2). Further investigations are underway to identify the driving force of this unique migration reaction.

Single-Crystal X-ray Analysis

To gain a deeper insight into the structure of **L1** and **L2**, crystals of the neat ligands were prepared and analyzed by single-crystal X-ray crystallography. As shown in Figure 2, the alkyl substituents of the phosphorus atom are oriented away from the urea core allowing for the frontal region of the phosphorus atom to bind to a metal. The most important distinction found in the new dialkylarylphosphine urea ligands from other arylphosphine ligands was the bond length of the phosphorous-arylcarbon bond ($P–C_{Ar}$). The measured P1 $C6_{Ar}$ bond length for **L1** (1.8442 Å) and **L2** (1.8475 Å) is longer than typically observed $P–C_{Ar}$ bond lengths of other phosphine ligands, 1.8211 Å[13] and 1.832 Å.[14] Lastly, the distinctions found between **L1** and **L2** are that the P1–C6–C1 angle is greater for **L1** compared to **L2** (122.18° vs 120.58°), but the dihedral angle P1–C6–C1–N1 is more pronounced in **L2** than **L1** (−3.6° vs −0.9°).

Application of Dialkylarylphosphine Ligands in Palladium-Catalyzed Cross-Coupling Reactions

Having established the synthesis for the dialkylarylphosphine urea ligands **L1** and **L2**, we then focused our attention on their ability to perform palladiumcatalyzed cross-coupling reactions. To test the ligand's activity, we focused on the synthesis of simple carbon(sp^2)-carbon(sp^2) bonds to construct biaryl substrates, important structural functionalities in

biologically active compounds.[16–17] To compare the different palladium-catalyzed cross-coupling reactions, 4-bromobiphenyl **7** was chosen as the standard electrophile to be coupled with diverse types of organometallic nucleophiles. The results are summarized in Table 1.

First, we started with a standard Suzuki–Miyaura cross-coupling reaction using phenyl boroxine **8**. After a brief optimization of the reaction conditions using 2.0 mol% of Pd_2dba_3 and 8.0 mol% of the dialkylaryl phosphine urea ligand as the catalytic system (Table 1, entry 1), the reaction was effective at promoting carbon(sp^2)-carbon(sp^2) bond formation of biaryl target **9** in 93% **L1** and 80% **L2** yield. Second, to broaden the application of the dialkylphosphine urea ligands, we conducted biaryl synthesis using Stille–Migita reaction conditions. Here too, the ligands performed well to synthesize target biaryl **9** in 83% **L1** and 76% **L2** yield using tributylphenyltin(IV) **10** (Table 1 entry 2). Third, to conclude the C(sp^2)–C(sp^2) bond formation assessment, we carried out Negishi cross-coupling reactions at room temperature using phenyl zinc chloride **11** to give biaryl **9** in 90% **L1** and 83% **L2** yield (Table 1, entry 3).

Finally, to further establish the versatility of the dialkylaryl phosphine urea ligand, we turned our attention to the formation of carbon-nitrogen bonds. When we employed the ligands in Buchwald–Hartwig aminations, we were able to synthesize secondary aryl amine **13** from aryl aniline **12** in 80% **L1** and 91% **L2** yield (Table 1, entry 4). We also synthesized tertiary aryl amine **15** from morpholine **14** in up to 70% yields (Table 1, entry 5).

Conclusion

We report the design and synthesis of a new class of dialkylarylphosphine ligands bearing a urea functional group within their framework. The total synthesis of the ligand was completed in six synthetic steps. Key to this ligand design was the final step where, upon metalation, the fixed arylurea fragment **5** was coupled with diverse R_2PCl units to easily generate ligand variants. The newly developed **L1** and **L2** ligands were found to undergo prototypical C–C and C–N bond formation under various cross-coupling conditions: Suzuki–Miyaura, Stille–Migita, Negishi, and Buchwald–Hartwig aminations in good to high yields. Current studies are ongoing in our laboratories to gain a better understanding of the roles of urea subunits and their aptitude as a secondary coordination site for metal catalysis.

Experimental Section

General methods and detailed experimental procedures for the synthesis of intermediates and final dialkylarylphosphine urea ligands **L1** and **L2** are available and free of charge in the Supporting Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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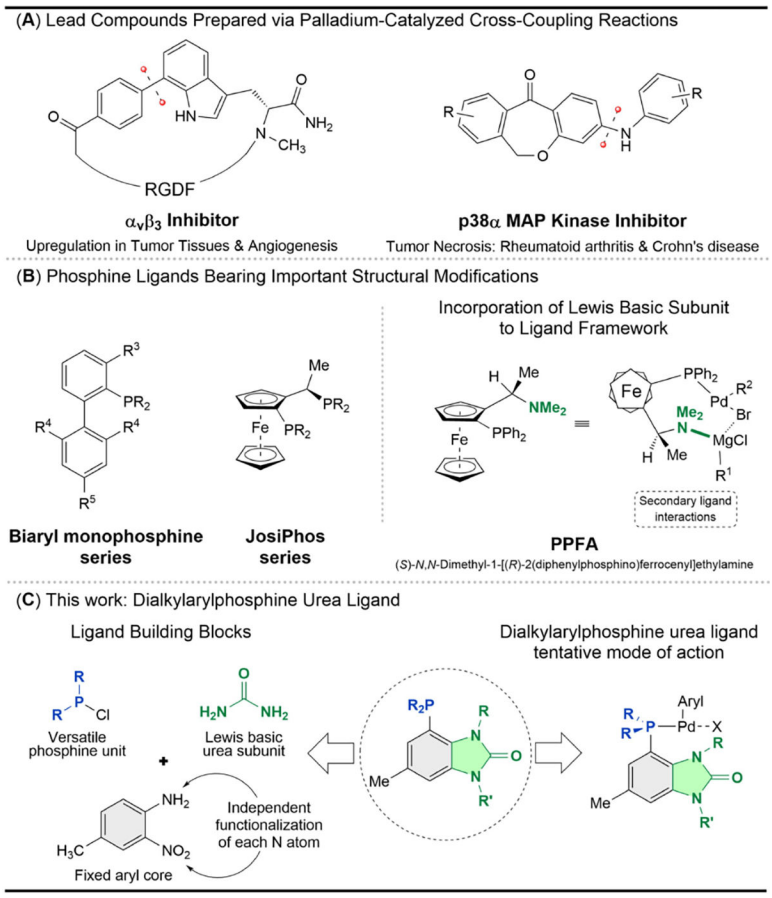


Figure 1.

(A) Complex lead compounds synthesized using specialized SPhos ligand ($\alpha_v\beta_3$ Inhibitor) and XPhos ligand (p38α MAP Kinase Inhibitor); (B) Phosphine ligands possessing primary and/or secondary ligand interactions; (C) This work.

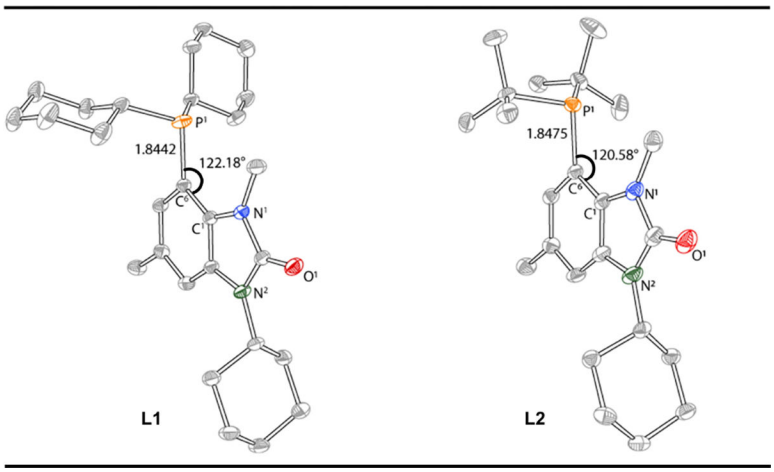
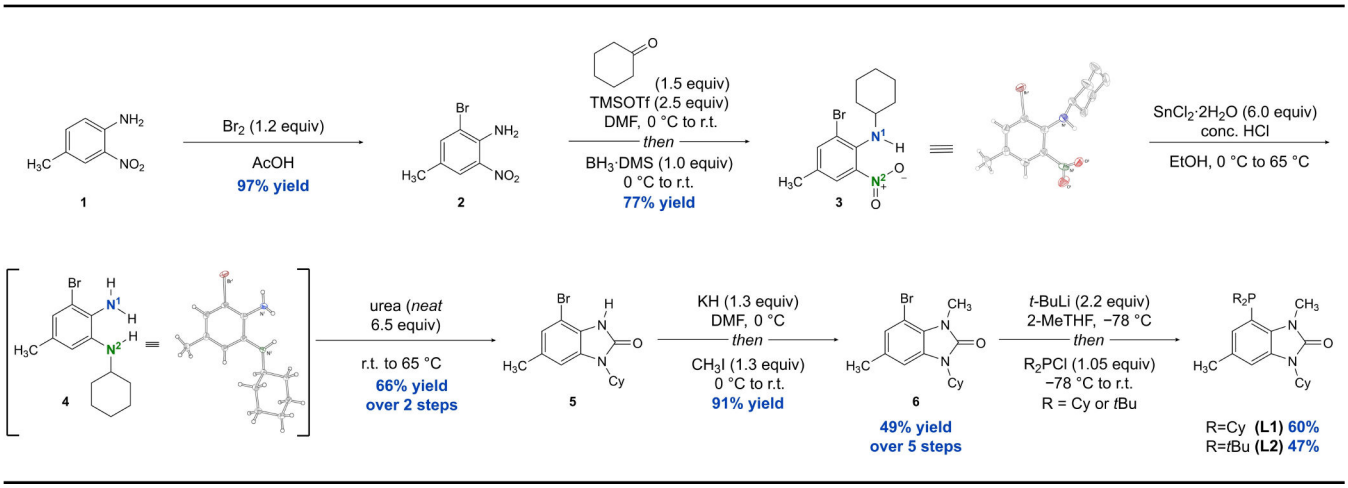
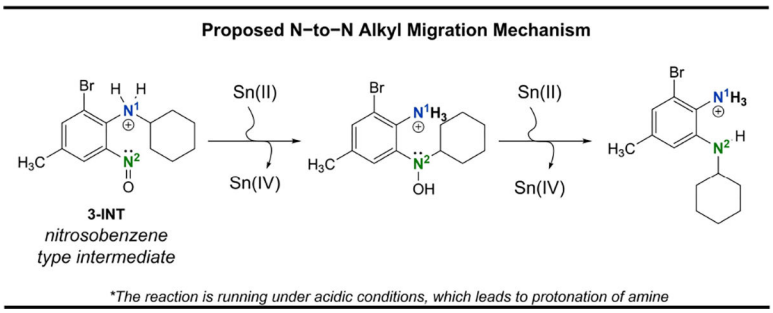


Figure 2.
Displacement ellipsoid plots of **L1** and **L2** ligands are plotted at 50% probability. H-atoms and solvents are removed for clarity.



Scheme 1.

Synthetic route for the development of dialkylarylphosphine urea ligands **L1** and **L2**.

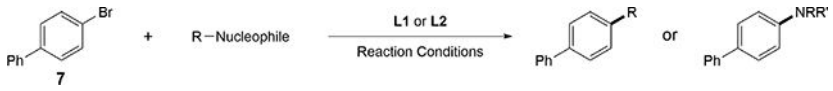


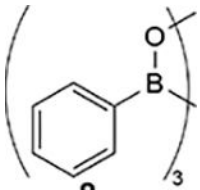
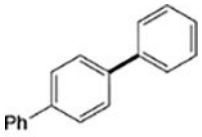
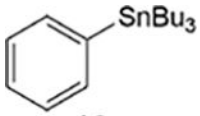
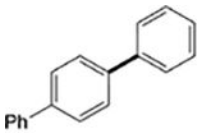
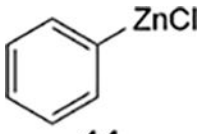
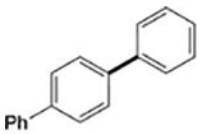
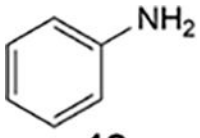
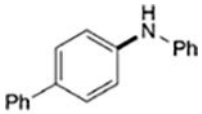
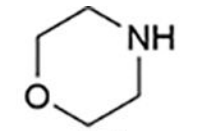
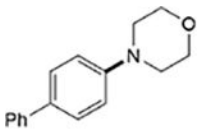
Scheme 2.

Proposed reaction mechanism of the N-to-N alkyl migration leading to the formation of intermediate **4**.

Table 1.

Palladium-catalyzed cross-coupling reactions employing newly synthesized **L1** and **L2** ligands.



Entry	Nucleophile	Reaction Conditions	Product	Yield L1	Yield L2
1.	 **8** (0.5 equiv)	Pd_2dba_3 (2.0 mol%), Ligand (8.0 mol%) Cs_2CO_3 (2.2 equiv) 1,4-dioxane (0.3 M), reflux, 18h	 **9**	93%	80%
2.	 **10** (1.5 equiv)	Pd_2dba_3 (1.5 mol%), Ligand (6.0 mol%) CsF (2.5 equiv) 1,4-dioxane (0.3 M), reflux, 16h	 **9**	83%	76%
3.	 **11** (1.5 equiv)	Pd_2dba_3 (2.0 mol%), Ligand (8.0 mol%) THF (0.13 M), r.t., 4h	 **9**	90%	83%
4.	 **12** (1.2 equiv)	$CODPd(CH_2TMS)_2$ (4.0 mol%) Ligand (8.0 mol%), NaO*t*Bu (1.3 equiv) Toluene (0.14 M), reflux, 17h	 **13**	80%	91%
5.	 **14** (1.2 equiv)	Pd_2dba_3 (2.0 mol%), Ligand (8.0 mol%) NaO*t*Bu (1.1 equiv) Toluene (0.14 M), reflux, 16h	 **15**	62%	70%

Reaction conditions were carried out on 0.5 mmol scale. Detailed reaction conditions can be found in Supporting Information. Yields reported are isolated yields of spectroscopically pure products.