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Pd-Catalyst Containing a Hemilabile P,C-Hybrid Ligand in Amino Dicarbonylation of Aryl Halides for Synthesis of α-Ketoamides

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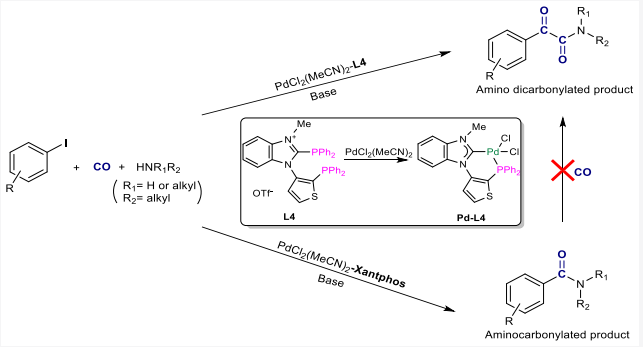
ABSTRACT: The amino dicarbonylation of aryl halides affording α-ketoamides with Pd catalysts is highly dependent on the stereoelectronic properties of the involved ligands. Ionic diphosphine ligand **L4** can serve as precursor of a hemilabile P,C (phosphine, carbene)-hybrid ligand to form a stable Pd(II)-complex, **Pd-L4**. In contrast, analogues **L1**−**L3** with a similar 1-(thiophen-3-yl)-benzimidazolyl skeleton behave as typical (mono/di)phosphines. The catalytic system resulting from the complexation of $PdCl_2(MeCN)_2$ and **L4** exhibits good catalytic performance in terms of aryl iodides conversion (81−95%) and α-ketoamide selectivity (80−91%), as well as the available recyclability in the RTIL of $[Bpy]BF_4$. The *in situ* FT-IR analysis reveals that the $PdCl_2(MeCN)_2$−**L4** catalytic system favors the amino dicarbonylation toward α-ketoamides according to the proposed mechanism of cycle I, which involves two independent CO-insertion steps.



INTRODUCTION

α-Ketoamides, a unique class of amines containing adjacent carbonyl and acylamino groups in their structures [−C(═O)−C(═O)−N−] are often found in the natural products. Due to good biological activities, they are widely applied to manufacture important pharmaceuticals such as various protease inhibitors,[1−3] and medicines for the treatment of chronic hepatitis C.[4,5] In addition, α-ketoamides featured with multiple-reactive centers are able to serve as precursors for the synthesis of α-amino acids, α-hydroxy acids, and heterocyclic compounds, among others.[6,7] On the basis of their wide applications and important roles in the fields of biochemistry, agrochemistry, and food production, the synthesis of α-ketoamides has attracted much attention.

In comparison to the traditional multiple-step synthesis under harsh conditions,[8−10] the one-pot amino dicarbonylation of readily available aryl halides provides a convenient protocol for the production of α-ketoamides as summarized in many reviews,[11−15] wherein a variety of elaborately selected Pd-complex catalysts have been applied. It has been recognized that ligands play a crucial role in adjusting the performance of the involved Pd catalysts for this transformation. For example, Kondo et al.[16] showed that a t-Bu_3P-modified $Pd_2(dba)_3$ complex exhibited excellent catalytic performance for the amino dicarbonylation of *p*-iodonitrobenzene, leading to the formation of the target α-ketoamides in yields of 77%. Jensen et al.[17] found that when Xantphos, a widely used bidentate phosphine ligand, was applied in this reaction, the more efficient amino dicarbonylation of aryl halides was observed under microwave irradiation. In addition, the other protocols for amino dicarbonylation of amines have been achieved with dppf-modified Pd catalyst[18] as well as NHC-modified Cu-catalyst.[19]

Compared with the classic bidentate phosphines, hybrid ligands containing P,O-, P,N-, or the other hybrid double-coordination sites are more versatile for design of the powerful transition-metal catalysts in chemistry of homogeneous catalysis. Beller and his co-workers have reported many successful carbonylations such as the alkoxycarbonylation of alkynes[20] and cyclocarbonylation of alkynols[21] over the transition-metal complexes modified by the P,N-hybrid ligands. Braunstein et al.[22] also designed and synthesized a new type of P,O-hybrid ligand to anisotropically chelate Pd center, which played crucial roles in affording the stabilized Pd-acyl complex intermediate upon CO insertion and then promoting the reaction rate dramatically. Without a doubt, many hybrid ligands have also been used in the research of amino dicarbonylation. As an example, Inoue et al.[23] found that a dinuclear palladium complex bridged by a novel PNNP ligand

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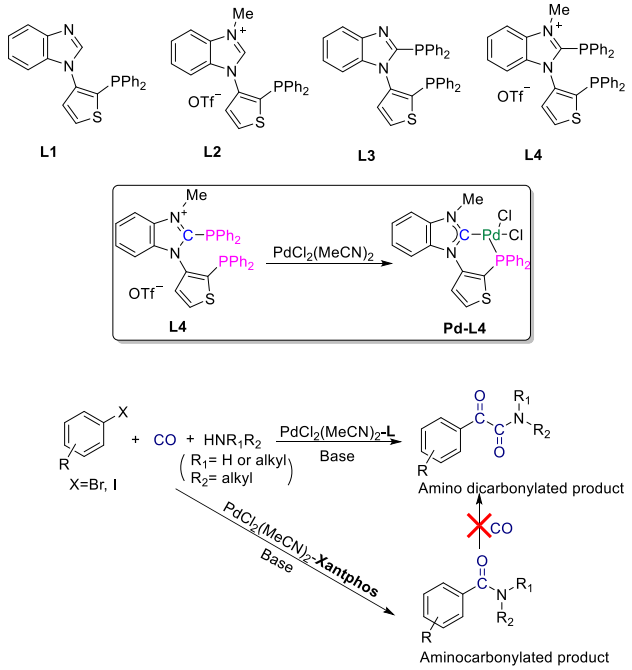
was an efficient and selective catalysts for the amino dicarbonylation of PhI.

In recent years, the research on design/synthesis of phosphine, carbene (P,C)-hybrid ligands and applications in homogeneous catalysis has attracted much attention.[24−26] For example, in Zhou's group,[27] a novel P,C-hybrid ligand was prepared successfully, which proved to spur Pd-catalyzed asymmetric hydroarylation of olefins greatly. In comparison to typical phosphine ligands, P,C-hybrid ligands are advantageous with the following merits. First, due to the stronger σ-donating ability as well as the weaker π-accepting nature, carbene ligands can form a more stable M═C bond with a bond energy higher than that of the typical M−P bond if phosphines are involved, which is beneficial to the stability of the transition-metal catalysts;[28] Second, P,C-hybrid ligands possess one weakly coordinating group (soft P-donor) that can reversibly release during the catalytic cycle providing unsaturation at the metal center. Thus, the less strongly bound moiety (−PPh_2) of this ligand, called hemilabile, is capable of temporarily holding a coordination site on the metal for protection and then being released for the substrate insertion timely.[29−34] Obviously, the available carbene can protect the metal catalytic center against deactivation via the consolidated M═C ligation, while the coexisting phosphino-moiety can dissociate in a timely manner from the metal center to accommodate substrate activation. Third, the coordination nature of the P,C-hybrid ligands is sensitively discriminated by their steric and electronic properties. Accordingly, P,C-hybrid ligands in combination of phosphines with carbenes in one molecular units can effectively warrant the stability as well as the activity of the corresponding metal catalysts because of the inherent dissimilar coordination ability.

Interestingly, the ionic bidentate imidazoliophosphines have been observed as the available precursors of P,C-hybrid ligands for the preparation of P,C-ligand-chelating transition metal complexes, as reported by Chauvin.[35,36] Led by Chauvin's synthesis method, herein we designed and synthesized a novel ionic 3-thiophenyl-benzimidazolium-based diphosphine, **L4**, as precursor of a hemilabile P,C-hybrid ligand to afford corresponding complex **Pd-L4**, which proved an efficient and recyclable catalyst for the amino dicarbonylation of aryl halides for the first time (Scheme 1). In addition, the *in situ* high-pressure FT-IR spectroscopic technique was applied to demonstrated the predominant amino dicarbonylation over aminocarbonylation catalyzed by a **L4**-modified Pd catalyst. For comparison, phosphines **L1**−**L3** with the same 3-thiophenyl-benzimidazolyl skeleton were prepared in parallel.

Scheme 1. Amino Dicarbonylation of Aryl Halides for the Synthesis of α-Ketoamides Catalyzed by Pd-Catalyst Containing a Phosphine Ligand



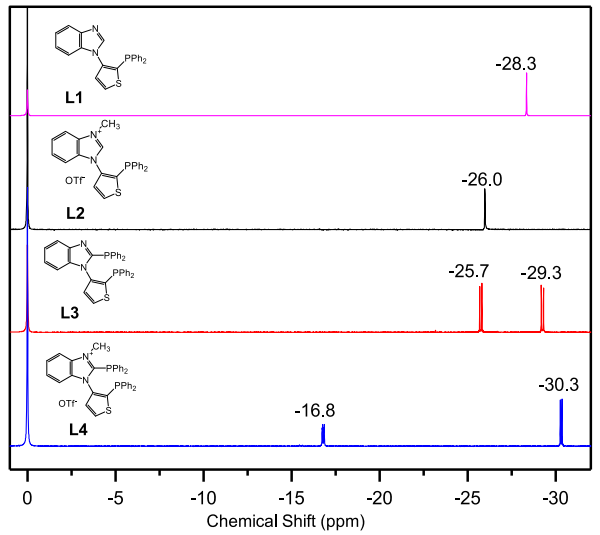


Figure 1. ^{31}P NMR spectra (202 MHz) of phosphines **L1**−**L4** (with 85% H_3PO_4 sealed in a capillary tube as an internal standard).

RESULTS AND DISCUSSION

Characterization of As-Synthesized Phosphines (L1−L4) and the Corresponding Pd-Complexes. First, monophosphines **L1** and **L2** as well as diphosphines **L3** and **L4** were successfully prepared according to the procedures reported by our group with some modifications.[37] In this work, benzimidazole instead of imidazole was used as the starting material in order to guarantee the stability of the target phosphines (**L1**−**L4**). The ^{31}P NMR spectra of **L1**−**L4** are shown in Figure 1. It is evident that the characteristic signals of **L1**−**L4** all appeared at much higher field (δ < −16 ppm) than that of PPh_3 (δ = −5.5 ppm),[38] indicating the enhanced electron density of the involved P atoms in these phosphines due to the electron-donating nature of the adjacent N/S atom. As for ionic diphosphine **L4**, the signal of PPh_2 frgament neighbored to imidazolium moiety dramatically shifts to the much lower field (δ = −16.8 ppm) in comparison to the counterpart in **L3** linked to neutral imidazolyl ring (δ = −25.7 ppm), due to the intensive electron-withdrawing nature of the positive-charged imidazolium cation, which implied that the coordination behaviors of the two PPh_2 frgaments in **L4** are completely different. The PPh_2 frgament with a chemical shift of −16.8 ppm was featured with the relatively intensive electron-deficient character, whereas the PPh_2 frgament at −30.3 ppm was more electron-rich. As for ionic monophosphine **L2** (δ = −26.0 ppm), the chemical shift of the PPh_2 fragment was just changed slightly in comparison to that in **L1** (δ = −28.3 ppm), due to the negligible influence of imidazolium cation on the remote PPh_2 fragment.

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The single-crystal X-ray diffraction analyses of **L3** and **L4** as well as that of their corresponding Pd-complexes, **Pd-L3** and **Pd-L4**, are presented in Figure 2. As for the neutral bidentate

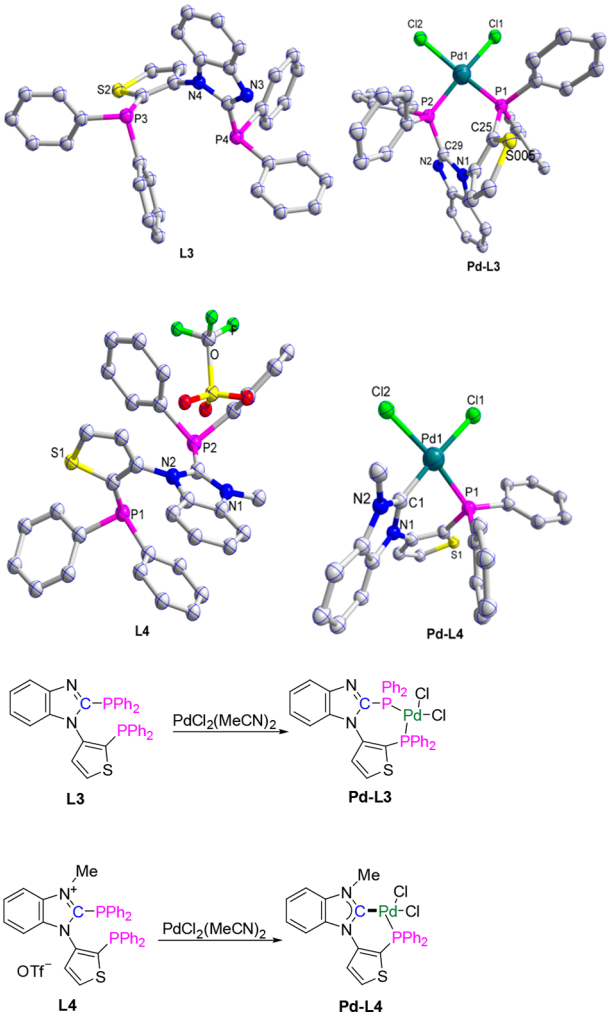

Figure 2. Single-crystal structures of **L3** and **L4** as well as their corresponding complexes, **Pd-L3** and **Pd-L4** (all H atoms and solvent molecules have been omitted for clarity). The selected bond distances (Å): (a) **Pd-L3**: Pd−P1 2.245(5), Pd−P2 2.243(3), Pd−Cl1 2.330(4), Pd−Cl2 2.365(5); (b) **Pd-L4**: Pd−C1 1.990(4), Pd−P1 2.231(10), Pd−Cl1 2.346(8), Pd−Cl2 2.363(9).

phosphine of **L3**, the two PPh_2 fragments are located in distorted *Z*(*cis*)-geometry configuration with P···P distance of 4.83 Å. The interplanar dihedral angle (θ) between benzimidazolyl and thiophenyl is 74.44°. As for the ionic bidentate analogue of **L4**, the two PPh_2 fragments are positioned in a distorted *E*-geometry with P···P distance of 3.54 Å, and the interplanar dihedral angle (θ) between benzimidazolium and thiophenyl is 65.83°. The TG/DTG analyses of **L1**−**L4** in air flow (see Figure S1) show that the thermal decomposition temperature of the ionic phosphines (**L2** and **L4**) is universally higher than their neutral analogues (**L1** and **L3**), indicating the improved stability of the ionic phosphines in open air.

The structures of the corresponding complexes, **Pd-L3** and **Pd-L4** (Figure 2), convince us that the coordination behaviors of **L3** and **L4** are substantially different, leading to the dissimilar four-coordinated Pd(II)-complexes in terms of geometry configuration and coordinating sites as well as the properties in catalysis (see below). **Pd-L3** is a typical diphosphine-chelating Pd(II)-complex, in which the two phosphorus atoms coordinated to the Pd center to form a twisted seven-membered ring structure. The bond length of Pd−P is 2.24 Å, and the P−Pd−P angle in **Pd-L3** is 92.95°. The dihedral angle between benzimidazolyl and thiophenyl is 56.74°, but it s 74.44° in **L3**. In comparison, **Pd-L4** is a P,C-chelating Pd(II)-complex with a more stabilized six-membered ring structure. The length of the Pd−C bond is just 1.99 Å, whereas the length of the Pd−P bond is 2.23 Å, which is much shorter than that in **Pd-L3** (Pd−P, 2.24 Å). The dihedral angle between benzimidazolyl and thiophenyl is 47.90°, but it is 65.83° in **L4**. Accordingly, the structure of **Pd-L3** is more severely distorted than that of **Pd-L4**. The latter is featured with better stability (see Figure S2) with indication of more consolidated Pd−P and Pd−C linkages as well as the energy-satisfied six-membered-ring configuration.

The complexation of $PdCl_2(MeCN)_2$ with **L3** and **L4** respectively upon heating at 100 °C was recorded via ^{31}P NMR spectral spectroscopy (Figure 3). It was found that the mixture

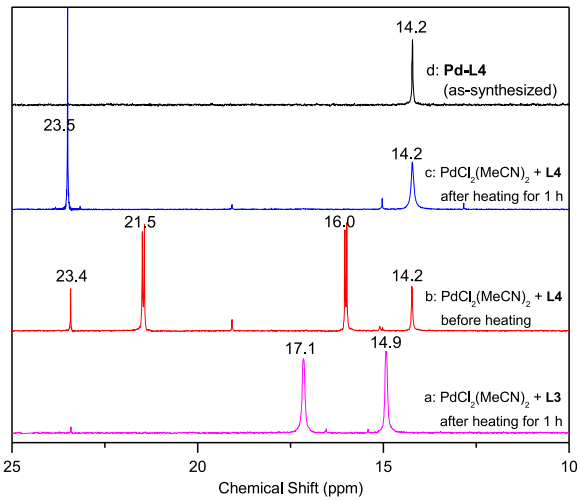

Figure 3. ^{31}P NMR spectra recorded at RT (202 MHz): a, mixture of $PdCl_2(MeCN)_2$ and **L3** after heating at 100 °C for 1 h; b, mixture of $PdCl_2(MeCN)_2$ and **L4** before heating; c: mixture of $PdCl_2(MeCN)_2$ and **L4** after heating at 100 °C for 1 h; d, as-synthesized **Pd-L4** as reference. Reaction conditions: $PdCl_2(MeCN)_2$ 0.04 mmol, **L3** or **L4** 0.04 mmol, P/Pd = 2:1, 100 °C, reaction time 1 h.

of $PdCl_2(MeCN)_2$ and **L3** after heating 100 °C for 1 h resulted in the formation of the corresponding complex, **Pd-L3**, with the characteristic signals of 17.1 and 14.9 ppm (Figure 3, spectra a), which were the same as those of as-synthesized **Pd-L3** (see the Experimental Section). Comparatively, the mixture of $PdCl_2(MeCN)_2$ and **L4** before heating showed the doublet signals of 21.5 and 16.0 ppm as well as the singlet peaks of 14.2 and 23.4 ppm (Figure 3, spectra b). After the treatment at 100 °C for 1 h, the doublet signals of 21.5 and 16.0 ppm disappeared totally, just leaving the always observed signal of 14.2 ppm (Figure 3, spectra c), which was attributed to the *in situ* formation of **Pd-L4** with reference of the as-synthesized sample of **Pd-L4** (Figure 3, spectra d). Accordingly, the doublet signals of 21.5 and 16.0 ppm in Figure 3 (spectra b) were ascribed to the *in situ* formation of the precursor of **Pd-L4**, in which ionic **L4** behaved as a normal bidentate phosphine to chelate the Pd center as in **Pd-L3**, accounting

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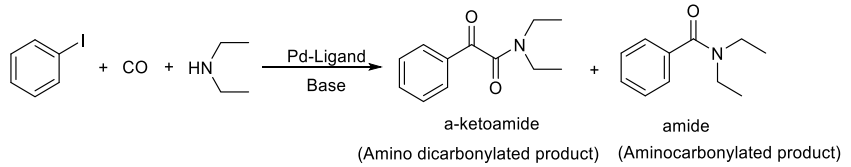
Table 1. Optimization of the Reaction Conditions for Amino Dicarbonylation of PhI with Et_2NH over L4-Modified $PdCl_2(MeCN)_2$[a]



entry	P/Pd (molar ratio)	temp. (°C)	P_{co} (MPa)	sol.	PhI/Et_2NH (molar ratio)	conv. of PhI (%)[b]	sel. (%)[b] α-ketoamide	sel. (%)[b] amide	yield of α-ketoamide (%)
1	1/1	120	3	1,4-dioxane	1/5	88	78	22	69
2	2/1	120	3	1,4-dioxane	1/5	100	83	17	83
3	4/1	120	3	1,4-dioxane	1/5	100	79	21	79
4	2/1	100	3	1,4-dioxane	1/5	93	86	14	80
5	2/1	80	3	1,4-dioxane	1/5	72	89	11	64
6	2/1	100	2	1,4-dioxane	1/5	90	84	16	76
7	2/1	100	1	1,4-dioxane	1/5	84	79	21	66
8	2/1	100	2	THF	1/5	95	91	9	86
9	2/1	100	2	toluene	1/5	100	57	43	57
10	2/1	100	2	DMF	1/5	100	83	17	83
11	2/1	100	2	THF	1/2	93	69	31	64
12	2/1	100	2	THF	1/1	92	42	58	39

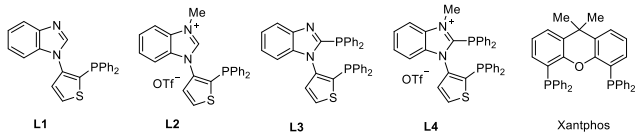
[a]Reaction conditions: $PdCl_2(MeCN)_2$ 0.02 mmol (Pd 1 mol %), PhI 2.0 mmol, K_2CO_3 4.0 mmol, solvent 3.0 mL, reaction time 8 h. [b]Determined by GC.

for the as-observed typical doublet P-signals at 21.5 and 16.0 ppm. However, the unstable precursor of **Pd-L4** was susceptible to transform into the more stable final form, **Pd-L4**, upon the cleavage of C−P bond (after heating) to provide a unique P,C-chelation mode. Simultaneously, the derivative of the ruptured PPh_2-moiety corresponded to the low-field signal of 23.4 ppm (Figure 3, spectra b and c), which was not clearly identified at present stage.[35,36,39]

Amino Dicarbonylation of Aryl Halides over Pd-Catalyst with Involvement of Different Phosphine Ligands. First, the amino dicarbonylation of PhI with Et_2NH over a **L4**-modified Pd catalyst was studied as a model reaction. The effects of various parameters such as P/Pdratio, reaction temperature, pressure of CO, solvent, and the amount of Et_2NH were investigated, and the results were listed in Table 1. The molar ratio of P/Pd displayed a significant influence on the catalytic performance in terms of conversion and selectivity of the α-ketoamide. The increase of the P/Pd ratio to 2/1 gave rise to double carbonylation, resulting in the enhanced yield of the target α-ketoamide (83%) (entry 2 vs 1). Further increase of the P/Pd ratio to 4 led to the decreased selectivity to α-ketoamide (entry 3 vs 2). Although decreasing the reaction temperature from 120 to 80 °C facilitated the selectivity to the α-ketoamide (89%), the reaction rate decreased dramatically, giving just 72% conversion of PhI (entry 5). Accordingly, 100 °C was selected as the suitable temperature (entry 4 vs 5). As expected, increasing the CO pressure as well as the amount from 1.0 to 3.0 MPa led to an increased yield for the target α-ketoamide from 66 to 80% (entries 7 and 6 vs 4). Notably, a high concentration of Et_2NH (PhI/Et_2NH ratio of 1/5) was required to drive the transformation to afford α-ketoamide rather than the amide (entries 8 vs 11 and 12). In addition, THF was selected as the best solvent upon comparing to toluene or DMF (entry 8 vs 9 and 10), leading to the formation of the α-ketoamide in the highest yield of 86% (entry 8).

With the optimal reaction conditions in hand, the effect of different phosphines on the performance of Pd catalysts was explored in the same carbonylation (Table 2). It was evident

Table 2. Pd-Catalyzed Amino Dicarbonylation of PhI with Et_2NH with the Involvement of Different Phosphine Ligands[a]



entry	ligand	conv. of PhI (%)[b]	sel. (%)[b] α-ketoamide	sel. (%)[b] amide	yield (%)
1		61	26	74	16
2	**L1**	99	81	19	80
3	**L2**	89	73	27	65
4	**L3**	100	71	29	71
5	**L4**	95	91	9	86
6[c]		93	90	10	84
7	Xantphos	100	5	95	5

[a]Reaction conditions: $PdCl_2(MeCN)_2$ 0.02 mmol (Pd 1 mol %), 0.02 mmol for diphosphine or 0.04 mmol for mon-phosphine (P/Pd = 2 molar ratio), PhI 2.0 mmol, Et_2NH 10 mmol (PhI/Et_2NH = 1/5), K_2CO_3 4.0 mmol, THF 3.0 mL, temp. 100 °C, CO 2.0 MPa, reaction time 8 h. [b]Determined by GC. [c]**Pd-L4** (0.02 mmol) was applied instead of the mixture of $PdCl_2(MeCN)_2$ (0.02 mmol) and **L4** (0.02 mmol).

that the involvement of phosphine ligands **L1**−**L4**, respectively (with P/Pd molar ratio of 2), could universally improve the transformation rate of PhI as well as the selectivity to the α-ketoamide in comparison to the case free of any ligand (entries 2−5 vs 1). Notably, the **L4**-modified $PdCl_2(MeCN)_2$ system exhibited the best catalytic performance, leading to the formation of the α-ketoamide in the yield of 86%, in

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comparison to **L1**−**L3** involved systems (entry 5 vs 2−4). As-synthesized **Pd-L4** exhibited catalytic performance nearly identical to that of the mixture of $PdCl_2(MeCN)_2$ and **L4** (entry 5 vs 6). In contrast, under the same conditions, Xantphos-involved catalytic system was predominantly responsible for the monocarbonylation to produce the amide rather than the amino dicarbonylation, resulting in just 5% yield of the ketoamide (entry 7). Accordingly, the Pd catalyst modified by **L1**−**L4** universally corresponded to the required double carbonylation to afford α-ketoamide as the major product. Especially over the **L4**-involved system with an available P,C-hybrid-chelation mode, the double carbonylation definitely dominated over the monocarbonylation process.

The evolving reaction profile for amino dicarbonylation of PhI with Et_2NH over the $PdCl_2(MeCN)_2$−**L4** system (Figure 4) showed that the transformation rate of PhI gradually

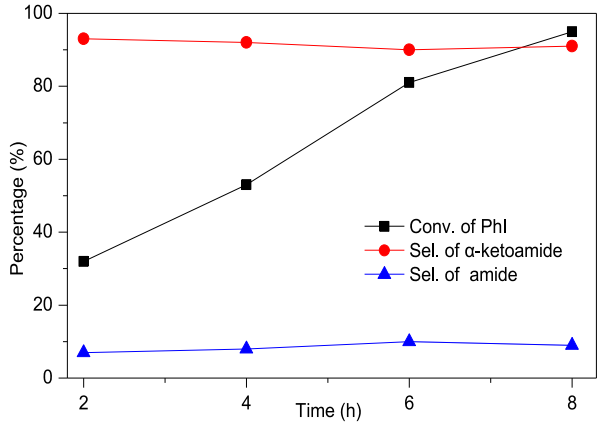

Figure 4. Evolving reaction profile for amino dicarbonylation of PhI with Et_2NH over **L4**-$PdCl_2(MeCN)_2$ system under the optimal conditions ($PdCl_2(MeCN)_2$ 0.02 mmol, **L4** 0.02 mmol, PhI 2.0 mmol, Et_2NH 10 mmol, K_2CO_3 4.0 mmol, THF 3.0 mL, temp. 100 °C, CO 2.0 MPa).

increased with the prolongation of the reaction time, but the selectivities of the two products nearly maintained the same without a waning and waxing phenomenon (selectivity for α-ketoamide, 93−91%). It was clear that the formation of the α-ketoamide was not derived from the second carbonylation of the aminocarbonylated product of *N*,*N*-diethylbenzamide, revealing that these two products were formed respectively through the independent pathways.

In order to deeply understand the reaction pathway towards the amino dicarbonylation or aminocarbonylation over different Pd catalysts, the evolving reaction processes of PhI with Et_2NH in CO atmosphere (0.5 MPa) were further monitored *in situ* by FT-IR spectroscopy[40] (Figure 5). As shown in Figure 5A, over the $PdCl_2(MeCN)_2$-Xantphos catalytic system, the absorption at 1598 cm^{-1} appeared gradually when the temperature increased from 30 up to 100 °C, which was attributed to the characteristic peak of carbonyl group in *N*,*N*-diethylbenzamide as the aminocarbonylated product (see Figure S3a with the authentic sample as reference). Comparatively, over the $PdCl_2(MeCN)_2$−**L4** system (Figure 5B), the two absorption peaks at 1640 and 1679 cm^{-1} grew to reach the maximum magnitude as the temperature increased from 30 to 100 °C, which was attributed to the formation of the α-ketoamide as the amino dicarbonylated product (see Figure S3b with the authentic sample as the reference). In Figure 5B, the absorption of 1598 cm^{-1} belonging to the aminocarbonylated product of *N*,*N*-diethylbenzamide was just slightly observable without waxing and waning phenomena, revealing that the formation of the α-ketoamide was due to the continuous CO-insertion over the $PdCl_2(MeCN)_2$−**L4** catalyst rather than the outcome of second carbonylation of *N*,*N*-diethylbenzamide. This means that the amino dicarbonylation toward α-ketoamides over the $PdCl_2(MeCN)_2$−**L4** system and the aminocarbonylation toward amides over $PdCl_2(MeCN)_2$-Xantphos system proceed by following a completely distinct mechanism. Anyway, the characteristic vibrations of CO-ligated Pd-intermediate complexes[41−43] were unobservable, which overlapped with the intensive absorptions of the products of the α-ketoamide or/and the amide (1600−1700 cm^{-1}).

On the basis of the above results and the previous reports,[43,44] the mechanism of carbonylation of aryl iodides with amine over Pd catalyst containing different phosphines was proposed in Scheme 2. Initially, mixing of $PdCl_2(MeCN)_2$ with the diphosphine ligand in CO atmosphere leads to the formation of an active Pd(0)-intermediate (**A**). In cycle I, when **L4** as a more suitable precursor to a hemilabile P,C-hybrid ligand is applied, intermediate **B** will be readily formed, wherein the involved P,C-hybrid ligand is featured with hemilabile "coordination−dissociation" character.[29−34] Immediately, the intermediate **B** serving as the real active catalyst is oxidatively added by ArI to afford intermediate **C**, which is able to irreversibly dissociate the labile PPh_2 fragment to make accommodation for the amine to form intermediate **D** upon scavenging HI by K_2CO_3 and concurrent CO-coordination. **D** is then rapidly converted to acylpalladium intermediate **E** after CO insertion to the Pd−Ar bond along with the second CO coordination. The continuous migration and insertion of the coordinated CO to the Pd−N bond affords diacylpalladium intermediate **F**,[42] which corresponds to the formation of the target α-ketoamide upon reductive coupling of two carbonylated moieties, accompanied by the regeneration of catalyst **B**. Reasonably, the presence of the amine substrate in much high concentration definitely gives rise to the formation of **D** and consequently the enhanced selectivity to α-ketoamide as observed in Table 1 (entry 8 vs 12). Alternatively, in cycle II, when Xantphos as a rigid and highly symmetrical diphosphine is applied, stabilized intermediate **A** is readily added by ArI to afford intermediate **B′**, wherein the dissociation of one $-PPh_2$ fragment from the Pd center accommodate the amine substrate was greatly suppressed due to the favorable pincer-type chelation. As a result, **B′** transforms into **C′** after ligand-exchange of I^- by CO. Then **C′** is converted into the acylpalladium intermediate **D′** upon insertion of CO to the Pd−Ar bond, along with the concurrent coordination of the amine substrate. Since the successive CO insertion into Pd−CO bond in **D′** (giving a Pd−CO−COAr species) is not going to take place, **D′** finally affords the amide as the final product via reductive elimination. In comparison to **L1**−**L3**, **L4** as the most suitable precursor to a hemilabile P,C-hybrid ligand inherently facilitates the amino dicarbonylation.

In contrast, the use of room-temperature ionic liquids (RTILs) has been regarded as the efficient alternative to immobilize the homogeneous catalysts.[45−48] **Pd-L4** obtained by complexation of $PdCl_2(MeCN)_2$ with **L4** was featured with good stability and high polarity, which was readily soluble and compatible in many RTILs. Thus, the recycling of $PdCl_2(MeCN)_2$−**L4** system in RTIL was conducted in the

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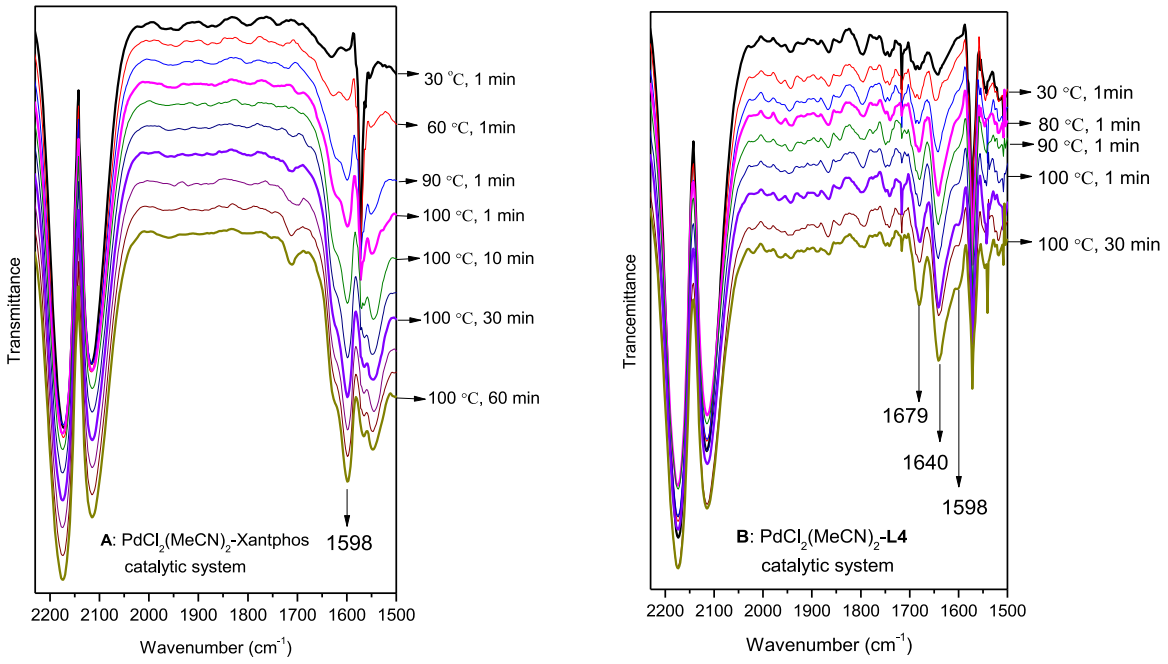
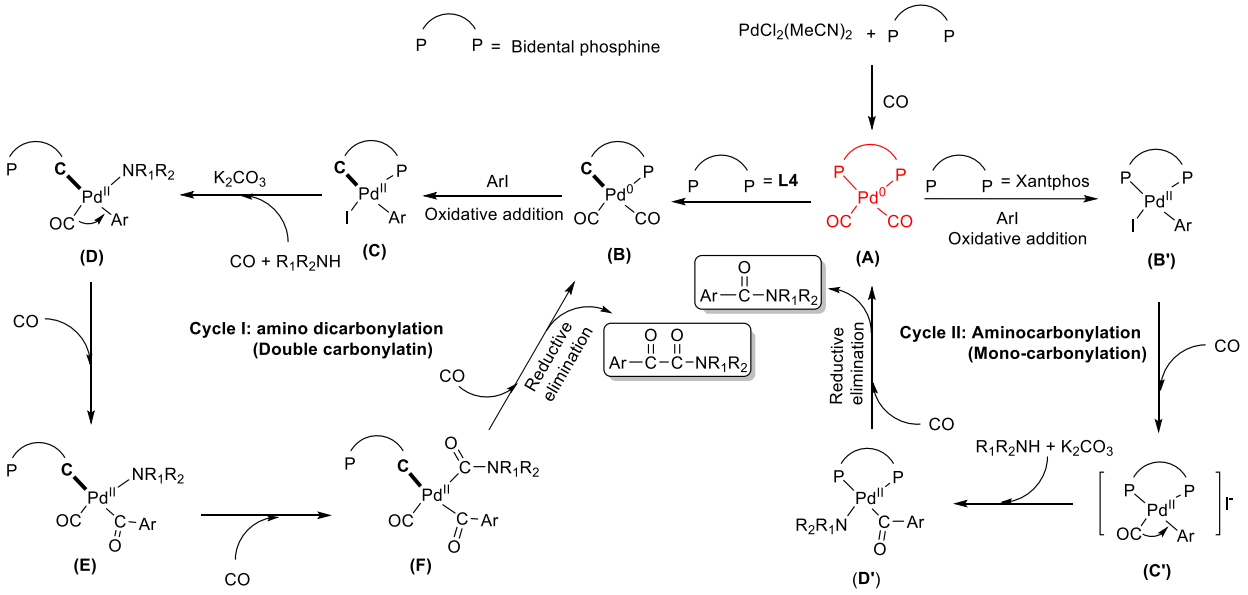


Figure 5. Evolving reaction processes of PhI with Et_2NH in CO atmosphere (0.5 MPa) over $PdCl_2(MeCN)_2$-Xantphos (A) and $PdCl_2(MeCN)_2$–**L4** (B), respectively, (THF as solvent) monitored by FT-IR spectroscopy.

Scheme 2. Proposed Mechanism over Pd-Catalyst Containing Different Ligands for Carbonylation of ArI with Amine



amino dicarbonylation of PhI with Et_2NH (Table 3). Upon screening the different RTILs as the reaction media (see Table S1), $[Bpy]BF_4$ was found to be the best one in which the $PdCl_2(MeCN)_2$–**L4** system could be recycled for 6 runs with well-maintained activity and selectivity. The leaching of Pd in the combined organic phase upon 6 runs was just 0.37% (ICP-OES analysis). During the recycling uses, the continuously increased concentration of Et_2NH upon accumulation gave further rise to the selectivity of the α-ketoamides.

In addition, the generality of the $PdCl_2(MeCN)_2$–**L4** system for the amino dicarbonylation of different aryl halides with amines was investigated in Table 4. When the electron-donating substituents like $-CH_3$ or $-OCH_3$ were introduced at the *ortho*-/*para*-position of PhI, the target α-ketoamide was obtained with high yields (entries 2–5, 73–85%). However, the electron-withdrawing groups like $-CN$ or $-NO_2$ at the *para*-position of PhI led to the drop of the selectivity to α-ketoamide, while the conversion of PhI was well-maintained (entries 6 and 7). Reasonably, $-CN$ or $-NO_2$ substituted PhI resulted in the weakened Pd–Ar linkage while consolidating Pd–P bond in intermediate **C** (Scheme 2), which did not favor the timely dissociation of PPh_2 fragment along with to the increased tendency to follow cycle II. The $PdCl_2(MeCN)_2$–**L4** system was also applicable to the efficient conversion of 2-iodonaphthalene, leading to 76% yield of the corresponding α-ketoamide (entry 8). When the different (primary/secondary) amines with less steric hindrance such as Me_2NH, pyrrolidine, and cyclohexylamine were applied instead of Et_2NH, good-to-

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Table 3. Recycling Uses of $PdCl_2(MeCN)_2$–L4 Catalytic System in the RTIL of $[Bpy]BF_4$ for the Amino Dicarbonylation of PhI with Et_2NH[a]

run	conv. of PhI (%)[b]	sel. (%)[b]		yield (%)
		α-ketoamide	amide	
1 (fresh)	99	89	11	88
2	100	94	6	94
3	99	92	8	91
4	96	95	5	91
5	97	94	6	91
6	94	91	9	86

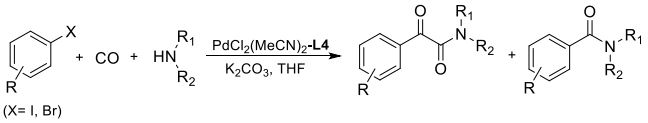
[a]Reaction conditions: $PdCl_2(MeCN)_2$ 0.02 mmol (Pd 1 mol %), **L4** 0.02 mmol (P/Pd = 2 molar ratio), PhI 2.0 mmol, Et_2NH 10.0 mmol, K_2CO_3 4.0 mmol, $[Bpy]BF_4$ (*N*-butyl-pyridinium tetrafluoroborate) 3.0 mL, temp. 100 °C, CO 2.0 MPa, reaction time 8 h. [b]Determined by GC.

moderate yields of α-ketoamides (64–85%) were obtained (entries 9–12). Notably, when *n*-$BuNH_2$ was used as a primary amine, 87% conversion of PhI along with 82% selectivity to α-ketoamide was observed (entry 12), but without the formation of Schiff base (which was the product from the subsequent reaction of the obtained α-ketoamide with *n*-$BuNH_2$).[43] As for diisopropylamine with bulky steric hindrance, the low conversion of PhI (28%) and 100% selectivity to the amide were observed (entry 13), due to the completely inhibited amine coordination to form intermediate **D** in cycle I (Scheme 2). When aniline was applied to repeat the reaction under the same conditions, only the aminocarbonylation proceeded smoothly, affording 76% yield of *N*-phenylbenzamide (entry 14) since aniline could not serve as a competitive N-containing ligand (due to its weak basicity) to supplant the occupied phosphine as depicted in cycle I (Scheme 2). When PhBr was applied in place of PhI, 56% conversion of PhBr was obtained (entry 15 vs 1) along with 86% selectivity to the α-ketoamide. Due to the C–Br bond being stronger than C–I, the sluggish oxidative addition of PhBr to Pd catalyst **A** (Scheme 2), which was the rate-determining step for this carbonylation,[40] dramatically limited the transformation rate of PhBr.

CONCLUSION

The novel 1-(thiophen-3-yl)-benzimidazolyl-based phosphines **L1–L4** were purposefully synthesized in order to evaluate their electronic and steric effects on Pd-catalyzed amino dicarbonylation of aryl halides with amines for the synthesis of α-ketoamides. It was found that the ionic bidentate phosphine ligand of **L4** could serve as a potential P,C-hybrid ligand with hemilability, affording the stable P,C-chelating Pd(II)-complex, **Pd-L4**, whereas analogues **L1–L3** behaved as the typical (mono/di)phosphines. The **L4**-modifed $PdCl_2(MeCN)_2$ catalytic system, upon forming the P,C-chelating Pd catalyst under the applied reaction conditions, exhibited good catalytic performance in terms of aryl iodide conversion (81–95%) and α-ketoamide selectivity (80–91%). In addition, the $PdCl_2(MeCN)_2$–**L4** catalytic system could be reused in the RTIL of $[Bpy]BF_4$ (as the reaction medium instead of THF) at least for 6 runs without obvious activity loss. The leaching of Pd in the combined organic phase upon 6 runs was just 0.37% (ICP-OES analysis). *In situ* FT-IR analysis revealed that the $PdCl_2(MeCN)_2$–**L4** catalytic system absolutely preferred the amino dicarbonylation toward α-ketoamides by following the proposed mechanism of cycle I, wherein the two CO insertions

Table 4. Generality of $PdCl_2(MeCN)_2$–L4 Catalytic System for the Amino Dicarbonylation of Different Aryl Halides with Amines[a]



Entry	Aryl halide	Amine	Conv. (%)[b]	Sel. (%)[b]		Yield (%)
				α-ketoamide	Amide	
1			95	91	9	86
2			95	90	10	85
3			84	81	19	68
4			92	88	12	80
5			89	83	17	73
6			98	52	48	51
7			100	31	69	31
8			90	85	15	76
9			98	87	13	85
10			81	80	20	64
11			89	84	16	74
12			87	82	18	71
13			28	0	100	0
14			76	0	100	0
15			56	86	14	48

[a]Standard reaction conditions: $PdCl_2(MeCN)_2$ 0.02 mmol (Pd 1 mol %), **L4** 0.02 mmol, aryl iodide 2.0 mmol, amine 10.0 mmol, K_2CO_3 4.0 mmol, THF 3.0 mL, temp. 100 °C, CO 2.0 MPa, reaction time 8 h. [b]Determined by GC and the isolated α-ketoamides were further characterized by $^1H/^{13}C$ NMR spectra provided in the Supporting Information.

happened successively, rather than the tandem second carbonylation of the aminocarbonylated product of amide. It was noted that the excess presence of the aliphatic amine substrate dually as the competitive ligands gave rise to the dissociation of coordinated PPh_2 fragment from Pd center, warranting the target amino dicarbonylation for the generation of α-ketoamides.

EXPERIMENTAL SECTION

Reagents and Analysis. Chemical reagents were purchased from Shanghai Bide Pharmatech Ltd. and Shanghai Aladdin Chemical Reagent Co., Ltd., and used as received. The solvents were dried and distilled before use. $^1H/^{13}C$ NMR and ^{31}P NMR spectra were recorded on a Bruker Avance 500 spectrometer. Gas chromatography (GC) was performed on a SHIMADZU-2014 equipped with a DM-

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Table 5. Crystal Data and Structure Refinement for Pd-L3 and Pd-L4

	Pd-L3	Pd-L4
empirical formula	$C_{35}H_{26}Cl_2N_2P_2PdS$	$C_{24}H_{19}Cl_2N_2PPdS$
formula weight	745.88	575.74
crystal system	monoclinic	monoclinic
space group	$C2/c$	$P2_1/n$
a (Å)	33.2928(14)	10.97340(10)
b (Å)	10.3314(4)	15.11960(10)
c (Å)	19.5991(9)	13.54790(10)
α (deg)	90	90
β (deg)	96.624(4)	92.3220(10)
γ (deg)	90	90
V (Å^3)	6696.3(5)	2245.93(3)
Z	8	4
d_{calc}(g cm^{-3})	1.480	1.703
μ (mm^{-1})	7.636	10.516
T (K)	100	100
λ(Cu Kα) (A)	1.54184	1.54184
total reflections	30865	55168
unique reflections (R_{int})	5950 (0.1131)	3980 (0.1174)
R_1 [$I \geq 2\sigma(I)$]	0.1477	0.0444
wR_2 (all data)	0.3043	0.1162
F (000)	3008	1152

Wax capillary column (30 m × 0.25 mm × 0.25 μm). TG/DTG analysis was performed on a thermogravimetric analyzer (TGA/SDTA/SF/1100/851e). FT-IR spectra were obtained using a Nicolet NEXUS 670 spectrometer. The amounts of Pd and P in the sample were quantified by using an inductively coupled plasma optical emission spectrometer (ICP-OES) on an Optima 8300 instrument (PE Corporation).

Synthesis. *1-(2-(Diphenylphosphanyl)thiophen-3-yl)-1H-benzimidazole (**L1**).* **L1** was prepared according to the procedures reported by our group[37] with some modifications. Under N_2 atmosphere, benzimidazole (5.90 g, 50 mmol), 3-bromothiophene (9.78 g, 60 mmol), L-proline (2.30 g, 20 mmol), K_2CO_3 (14.51 g, 105 mmol), and CuI (1.91 g, 10 mmol) were added to DMSO (150 mL), and the mixture was stirred vigorously at 130 °C for 24 h. Water (150 mL) was added to the system after completion of the reaction, and the mixture was extracted with ethyl acetate (3 × 80 mL). After drying with anhydrous sodium sulfate, the combined organic phase was concentrated by vacuum. The residue was purified by column chromatography on silica gel, using petroleum ether/ethyl acetate (2:1) as eluant, to give the product 1-(thiophen-3-yl)-1*H*-benzimidazole as a white solid (5.60 g, yield of 56%). ^{1}H NMR ($CDCl_3$, ppm): 8.15 (s, 1H, NC*H*N), 7.90−7.92 (m, 1H, NCC*H*), 7.56−7.60 (m, 2H, 2SC*H*), 7.45 (dd, 1H, NCC*H*), 7.38−7.40 (m, 2H, 2CC*H*), 7.35 (dd, 1H, SCC*H*).

Under N_2 atmosphere, a solution of 1-(thiophen-3-yl)-1*H*-benzimidazole (2.00 g, 10 mmol) in dry THF (100 mL) was cooled to −78 °C, and then *n*-BuLi (2.5 M in hexane, 4.40 mL, 11 mmol) was added dropwise. After stirring vigorously for 1 h, the obtained reaction mixture was added dropwise to chlorodiphenylphosphine (PPh_2Cl, 2.30 g, 11 mmol). The resultant mixture was stirred for another 1 h at −78 °C and then warmed up to room temperature naturally. After quenching the excess *n*-BuLi with deionized water, the mixture was extracted with ethyl acetate (3 × 80 mL), and the combined organic phase was concentrated by vacuum. The residue was purified by column chromatography on silica gel, using petroleum ether/ethyl acetate (3:1) as eluant, to give product **L1** as a white solid (2.34 g, yield of 61%). ^{1}H NMR ($CDCl_3$, ppm): 7.87−7.90 (m, 2H, SC*H*C*H*), 7.75 (dd, 1H, NC*H*N), 7.36−7.43 (m, 12H, P*Ph*$_2$ + 2NCC*H*), 7.33−7.35 (m, 2H, 2CC*H*). ^{31}P NMR ($CDCl_3$, ppm): −28.3 (s, *P*Ph$_2$). CHN elemental analysis of **L1** ($C_{23}H_{17}N_2PS$) (found, %): C 71.59, H 4.17, N 7.61 (calcd., C 71.86, H 4.46, N 7.29).

*1-(2-(Diphenylphosphanyl)thiophen-3-yl)-3-methyl-1H-benzimidazol-3-ium trifluoromethanesulfonate (**L2**).* Under N_2 atmosphere, a solution of **L1** (0.79 g, 2 mmol) in dry dichloromethane was cooled to −78 °C and then methyltrifluoromethanesulfonate (MeOTf, 0.33 g, 2 mmol) was added dropwise. The obtained mixture was stirred for 1 h at −78 °C and then warmed up to room temperature naturally. After removal of solvent under vacuum, the residue was recrystallized in dichloromethane/diethyl ether to give product of **L2** as a white solid (0.58 g, yield of 73%). ^{1}H NMR ($CDCl_3$, ppm): 9.55 (s, 1H, NC*H*N), 7.78−7.83 (m, 2H, SC*H*C*H*), 7.68−7.73 (m, 1H, CC*H*), 7.56−7.60 (m, 1H, CC*H*), 7.50 (dd, 1H, ***NCCH***), 7.32−7.46 (m, 11H, P*Ph*$_2$+NCC*H*), 4.22 (s, 3H, *CH*$_3$). ^{31}P NMR ($CDCl_3$, ppm): −26.0 (s, *P*Ph$_2$). CHN elemental analysis of **L2** ($C_{25}H_{20}F_3N_2O_3PS_2$) (found, %): C 54.95, H 3.48, N 4.92 (calcd., C 54.74, H 3.68, N 5.11).

*2-(Diphenylphosphanyl)-1-(2-(diphenylphosphanyl)thiophen-3′-yl)-1H-benozimidazole (**L3**).* **L3** was obtained with a yield of 69% according to the preparation procedures for **L1**. A small difference between the preparation procedures of **L1** and **L3** is that when the temperature droped to −78 °C, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (2 equiv) was added to the reaction solution before *n*-BuLi. A sample suitable for X-ray diffraction analysis was obtained by slow volatilization of an petroleum ether/ethyl acetate (5:1) solution containing **L3**. ^{1}H NMR ($CDCl_3$, ppm): 7.91 (d, 1H, SC*H*), 7.60 (dd, 1H, SCC*H*), 7.52 (td, 2H, 2CC*H*), 7.43−7.48 (m, 2H, P*Ph*$_2$), 7.32−7.36 (m, 17H, P*Ph*$_2$), 7.16 (t, 1H, P*Ph*$_2$), 6.97 (d, 1H, NCC*H*), 6.77 (dd, 1H, NCC*H*). ^{31}P NMR ($CDCl_3$, ppm): −25.7 (d, P^1Ph$_2$), −29.3 (d, P^2Ph$_2$). CHN elemental analysis of **L3** ($C_{35}H_{26}N_2P_2S$) (found, %): C 74.16, H 4.38, N 5.23 (calcd, C 73.93, H 4.61, N 4.93).

*2-(Diphenylphosphanyl)-1-(2-(diphenylphosphanyl)thiophen-3′-yl)-3-methyl-1H-benzimidazol-3-ium trifluoromethanesulfonate (**L4**).* **L4** was obtained with a yield of 65% after the quaternization of **L3** by MeOTf according to the preparation procedures for **L2**. A sample suitable for X-ray diffraction analysis was obtained by slow volatilization of an dichloromethane/diethyl ether (1:5) solution containing **L4**. ^{1}H NMR ($CDCl_3$, ppm): 8.02 (d, 1H, SC*H*), 7.66−7.71 (m, 2H, 2CC*H*), 7.27−7.58 (m, 21H, 2P*Ph*$_2$ + SC*H*), 7.08 (dd, 1H, NCC*H*), 6.92 (d, 1H, NCC*H*), 3.79 (s, 3H, *CH*$_3$). ^{31}P NMR ($CDCl_3$, ppm): −16.8 (d, P^1Ph$_2$), −30.3 (d, P^2Ph$_2$). CHN elemental analysis of **L4** ($C_{37}H_{29}F_3N_2O_3P_2S_2$) (found, %): C 60.89, H 4.33, N 4.11 (calcd, C 60.65, H 3.99, N 3.82).

*Pd(II)-Complexes **Pd-L3** and **Pd-L4**.* Under N_2 atmosphere, **L3** (0.23 g, 0.4 mmol) and $PdCl_2(MeCN)_2$ was dissolved in dry dichloromethane (2 mL). The mixture was stirred for 1 h at 100 °C. Then dichloromethane was removed to obtain a yellow solid, which was dried under vacuum to give product **Pd-L3** in a yield of 78% (0.23 g). A sample suitable for X-ray diffraction analysis was obtained by recrystallization from dichloromethane/methanol. ^{31}P NMR (DMSO-d_6, ppm): 14.9 (d, P^1Ph$_2$), 17.1 (d, P^2Ph$_2$). CHN lemental analysis of **Pd-L3** ($C_{35}H_{26}Cl_2N_2P_2PdS$) (found, %): C 56.66, H 3.23, N 3.92 (calcd, C 56.36, H 3.51, N 3.76).

Pd(II)-complex **Pd-L4** was prepared with a yield of 85% by following procedures similar to that described above for **Pd-L3**. A sample suitable for X-ray diffraction analysis was obtained by recrystallization from THF/MeOH. ^{31}P NMR (DMSO-d_6, ppm): 14.2 (s, *P*Ph$_2$). CHN elemental analysis of **Pd-L4** ($C_{24}H_{19}Cl_2N_2PPdS$) (found, %): C 50.29, H 3.23, N 4.66 (calcd, C 50.06, H 3.33, N 4.87).

X-ray Crystallography. Intensity data were collected for **L3**, **L4**, **Pd-L3**, and **Pd-L4** on a Bruker SMARTAPEX II diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 296 K. Data reduction included absorption corrections by the multiscan method. The structures were solved by direct methods and refined by full matrix least-squares using SHELXS-97 (Sheldrick, 1990), with all nonhydrogen atoms refined anisotropically. Hydrogen atoms were added at their geometrically ideal positions and refined isotropically. The crystal data and refinement details of **Pd-L3** and **Pd-L4** are given

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in Table 5 and the Supporting Information (see Table S2 for **L3** and **L4**).

General Procedures for Amino Dicarbonylation of Aryl Halides with Amines. In a 50 mL sealed Teflon-lined stainless-steel autoclave, the commercial complex of $PdCl_2(MeCN)_2$ (0.02 mmol) and pure **L4** (0.02 mmol) were mixed with PhI (2.0 mmol, or the other aryl halides), Et_2NH (10.0 mmol, or the other amine), K_2CO_3 (4 mmol), and THF (3 mL). The autoclave was purged with CO (0.5 MPa) three times and pressured with CO to 2.0 MPa, and then the reaction mixture was stirred vigorously at 100 °C for 8 h. Upon reaction completion, the autoclave was cooled down to room temperature and slowly depressurized, and then the solution was analyzed by GC to determine the conversions (*n*-dodecane as internal standard) and the selectivities (normalization method). The isolated products were further confirmed by ^1H NMR and ^{13}C NMR spectra.

In the recycling experiment, RTIL $[Bpy]BF_4$ was used as the solvent for the amino dicarbonylation. In the first run, $[Bpy]BF_4$ was mixed with PhI (2.0 mmol) and Et_2NH (10.0 mmol), $PdCl_2(MeCN)_2$ (0.02 mmol), **L4** (0.02 mmol), and K_2CO_3 (4 mmol) were added sequentially to form a homogeneous reaction solution. Upon reaction, the IL phase was washed with diethyl ether (3 mL × 3) to extract the reactants and products out of the IL phase completely. The yield and selectivity to the target product was analyzed by GC and the remaining RTIL phase was reused without further treatment for the next run, wherein PhI (2.0 mmol) and Et_2NH (10.0 mmol) were added. The amount of Pd in the combined organic phase was then quantified via ICP-OES.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.1c00024.

Experimental section; X-ray crystallographic data; Characterizations including TG/DTG analysis, FT-IR spectra, and $^{13}C/^{31}P/^1H$ NMR spectra(PDF)

Accession Codes

CCDC 2047448−2047451 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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