

Mimics of Pincer Ligands: An Accessible Phosphine-Free *N*-(Pyrimidin-2-yl)-1,2-azole-3-carboxamide Framework for Binuclear Pd(II) Complexes and High-Turnover Catalysis in Water

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ABSTRACT: We report for the first time cyclic phosphine-free “head to tail” *N,N,N* pincer-like (pincer complexes mimicking) *N*-(pyrimidin-2-yl)-1,2-azole-3-carboxamide Pd(II) complexes with deprotonated amide groups as high-turnover catalysts (TON up to 10^6 , TOF up to $1.2 \times 10^7 \text{ h}^{-1}$) for cross-coupling reactions on the background of up to quantitative yields under Green Chemistry conditions. The potency of the described catalyst family representatives was demonstrated in Suzuki–Miyaura, Mizoroki–Heck, and Sonogashira reactions on industrially practical examples. Corresponding ligands could be synthesized based on readily available reagents through simple chemical transformations. Within the complex structures, a highly unusual 1,3,5,7-tetraza-2,6-dipalladocene frame could be observed.

The formation of new carbon–carbon bonds by Pd-catalyzed cross-coupling reactions, including stereospecific protocols, awarded the Nobel Prize in 2010, is a fundamental process in modern organic synthesis and is widely used in the development of new materials for pharmacy, agriculture, and electronics.¹ Despite the advances in the research of cross-coupling reactions, their large-scale applications are still limited, mainly due to the toxicity and very high cost of palladium and phosphine ligands.² Enormous practical interest in cross-coupling chemistry has stimulated further research to solve the problem of replacing costly palladium catalysts with more available transition metals, and some progress has been made in this direction.³ However, palladium catalysts remain out of the competition due to the high speeds, selectivity, and yields of the cross-coupling products under relatively mild conditions. For these reasons, the task of developing palladium high-turnover-number (TON) and high-turnover-frequency (TOF) catalysts that exhibit sufficient activity even in trace (“homeopathic”, ppm level) amounts is highly relevant.²

As in other homogeneous catalytic reactions, in cross-coupling reactions the nature of the ligand environment around the Pd center also holds the key to tuning the efficiency of the catalytic system. Along with the most commonly used phosphine ligands,^{2b} which are toxic, oxidizable, and difficult to reuse, many nitrogen-containing ligands were developed, with carbene and pincer ligands occupying a special place among them.⁴ Yields from high to quantitative were usually reported for *N*-ligand palladium complexes in cross-coupling reactions; however, only some of them are actually highly efficient catalysts: complexes of 2-aminopyrimidines,^{4c} 3-aminoisoxazole,^{4d} aminopyridines,^{4e} and pipercolinic acid.^{4f} Therefore, the development of efficient (high TON and TOF), easily

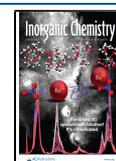
prepared, inexpensive, stable, and also environmentally friendly catalytic systems remains an urgent and essential task.

Initially we assumed that the combination of the 1,2-azole and pyrimidine cores in the ligand framework can promote the catalytic activity of palladium complexes. The 2-amino-pyrimidine moiety ($\text{p}K_{\text{a}} = 3.66$) contains effective *N*-coordinating centers and easily forms palladium complexes.^{4c} Since isoxazole (isothiazole) and pyrimidine heterocycles differ in their electronic structure and donor ability (electron-withdrawing and electron-donating groups),^{5a} we expected that hybrid ligands on their basis might stabilize both Pd(0) and Pd(II) species formed along the catalytic cycle and thus increase the stability and efficiency of the catalyst. Recently, we have synthesized dimeric 1-(isoxazol-3-yl)methyl-1*H*-1,2,3-triazoles Pd-complexes containing two heterocycles with significantly different electronic properties, and have shown that their catalytic activities greatly exceed that of the 3-aminoisoxazole and 1,2,3-triazole Pd-complexes.^{5b} In continuation of our previous studies of cross-coupling reactions⁶ and chemistry of isoxazoles and isothiazoles,⁷ herein we describe the synthesis of isoxazole/isothiazole-2-aminopyrimidine ligands with an amide bridge between the heterocycles and their complexes with PdCl₂ as new catalysts for the cross-coupling reactions in aqueous media.

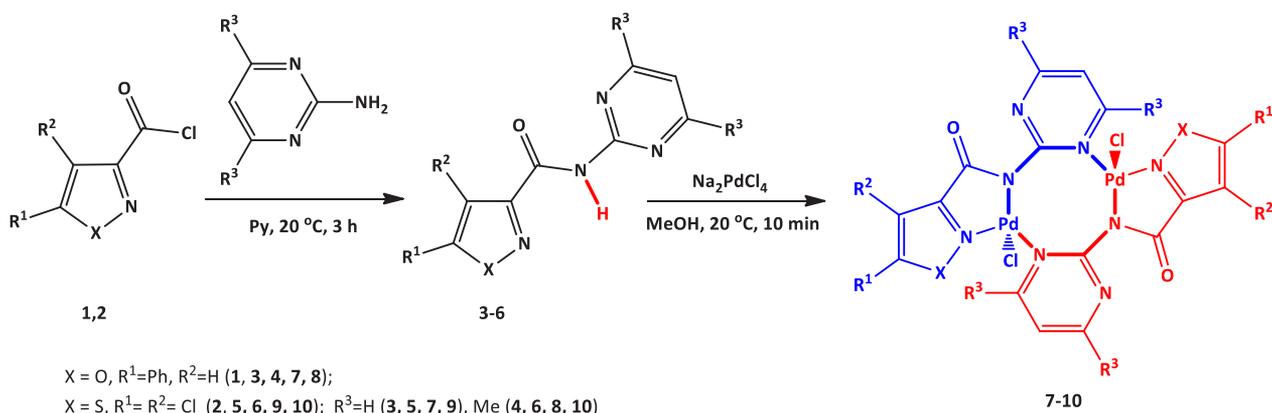
Amides were synthesized in 83–87% yields by acylation of 2-aminopyrimidine and 2-amino-4,6-dimethylpyrimidine with

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Scheme 1. Synthesis of *N*-(Pyrimidin-2-yl)-1,2-azole-3-carboxamide Ligands and Their “Head to Tail” *N,N,N*-Pincer-Type Binuclear Palladium(II) Complexes 7–10



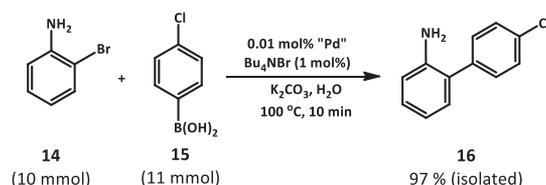
5-phenylisoxazole- and 4,5-dichloroisothiazole-3-carboxyl chlorides **1**, **2** in pyridine (Scheme 1). Synthesized amide ligands **3–6** (L^1-L^4) easily reacted with Na_2PdCl_4 in methanol forming the corresponding complexes **7–10** with 92–97% yields. According to TLC, a complete consumption of the starting ligands **3–6** in the reaction mixture was observed within 5 min. The pyrimidine complexes $\text{Pd}_2\text{Cl}_2(L^1-H)_2$ **7** and $\text{Pd}_2\text{Cl}_2(L^3-H)_2$ **9** had extremely low solubility and immediately precipitated from the reaction mixture, while dimethylpyrimidine analogues $\text{Pd}_2\text{Cl}_2(L^2-H)_2$ **8** and $\text{Pd}_2\text{Cl}_2(L^4-H)_2$ **10** turned out to be moderately soluble in methanol and the concentration of the reaction mixtures was required for their isolation (details can be found in the Supporting Information

Table 1. Suzuki–Miyaura Reaction of 3-Bromobenzoic Acid **11 with 4-Methoxyphenylboronic Acid **12** in the Presence of Complexes $\text{Pd}_2\text{Cl}_2(L-H)_2$ ^a**

entry	“Pd”	T, °C	time, min	yield, % ^b
1	$\text{Pd}_2\text{Cl}_2(L^1-H)_2$	20	30	95
2	$\text{Pd}_2\text{Cl}_2(L^1-H)_2$	40	15	97
3	$\text{Pd}_2\text{Cl}_2(L^1-H)_2$	100	2	100
4	$\text{Pd}_2\text{Cl}_2(L^2-H)_2$	20	30	100
5	$\text{Pd}_2\text{Cl}_2(L^2-H)_2$	40	15	100
6	$\text{Pd}_2\text{Cl}_2(L^2-H)_2$	100	<1	100
7	$\text{Pd}_2\text{Cl}_2(L^2-H)_2$ 0.01 mol % Pd	100	4	100
8	$\text{Pd}_2\text{Cl}_2(L^2-H)_2$ 0.001 mol % Pd	100	5	100
9 ^c	$\text{Pd}_2\text{Cl}_2(L^2-H)_2$ 0.0001 mol % Pd	100	5	100
10	$\text{Pd}_2\text{Cl}_2(L^3-H)_2$	20	60	31
11	$\text{Pd}_2\text{Cl}_2(L^3-H)_2$	40	15	49
12	$\text{Pd}_2\text{Cl}_2(L^3-H)_2$	100	20	92
13	$\text{Pd}_2\text{Cl}_2(L^4-H)_2$	20	60	37
14	$\text{Pd}_2\text{Cl}_2(L^4-H)_2$	40	15	52
15	$\text{Pd}_2\text{Cl}_2(L^4-H)_2$	100	20	96
16 ^d	Na_2PdCl_4	20	60 (240)	85 (91)
17 ^d	Na_2PdCl_4	100	5	99

^aAryl halide (0.5 mmol), arylboronic acid (0.6 mmol), K_2CO_3 (1.25 mmol), 5 mL of H_2O . ^b¹H NMR yield with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard. ^cReaction with 3-iodobenzoic acid. ^dReactions in the presence of Na_2PdCl_4 . Pd-black formation was observed.

Scheme 2. Synthesis of the Key Structure **16 of Boscalid on the Basis of **14** and **15** by $\text{Pd}_2\text{Cl}_2(L^2-H)_2$ Catalysis**



the ratio ligand/Pd/Cl is approximately 1:1:1. This is possible due to deprotonation of the amide group NH by the

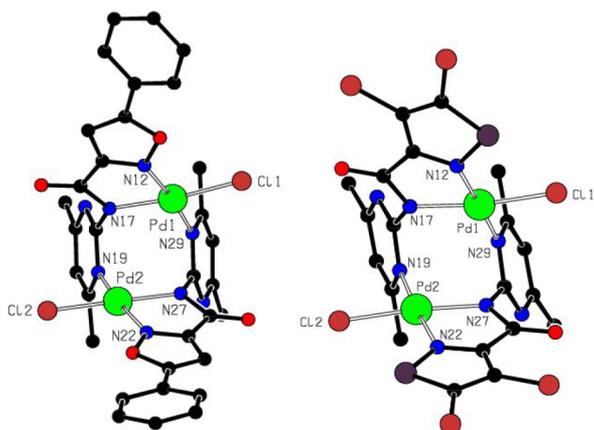


Figure 1. Binuclear molecules of complexes $\text{Pd}_2\text{Cl}_2(L^2-H)_2$ **8** (left) and $\text{Pd}_2\text{Cl}_2(L^4-H)_2$ **10** (right), with the atom numbering for coordination environment of Pd1 and Pd2 atoms. All hydrogen atoms are omitted for clarity. Color scheme for atoms: Pd, green; Cl, orange; N, blue; C, black; O, red; S, violet.

(SI)) (hereinafter L-H denotes the ligand with deprotonated amide group).

The obtained palladium(II) complexes were identified by elemental analysis and IR spectroscopy. The sufficient solubility of complexes **8** and **10** in organic solvents made it possible to record their ¹H NMR, ¹³C NMR, and ESI-MS spectra as well as obtain suitable single crystals for X-ray analysis (details can be found in the SI).

It turned out that the complexation process proceeds unusually. From the data of elemental analysis, it follows that

Scheme 3. Synthesis of 2',4'-Difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic Acid 19 on the Basis of 17 and 18 by Pd₂Cl₂(L²-H)₂ Catalysis

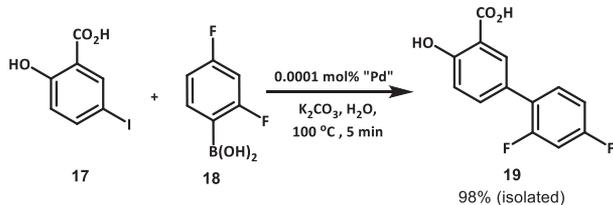


Table 2. Mizoroki–Heck Reaction of *m*-Bromobenzoic acid 11 and Acrylic Acid 20 for the Synthesis of 21 in the Presence of Complexes Pd₂Cl₂(L-H)₂^a

entry	Pd ₂ Cl ₂ (L-H) ₂	time, min	yield, % ^b
1	Pd ₂ Cl ₂ (L ¹ -H) ₂	20	97
2	Pd ₂ Cl ₂ (L ² -H) ₂	20	100 (96) ^c
3	Pd ₂ Cl ₂ (L ² -H) ₂	200 (20 °C)	0
4	Pd ₂ Cl ₂ (L ³ -H) ₂	20	95
5	Pd ₂ Cl ₂ (L ⁴ -H) ₂	20	98
6	Pd ₂ Cl ₂ (L ⁴ -H) ₂	200 (20 °C)	0

^aAryl halide (0.5 mmol), acrylic acid (0.6 mmol), K₂CO₃ (1.25 mmol), 5 mL of H₂O, 100 °C. ^b¹H NMR yield with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard. ^cIsolated yield.

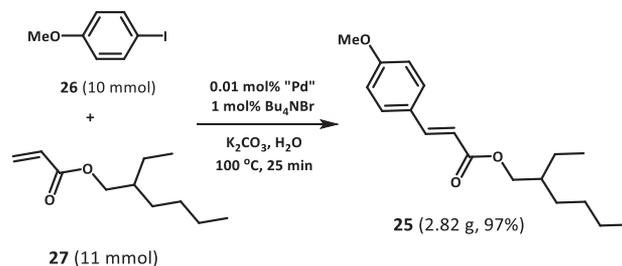
Table 3. Sonogashira Reaction between Methyl *p*-Iodobenzoate 22 and Prop-2-yn-1-ol 23 for the Synthesis of 24 in the Presence of Complexes Pd₂Cl₂(L-H)₂^a

entry	Pd ₂ Cl ₂ (L-H) ₂	time, min	Yield, % ^b
1	Pd ₂ Cl ₂ (L ¹ -H) ₂	10	95
2	Pd ₂ Cl ₂ (L ² -H) ₂	10	100 (95) ^c
3	Pd ₂ Cl ₂ (L ² -H) ₂	150 (20 °C)	98
4	Pd ₂ Cl ₂ (L ³ -H) ₂	10	93
5	Pd ₂ Cl ₂ (L ⁴ -H) ₂	10	96
6	Pd ₂ Cl ₂ (L ⁴ -H) ₂	200 (20 °C)	87

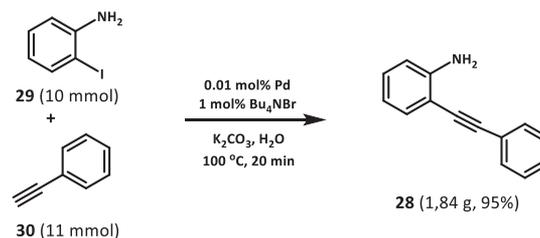
^aAryl halide (0.5 mmol), prop-2-yn-1-ol (0.65 mmol), K₂CO₃ (1.25 mmol), Bu₄NBr (1 mol %), 100 °C. ^b¹H NMR yield with 1,1,2,2-tetrachloroethane (0.5 mmol) as internal standard. ^cIsolated yield.

elimination of HCl in the coordination process. A similar deprotonation process occurs during the complex formation of *N*-(2-pyridyl)pyridine-2'-carboxamide with PdCl₂.⁸ As a result, palladium forms a covalent bond with the nitrogen atom of the amide group. In addition, it can form two coordination bonds with heterocyclic fragments of isoxazole (or isothiazole)^{8b,c} and pyrimidine.^{4c} In the pyrimidine molecule, both N atoms are equivalent; therefore, a choice between them is a priori impossible. The accurate structural information for the complexes was obtained by single crystal X-ray analysis of compounds **8** and **10** (Figure 1). Crystal data and structure

Scheme 4. Gram-Scale Synthesis of the UV-Sunscreen Agent Octinoxate 25 from 26 and 27 in the Presence of the Pd₂Cl₂(L²-H)₂ Complex



Scheme 5. Gram-Scale Synthesis of 2-(Phenylethynyl)aniline 27 in the Presence of the Pd₂Cl₂(L²-H)₂ Complex



refinement details for complexes **8** and **10** are gathered in Table 1S (SI). The compounds are “head to tail” N,N,N binuclear palladium(II) complexes of the composition Pd₂Cl₂(L-H)₂, where L is ligand **4** for complex **8** and ligand **6** for complex **10** (Scheme 1). The obtained complexes conceptually mimic coordination centers of much less accessible N,N,N-pincer-type complexes, but represent a different type of coordination compounds. In traditional pincer complexes, one ligand provides three coordination centers, two of which have identical or different electronic properties, for one palladium atom. The functionality of ligand elements in accordance with a specific place in the coordination sphere of the presented complexes family is similar to that of the traditional monoligand N,N,N-pincer-type complexes. However, the implementation of such coordination in the discussed framework is possible only when binuclear complexes are formed, in which one ligand provides three coordination centers, but for two atoms of palladium, and participation of the second ligand is mandatory. As a result, the formation of a binuclear complex with three N-coordinating centers per one palladium atom is observed.

Complex molecules of **8** and **10** include all atoms of their asymmetric units. In both complexes, each of the two palladium atoms shows distorted square planar coordination, formed by one chlorine atom, amide and azole nitrogen atoms of one ligand, and the pyrimidine nitrogen atom of another ligand. The τ -descriptor of four-coordination⁹ takes the values of 0.11 and 0.09 for complex **8** and of 0.09 and 0.08 for complex **10**, pointing to slight distortion of coordination squares. Coordination bond lengths in complexes **8** and **10** are usual (Table 2S, SI). Complexes **8** and **10** belong to highly unusual 1,3,5,7-tetraza-2,6-dipalladocane frame.

Initially, the catalytic activity of novel complexes Pd₂Cl₂(L¹-H)₂–Pd₂Cl₂(L⁴-H)₂ was investigated in the model Suzuki–Miyaura reaction of 3-bromobenzoic acid **11** with 4-methoxyphenylboronic acid **12** in the presence of 0.1 mol % Pd. The reaction was carried out in an aqueous medium in the

presence of K_2CO_3 as a base using our previously optimized conditions.^{4d,e} A high yield of the corresponding cross-coupling product was obtained when the reaction proceeded at 20–40 °C for 15–30 min using isoxazole complexes $Pd_2Cl_2(L^1-H)_2$ and $Pd_2Cl_2(L^2-H)_2$ (Table 1, entries 1, 2, 4 and 5), whereas at 100 °C the reaction time decreased to 1–2 min for isoxazole complexes (entries 3 and 6) and 20 min for isothiazole complexes (entries 12 and 15). It is noteworthy that under the catalysis by new complexes we did not observe the formation of Pd black even after full completion of the reaction (controlled by optical microscopy). It is possible that only a “homeopathic” part of the initial palladium complex participates in the catalytic cycle, and it is logical to try to reduce its amount. Indeed, when the amount of palladium was decreased to 0.01–0.001 mol % Pd [complex $Pd_2Cl_2(L^2-H)_2$], a quantitative amount of cross-coupling product was obtained after 4–5 min at 100 °C with TON up to 100 000 and TOF up to 1 200 000 h^{-1} (entries 7 and 8). When using aryl iodides in the reaction, the amount of catalyst can be reduced even to 0.0001 mol % (1 ppm). Under these conditions, the reaction proceeded quantitatively in 5 min with high TON of 1 000 000 and TOF of 12 000 000 h^{-1} (entry 9). It is important to note that in the presence of Na_2PdCl_4 (without N-ligands) reaction mixtures quickly changed to a dark color and Pd-black formation was observed (entries 16 and 17).

The reaction of different aryl bromides **11a–d** with electron-deficient arylboronic acids **12a–f** in the presence of 0.01 mol % Pd led to the desired biaryls in high yields (93–98%, Table 3S, entries 1–7, SI). Moreover, sterically hindered 2-formylphenylboronic acid **12d** underwent coupling with **11d** to produce the bifunctional product **13dd** in 95% yield (Table 3S, entry 5). These results indicate that *N*-(pyrimidin-2-yl)-1,2-azole-3-carboxamide complexes $Pd_2Cl_2(L^1-H)_2$ – $Pd_2Cl_2(L^4-H)_2$ are very effective catalysts for the Suzuki reaction in aqueous media (comparison with other catalytic systems is presented in Table 6S, SI).

To demonstrate the potential utility of the new catalytic system, the gram-scale synthesis of the key intermediate in the synthesis of Boscalid fungicide was performed (Scheme 2, compound **16**),¹⁰ as well as one-step synthesis of 2',4'-difluoro-4-hydroxy-[1,1'-biphenyl]-3-carboxylic acid (diflunisal) **19**, a nonsteroidal anti-inflammatory drug (NSAID) (Scheme 3).¹¹

We also evaluated the catalytic activity of $Pd_2Cl_2(L-H)_2$ complexes in the Mizoroki–Heck reaction and the Sonogashira reaction (Tables 2, 3, 3S, and 4S). The practical applicability was demonstrated by the scaled-up synthesis of the UV-sunscreen agent octinoxate (Scheme 4) and 2-(phenylethynyl)aniline **28** (Scheme 5), as 2-alkynyl anilines, key intermediates in the indole synthesis.¹²

It should be emphasized that the reactions of water-insoluble reagents easily proceed in water in the presence of trace amounts (1 mol %) of Bu_4NBr as the phase transfer catalyst (Tables 2 and 3; Schemes 2, 4, and 5). No byproducts were detected for the catalysts, and cross-coupling products were isolated without the application of chromatography.

For the first time, cyclic phosphine-free “head to tail” *N,N,N*-pincer-like Pd(II) complexes on *N*-(pyrimidin-2-yl)-1,2-azole-3-carboxamide frameworks with deprotonated amide groups were obtained and used as high TON and TOF catalysts for C–C cross-coupling reactions under green conditions. The obtained complexes conceptually mimic the coordination centers of much less accessible *N,N,N*-pincer-type complexes

and represent a new family of catalysts containing an unusual 1,3,5,7-tetraza-2,6-dipalladocene frame.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c01035>.

Details of synthesis, X-ray diffraction studies, and catalysis (PDF)

Accession Codes

CCDC 1976251–1976252 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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