A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201705525
Angew. Chem. 10.1002/ange.201705525

Link to VoR: http://dx.doi.org/10.1002/anie.201705525
http://dx.doi.org/10.1002/ange.201705525

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Mechanistic Insight Leads to a Ligand That Facilitates the Pd-Catalyzed Formation of 2-(Hetero)Arylaminooxazoles and 4-(Hetero)Arylaminothiazoles.

Esben P. K. Olsen, Pedro L. Arrechea, and Stephen L. Buchwald*

Abstract: Using mechanistic insight, a new ligand (EPhos) for the Pd-catalyzed C–N cross-coupling between primary amines and aryl halides has been developed. Employing an isopropoxy group at the *C3*-position favors the *C*-bound isomer of ligand-supported Pd(II) complexes and leads to significantly improved reactivity. The use of a catalyst system based on EPhos with NaOPh as a mild homogeneous base proved to be very effective in the formation of 4-arylaminothiazoles and highly functionalized 2-arylaminooxazoles. Previously, these were not readily accessible using Pd-catalyzed methodology.

Palladium catalyzed C–N bond-forming reactions have impacted the synthesis of nitrogen-containing molecules in a range of scientific disciplines[1], including materials science[2], chemical biology[3] and medicinal/process chemistry[4]. Insights into the mechanism of the reaction have informed the development of better ligands and reaction conditions, resulting in C–N cross-coupling protocols of substantial utility and generality.[5] Nevertheless, important limitations to the scope of the reaction remain, especially with respect to the coupling of highly functionalized or heterocyclic substrates, which are of particular relevance to the synthesis of biologically active compounds.[6] Indeed, medicinal chemists at Merck recently disclosed that 55% of the metal-catalyzed C–N cross-coupling reactions performed at their facilities failed to deliver any desired product in late stage synthesis of drug leads, highlighting some of the persistent barriers to overcome in the development of this transformation.[7]

The cross-coupling of five-membered heteroarylamines with aryl halides remains challenging in many cases despite their frequent occurrence as substructures of natural products[8], pharmaceuticals and other biologically active molecules.[9] For example, researchers at AstraZeneca recently reported their difficulties in developing conditions for the palladium-catalyzed cross-coupling of 2-aminooxazoles.[10] The authors reported that only trace amounts of coupling product could be obtained in the case of the parent 2-aminooxazole (**4**), although a handful of 4- and 5-substituted derivatives could be coupled in low to moderate yield. To prepare the coupling product of **4**, a multistep procedure involving the saponification and decarboxylation of the 4-ethylester derivative was required. In general, improvements in the cross-coupling of five-membered heteroarylamines, such as 2-aminooxazole **4**, would be a useful advance for the field of transition metal-catalyzed cross coupling.

We previously reported BrettPhos[11] (Figure 1b/2a, **L1**) as an effective supporting ligand for selective monoarylation of primary amines catalyzed by palladium.[4b,12] The methoxy substituent at the *C3*-position (Figure 1b) has been found to play an important role in the selectivity and reactivity of catalysts supported by this ligand.[11a, 13] Reductive elimination studies have demonstrated that BrettPhos-supported palladium(II) complexes will reside as the *O*- and *C*-bound isomers (Figure 1b), and the *O*-bound isomer is less competent for reductive elimination. We thus hypothesized that the *O*-bound complexes may be "off-cycle" palladium intermediates that must be eventually converted to the product-producing *C*-bound complex (**IV**). We felt that the development of a ligand that favored *C*-bound isomers might enable a catalyst system with improved reaction rates and efficiencies for challenging substrate classes.

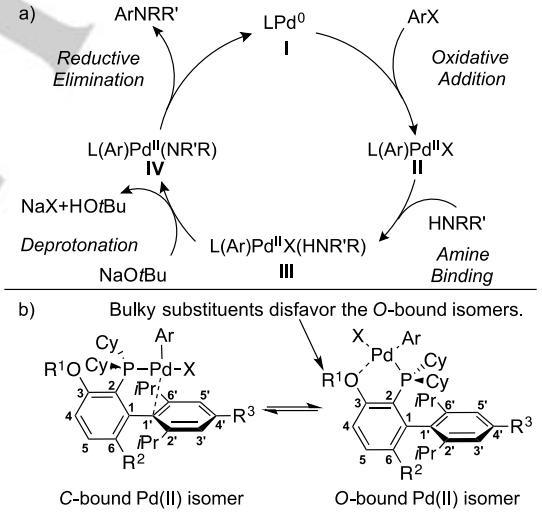

Figure 1. a) Simplified catalytic cycle for a palladium catalyzed C–N cross-coupling reaction. b) Bulky substituents for R^1 favor the *C*-bound isomer (see supporting information). Analogous *C*-bound/*O*-bound isomers have been observed for **III** and **IV**.

With this hypothesis in mind, we synthesized an array of **L1** analogues that we believed could decrease the percentage of the *O*-bound isomer. This study (detailed in the supporting information) led to the identification of EPhos (**L3**) as an effective ligand for the cross-coupling of **4** with an array of hindered and/or functionalized aryl chlorides and bromides, as well as commercial pharmaceuticals. In addition, the catalytic system was used to prepare several functionalized 4-(hetero)arylaminothiazoles. Studies that employed reaction calorimetry and NMR implied that reactions with palladium catalysts based on **L3** show improved reaction rates and the resting state of the catalyst is solely as the *C*-bound isomer.

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10.1002/anie.201705525

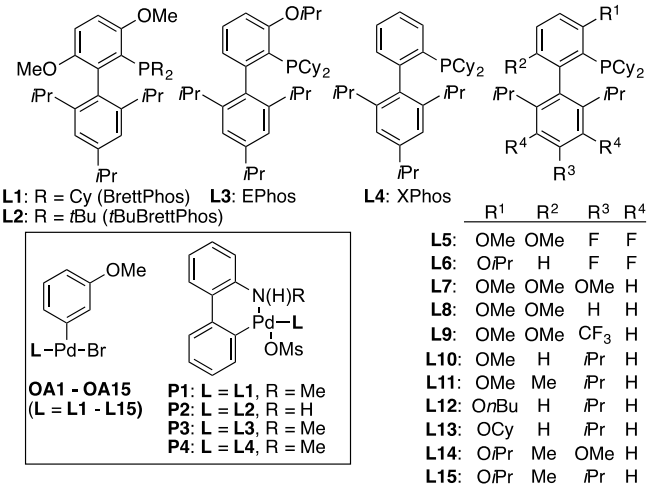

Figure 2. Ligands for palladium catalyzed C–N cross-couplings.

The results in Figure 3 show the improved reactivity observed with **L3**-based palladium catalysts. The cross coupling of 2-aminooxazole **4** with 3-chloropyridine (**5b**) and 2,6-dimethylchlorobenzene (**5c**) was examined with a range of ligands and reaction conditions. A series of precatalysts[14] based on BrettPhos (**P1**), *t*BuBrettPhos (**P2**), EPhos (**P3**), and XPhos (**P4**) as the supporting ligands were evaluated in the presence of either NaOPh (*Conditions A*) or K_2CO_3 (*Conditions B*), and it was determined that the use of **P3** provided the highest yields for either pair of starting materials (see the supporting information for the full set of details for this study). **P1**-**P3** each afforded product with 3-chloropyridine (**5b**), while no product was obtained using **P4**, highlighting the importance of the 3-alkoxy substituent in the ligand structure. In the case of 2,6-dimethylchlorobenzene (**5c**), **P2** was found to be ineffective, presumably due to the combined steric hindrance from the ligand and the aryl chloride.

With two sets of conditions (*Conditions A* and *B*) employing **P3** as the precatalyst, the scope of the cross coupling of aminooxazole **4** was explored with a wide variety of aryl chlorides and bromides. When relatively simple and unhindered aryl halides were employed, precatalysts based on BrettPhos (**P1**) and EPhos (**P3**) performed comparably. However, when the cross coupling of more complex or sterically hindered substrates was attempted, significantly better yields were obtained with the EPhos-supported Pd catalyst **P3** (**7h**-**7m**). A variety of functional groups could be tolerated, including a ketone (**7a**), a nitro group (**7d**), an unprotected alcohol (**7i**), an acetal (**7l**), and secondary and tertiary amines (**7m**, **7o**, **7r**, **7q**). A collection of heterocycles also proved to be efficiently transformed under these conditions. Importantly, *ortho*-substituted substrates (**7k**-**7n**) reacted efficiently when **P3** was employed and several densely functionalized pharmaceuticals also underwent coupling in high yields (**7o**-**7q**).

3-Chlorobenzonitrile did not undergo cross coupling with **4** when either BrettPhos (**P1**) or EPhos (**P3**) was employed, although a nitrile group was tolerated when a different heteroarylamine was used (**7d**). When using an aryl chloride bearing a methyl ester group in the *ortho* position, condensation took place, resulting in the formation of the tricyclic heterocycle **7j**. An appreciable yield could be obtained with **P3** in the presence of NaOPh (*Conditions A*). The unsubstituted 5*H*-oxazolo[2,3-b]quinazolin-5-one is previously unknown, although the thio-analog has been prepared using a copper catalyzed reaction.[15]

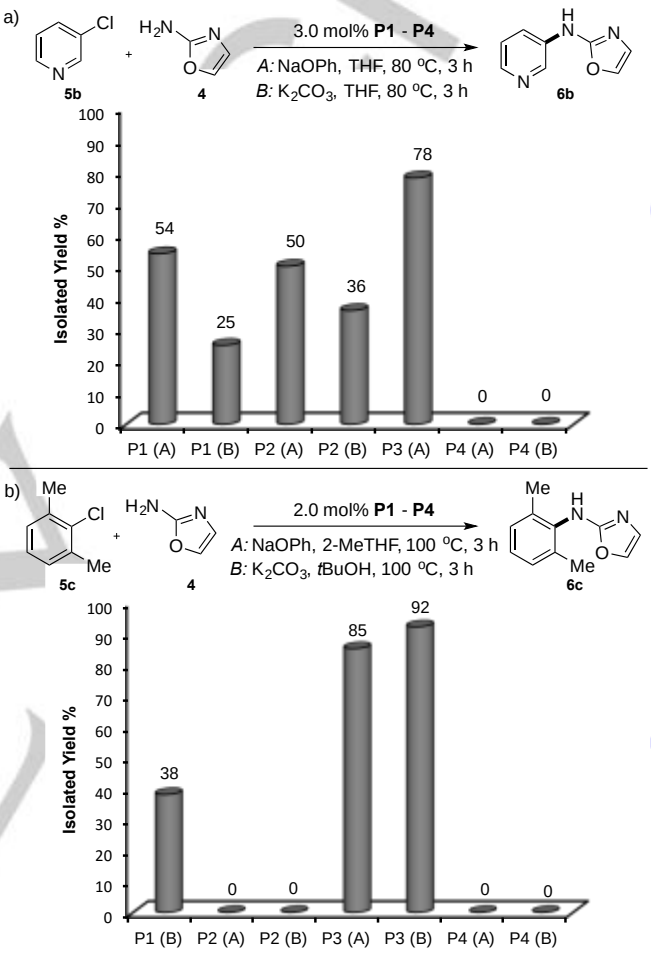

Figure 3. a) Precatalysts tested for the formation of **6b**. b) Precatalysts tested for the formation of **6c.**

As 4-bromothiazole is also sensitive to strong base, a mild homogeneous base was similarly expected to improve reaction outcomes with this coupling partner. **P3** *(A)* afforded **8a** and **8d** in significantly higher yields with lower catalyst loadings than what has previously been reported (Scheme 1).[10b] Furthermore, products **8b** and **8c** could be obtained in excellent yields with 2.0 mol% catalyst loading at 80 °C. Although the aryl bromide was used in excess for the case of **8c**, no diarylation product was observed, highlighting the high selectivity for the monoarylation product using this catalyst system. Notably, excellent yields were also obtained when aminopyrazine (**8e**) and aminopyrimidine (**8f**) were employed.

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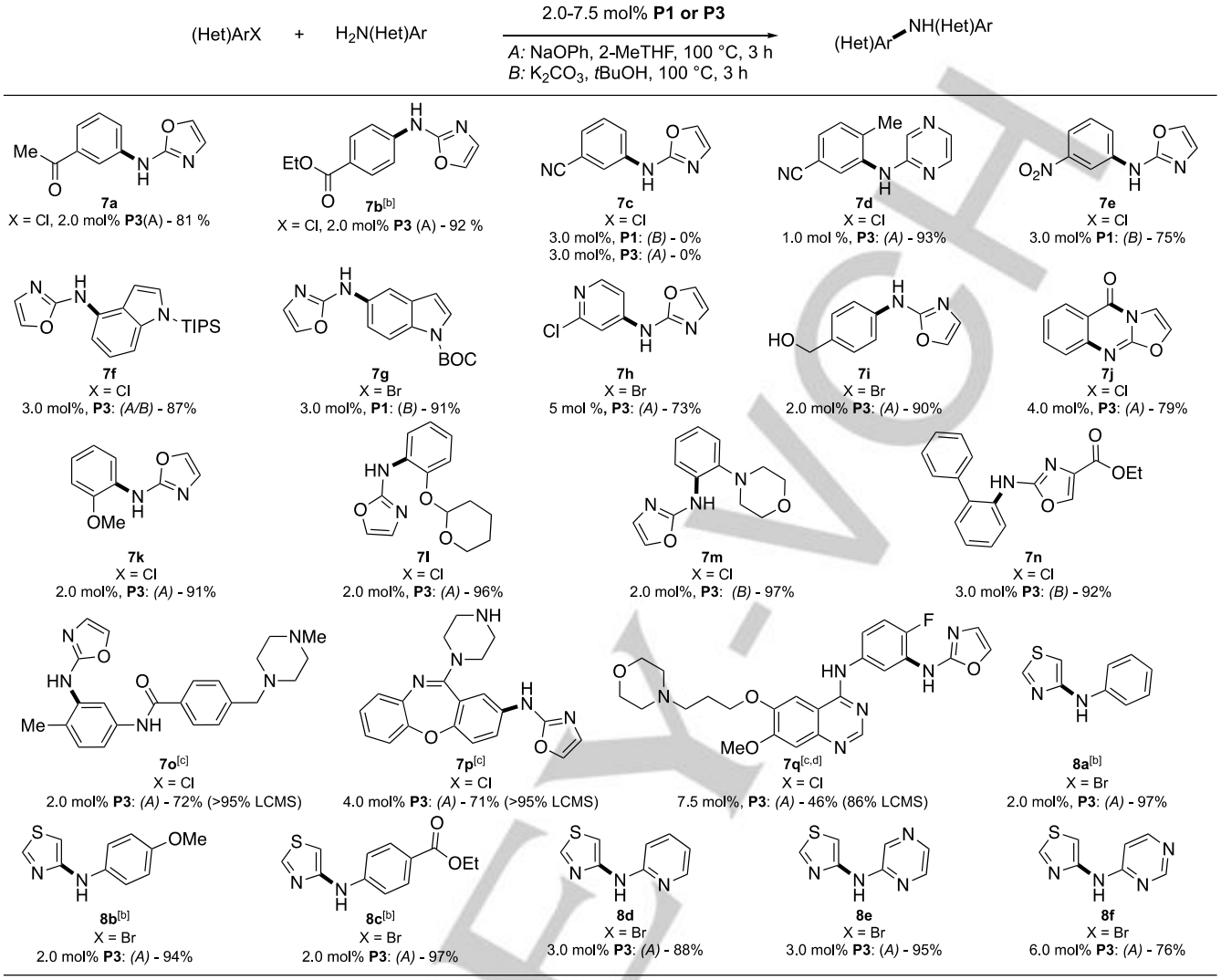

Scheme 1. Palladium catalyzed cross-couplings of 2-aminooxazoles with aryl chlorides and bromides. [a] Reaction conditions A: 2-aminooxazole (1.2 mmol), aryl halide (1.0 mmol), precat (0.02-0.075 mmol), NaO*t*Bu (1.2 mmol) PhOH (1.3 mmol), 2-MeTHF (4.0 mL), 100 °C, 3 h. Reaction conditions B: 2-aminooxazole (1.2 mmol), aryl halide (1.0 mmol), precat (0.02-0.075 mmol), K_2CO_3 (1.4 mmol), *t*BuOH (4.0 mL), 100 °C, 3 h. [b] THF (4.0 mL), 80 °C, 3 h. [c] 0.5 mmol scale. [d] 0.125 M.

Although NaOPh is a relatively uncommon base for palladium catalyzed C–N cross-coupling reactions, several previous reports have documented its use.[16] Hartwig reported that KOPh was optimal for the palladium-catalyzed arylation of fluoroalkylamines, and the resting state of the catalytic reaction was determined to be a LPd(Ar)OPh complex.[16a] We queried whether analogous phenoxo complexes based on **L1** or **L3** might be observable under catalytic conditions. Subjecting a solution of **L1**Pd(Ar)Cl (Ar=2-MeC_6H_4) (**OA1b**) or **L3**Pd(Ar)Cl (Ar=2-MeC_6H_4) (**OA3c**) in THF to NaOPh at room temperature gave rise to new signals in the ^{31}P NMR spectrum 4-5 ppm downfield of the signals for **OA1b** and **OA3c** (see the Supporting information). The cross-coupling of aniline and 2-chlorotoluene using NaOPh as the base, and **OA1b** (5.0 mol%) as the catalyst was monitored by ^{31}P NMR at 60 °C in THF-d_8. During the course of the reaction, these two phosphorus-containing species were predominant and were identified as the isomers of the phenoxo complex in which palladium is bound to either the 1'-aryl carbon (*C*-bound) or the 3-alkoxy group (*O*-bound) (Figure 1b).[11a] Interestingly, the *O*-bound isomer seemed to accumulate over the duration of the reaction. When the same experiment was conducted with **OA3c**, only the peak corresponding to the *C*-bound isomer was observed, suggesting that the bulky isopropoxy group disfavors the *O*-bound isomers.

While studying palladium-catalyzed amination reactions at room temperature, we observed a complex but reproducible kinetic profile for the cross-coupling of 3-bromoanisole (**1**) and *n*-propylamine (**2**) when using the **L1**-based complex LPd(II)ArBr (**OA1**, 0.7 mol%) as the palladium source and NaO*t*Bu as base (Figure 4).[17] In contrast, when the **L3**-based complex **OA3** was used, a rapid reaction with a simple kinetic profile was observed. Although the complex kinetics observed with **OA1** precluded a

quantitative comparison of rates, the calorimetric data indicated that **L3** was much more efficient with full consumption of starting material in less than 20 minutes (Figure 4, inset) compared to 250 minutes for **L1**.

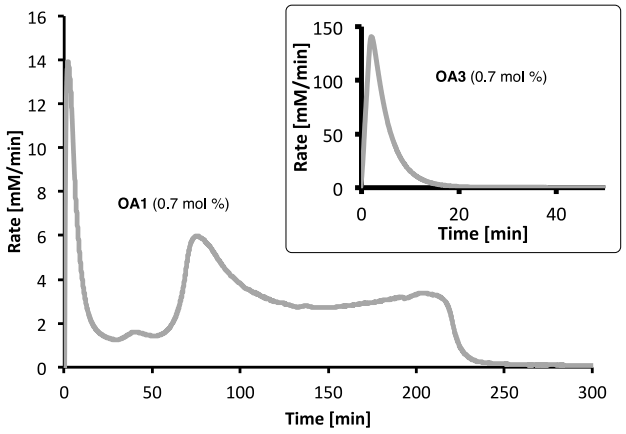

Figure 4. Reaction progress kinetic profiles for the Pd-catalyzed reaction of 3-bromoanisole with *n*-propylamine. NaO*t*Bu was used as the base, and **OA1** and **OA3** were used as the catalysts. Reactions were run at 20 °C in dioxane.

In conclusion, a new ligand (**L3,** EPhos) for the palladium catalyzed C–N cross-couplings has been developed, which was applied to the formation of 2-(hetero)arylaminooxazoles and 4-(hetero)arylaminothiazoles. Furthermore, experiments have demonstrated that the respective palladium(II) phenoxo complex is the resting state for this reaction when NaOPh is applied as the base. The *O*-bound isomer was not observed if **L3** was used as the supporting ligand (Figure 3). Although this phenomenon does represent a significant difference in behavior between **L1** and **L3**, ongoing studies will elucidate whether this equilibrium accounts for the difference in efficiency observed between these ligands.

Acknowledgements

Research reported in this publication was supported by the National Institutes of Health under award number GM58160 whom we gratefully acknowledge. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. E. O. thanks the Villum Foundation for a postdoctoral fellowship. We thank Dr. Yiming Wang, Dr. Michael Pirnot, and Dr. Mycah Uehling for their help in the preparation of this manuscript.

Keywords: EPhos • 2-aminooxazole • C–N cross-coupling • palladium catalysis • sodium phenoxide

[1] P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564-12649.

[2] a) J.-S. Yang, C.-J. Lin, *J. Photochem. Photobiol. A: Chem.* **2015**, *312*, 107-120. b) J. Lin, X. Ni, *RSC Adv.* **2015**, *5*, 14879-14886. c) B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599-1626. d) J.-S. Yang, Y.-H. Lin, C.-S. Yang, *Org. Lett.* **2002**, *4*, 777-780.

[3] a) V. Singh, S. Wang, E. T. Kool, *J. Am. Chem. Soc.* **2013**, *135*, 6184-6191. b) E. Benedetti, L. Kocsis, K. M. Brummond, *J. Am. Chem. Soc.* **2012**, *134*, 12418-12421. c) X. Jin, C. Uttamapinant, A. Y. Ting, *ChemBioChem* **2011**, *12*, 65-70.

[4] a) D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443-4458. b) C. Affouard, R. D. Crockett, K. Diker, R. P. Farrell, G. Gorins, J. R. Huckins, S. Caille, *Org. Process. Rec. Dev.* **2015**, *19*, 476-485. c) J. B. Sperry, K. E. P. Wiglesworth, I. Edmonds, P. Fiore, D. C. Boyles, D. B. Damon, R. L. Dorow, E. L. P. Chekler, J. Langille, J. W. Coe, *Org. Process. Rec. Dev.* **2014**, *18*, 1752-1758. d) Y. Liu, M. Prashad, W.-C. Shieh, *Org. Process. Rec. Dev.* **2014**, *18*, 239-245.

[5] a) Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc*. **2008**, *130*, 6586-6596. b) M. R. Biscoe, B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 6686-6687. c) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27-50. d) N. H. Park, E. V. Vinogradova, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2015**, *127*, 8377-8380; *Angew. Chem. Int. Ed.* **2015**, *54*, 8259-8262. e) P. Ruiz-Castillo, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc.* **2015**, *137*, 3085-3092.

[6] C. Fischer, B. Koenig, *Beilstein J. Org. Chem.* **2011**, *7*, 59-74.

[7] A. B. Santanilla, E. L. Regalado, T. Pereira, M. Shevlin, K. Bateman, L.-C. Campeau, J. Schneeweis, S. Berritt, Z.-C. Shi, P. Nantermet, Y. Liu, R. Helmy, C. J. Welch, P. Vachal, I. W. Davies, T. Cernak, S. D. Dreher *Science*, **2015**, *347*, 49-53.

[8] D. Davyt, G. Serra, *Mar. Drugs*, **2010**, *8*, 2755-2780.

[9] a) P. A. Harris, M. Cheung, R. N. Hunter III, M. L. Brown, J. M. Veal, R. T. Nolte, L. Wang, W. Liu, R. M. Crosby, J. H. Johnson, A. H. Epperly, R. Kumar, D. K. Luttrell, J. A. Stafford. *J. Med. Chem.* **2005**, *48*, 1610-1619. b) E. Vieira, J. Huwyler, S. Jolidon, F. Knoflach, V. Mutel, J. Wichmann. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1666-1669. c) L. Lintnerová, L. Kováčiková, G. Hanquet, A. Bohác. *J. Heterocyclic Chem* **2015**, *52*, 425-439.

[10] G. M. Noonan, A. P. Dishington, J. Pink, A. D. Campbell, *Tetrahedron Letters*, **2012**, *53*, 3038-3043.

[11] a) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552-13554. b) D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald. *Chem. Sci.* **2011**, *2*, 57-68

[12] *For recent literature examples from other research groups solving challenging C–N cross-couplings using BrettPhos as the supporting ligand see* a) M. Günther, M. Juchum, G. Kelter, H. Fiebig, S. Laufer, *Angew. Chem.* **2016**, *128*, 11050-11054: *Angew. Chem. Int. Ed.* **2016**, *55*, 10890-10894. b) J. Wlochal, A. Bailey, *Tetrahedron Letters*, **2015**, *56*, 6791-6794.

[13] a) P. L. Arrechea, S. L. Buchwald, *J. Am. Chem. Soc.* **2016**, *138*, 12486-12493. b) B. P. Fors, N. R. Davies, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 5766-5768. c) E. Gioria, J. D. Pozo, J. M. Martínez-Ilarduya, P. Espinet, *Angew. Chem.* **2016**, *128*, 13470-13474.: *Angew. Chem. Int. Ed.* **2016**, *55,* 13276-13280.

[14] N. C. Bruno, N. Niljianskul, S. L. Buchwald, *J. Org. Chem.* **2014**, *79*, 4161-4166.

[15] R. F. Pellón, M. L. Docampo, M. L. Fascio, *Synth. Commun.* **2007**, *37*, 1853-1864.

[16] a) A. T. Brusoe, J. F. Hartwig, *J. Am. Chem. Soc.* **2015**, *137*, 8460-8468. b) K. H. Hoi, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 804-807. c) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 8612-8615: *Angew. Chem. Int. Ed.* **2007**, *46*, 8460-8463. d) J. P. Schulte, S. R. Tweedie, *Synlett*, **2007**, *15*, 2331-2336.

[17] D. G. Blackmond, *Angew. Chem.* **2005**, *117*, 4374-4393: *Angew. Chem. Int. Ed.* **2005**, *44,* 4302-4320.

10.1002/anie.201705525

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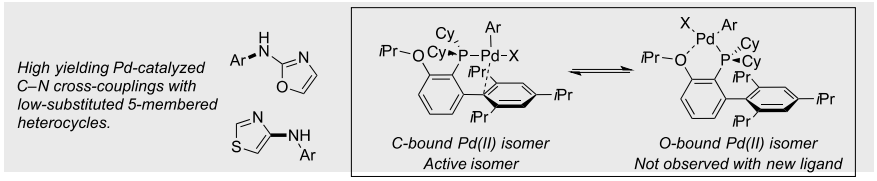

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A new ligand, EPhos, for Pd-catalyzed C–N cross-couplings has been developed based on a structure activity relationship of BrettPhos related ligands. The ligand was succesfully applied in the Pd-catalyzed formation of 2-(hetero)arylaminooxazoles and 4-(hetero)arylaminothiazoles, structures that have previously proven problematic to form by transition metal catalysis.