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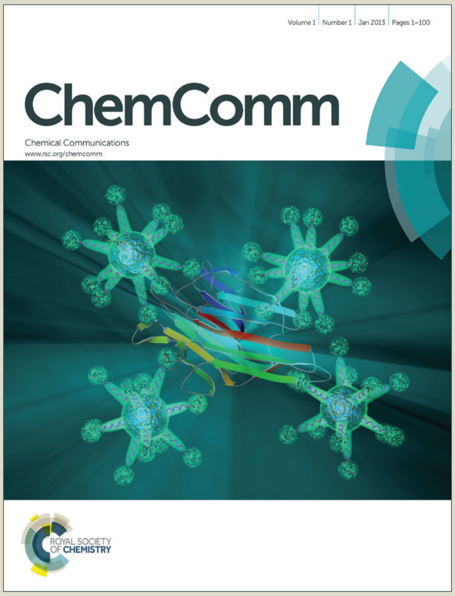

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Bifunctional Ligands in Combination with Phosphines and Lewis Acidic Phospheniums for Carbonylative Sonogashira Reaction

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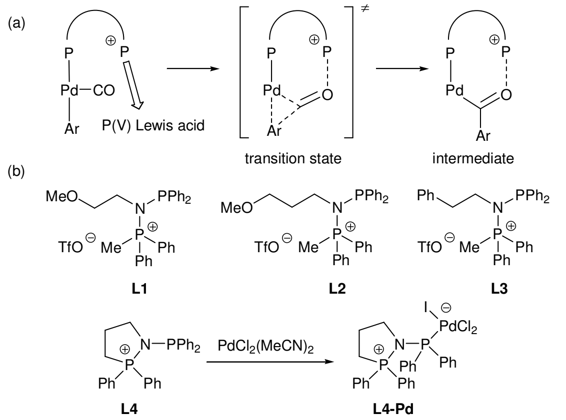
Chen Tan[a], Peng Wang[a], Huan Liu[a], Xiao-Li Zhao[a], Yong Lu[a] and Ye Liu[a]†

The combination of phosphine-ligated Pd catalysis and phosphenium(V) Lewis acid catalysis has been developed for carbonylative Sonogashira reaction by using phosphino-phosphenium salts (L1-L4) as bifunctional ligands, in which the Lewis acidic phosphenium(V) cations can form secondary bonds with O atoms (in C=O) to cooperatively stabilize Pd-acyl intermediates.

The combination of metal catalysis and organocatalysis has been emerged as a powerful strategy to promote new reactions and improves the reactivity in recent years. Various organocatalysts such as aminocatalysts, Lewis base catalysts, hydrogen-bonding catalysts, Brønsted acid catalysts, Brønsted base catalysts, phase transfer catalysts and N-heterocyclic carbene catalysts have been exploited [1]. Bifunctional ligand has a unique role in this field and combines activation modes of metal catalysts with organocatalysts by stable chemical bonds [2]. However, despite the combination of metal catalysis with B(III) Lewis acid catalysis has been developed by using phosphine-borane ligands [3], the application of other types of Lewis acidic organocatalysts has not been explored. In practice, molecules containing carbenium, silyl or phosphenium cations can function as Lewis acid catalysts like metal salts [4]. Markedly, many examples have proved that organophosphenium cations [P(V)$^+$] as typical Lewis acids [5] not only could catalyze isomerization of olefins, cationic polymerization, and hydrosilation of olefins and acetylene without involvement of any metal [6], but also exhibit activities towards C=O bond activation, such as in cyanosilylation of ketones [9], Baylis-Hillman reaction[10], and Aldol and Micheal reactions of carbonyl compounds [11] due to the secondary interaction of acidic P(V) centres with sp^2 hybrid O-atoms (in carbonyl compounds) to promote the reactions [4].

Highlighted by the promotion effect of phospheniums [P(V)$^+$] as Lewis acids to activate C=O bond [2d] and the significant modulating roles of phosphine [P(III)] ligands for transition metal catalysis for oxo-synthesis [12], herein, the diphenylphosphinoamino-phosphenium salts of **L1**~**L4**, in which the two P-atoms were closely bridged by one N(III)-atom with different substituents, were synthesized[13] and applied as the bifunctional ligands for Pd-catalyzed carbonylative Sonogashira reaction (Scheme 1). The present protocol provides a synergetic methodology to activate aryl halides and carbon monoxide (as –C=O source) with terminal alkynes. Meanwhile, a stable Pd(II)-complex of **L4-Pd** ligated by **L4** was obtained and investigated as the pre-catalyst in parallel.



Scheme 1 (a) Concept of bifunctional ligands that contain phosphines and Lewis acidic phosphenium [P(V)$^+$] sites. (b) Structures of **L1~L4** and **L4-Pd**.

Herein, the carbonylative Sonogashira coupling reaction between iodobenzene and phenylacetylene was selected as a model reaction under copper-free conditions (Table 1). Dramatically, both resulting yield and selectivity increased significantly with the increase of **L**/Pd molar ratio (Entries 1~3). This relationship indicates excess ligands play the essential role for carbonylation due to the well protection of Pd-catalytic centres against deactivation. Structurally similar ligands **L2**~**L4** lead to close results under same conditions (Entries 6~8). In contrast, only 73% conversion of PhI was found when the substantially electron-rich ligand PPh_3 was used (Entry 10). While

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[a] Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, 3663 North Zhongshan Road, 200062 Shanghai, China.

† Corresponding author. Email: yliu@chem.ecnu.edu.cn

Electronic Supplementary Information (ESI) available: the crystallographic data of CCDC-1037979 (**L4-Pd**), CCDC-1055592 (**L1-Au**), and CCDC-1055591 (**L3-Au**) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The Supplementary Information associated with this article can be found online. See DOI: 10.1039/x0xx00000x

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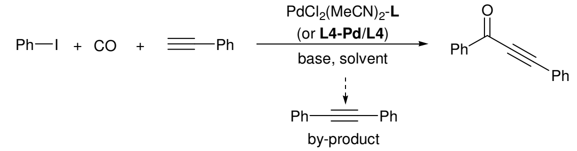
the reaction temperature was increased to 120 °C and time was decreased to 45 min, the highest TOF of 2270 h^{-1} and 99 % selectivity were obtained under the up-scaled conditions (Entry 11). Evidently, the decrease of CO pressure was seriously harmful to the transformation rate of PhI and the selectivity to 1,3-diphenylprop-2-yn-1-one (Entry 12: Conv. 20%, Sel. 45%), which implied that the low CO pressure was unfavourable to the oxidative addition of the substrate and the subsequent carbonylation, corresponding to the poor carbonylative Sonogashira reaction. It was also found that when **L4-Pd** (Fig. 1) was used to replace $PdCl_2(CH_3CN)_3$ as the pre-catalyst, nearly the same conversions of phenylacetylene were observed at the same conditions (Entries 9 *vs* 8), indicating the *in situ* formed **L4-Pd** exhibited the same activity as the as-synthesised one. However, when Lewis basic F^- (TBAF, tetrabutylammonium fluoride) was added to the reaction system, the conversion of PhI was declined to 84% (Entries 4 *vs* 3).

Table 1 Pd-catalyzed carbonylative Sonogashira coupling reaction of iodobenzene with phenylacetylene in presence of the bifunctional ligands [a]



Entry	Ligand	**L**/Pd[b]	Conv. (%)[c]	Sel. (%)[c]	TOF (h^{-1})
1	**L1**	1	54	91	72
2[c]	**L1**	2	60	98	80
3	**L1**	6	98	100	131
4[d]	**L1**	6	84	99	112
5[e]	**L1**	6	97	99	128
6	**L2**	6	92	99	123
7	**L3**	6	99	99	132
8	**L4**	6	92	99	123
9[f]	**L4**	6	93	99	124
10	PPh_3	6	73	99	97
11[g]	**L1**	6	85	99	2270
12[h]	**L1**	6	20	45	16

[a] $PdCl_2(MeCN)_2$ 0.5 mol% (0.025 mmol), PhI 5 mmol, phenylacetylene 6 mmol, Et_3N 7.5 mmol, CO 1.0 MPa, DMF 3 mL, 90 ºC, 1.5 h; [b] Molar ratio; [c] Determined by GC and GC-Mass analysis; [d] TBAF was added (10 mol%); [e] TBA triflate was added (10 mol%); [f] **L4-Pd** was used instead of $PdCl_2(MeCN)_2$; [g] $PdCl_2(MeCN)_2$ 0.05 mol% (0.005 mmol), PhI 10 mmol, phenylacetylene 12 mmol, Et_3N 15 mmol, CO 1.0 MPa, DMF 6 mL, 120 ºC, 45 min; [h] 0.1 MPa (balloon).

The UV-vis. spectra supportively indicated that, when **L1** was mixed with of F^-, a significant decrease of absorbance was observed (Fig. 2), indicating the quenching of the phosphenium site in **L1** by F^- due to its strong fluorophilicity, which was a typical character for Lewis acidic phosphononium cation [6,14]. Anyway, the phosphenium site in **L1** could not be quenched completely by the equivalent amount of TBAF at the room temperature, implying that the fluorophilic interaction of Lewis acidic phosphenium site towards F^- was a reversible process. Hence, under the reaction temperature (90 °C), an excess of TBAF was required to push the $P(V)^+\ldots F^-$ fluorophilic interaction. As a result, only the limited influence of TBAF on **L1** was observed with a 14% decrease of the conversion (Entries 4 vs 3) because of the always remaining of the Lewis acidic phosphenium sites in the reaction system. For comparison, the addition of TBA triflate (tetrabutylammonium trifluoromethanesulfonate) instead of TBAF led to the nearly unchanged PhI conversion (97%, entry 5), indicating the negligible influence of TBA cation and triflate anion (TfO^-). The latter universally existed in the reaction system. Thus, we proposed that the Lewis acidic phosphenium cation in **L** could stabilize the Pd-acyl intermediates (Scheme **2-B** and **C**) through forming the secondary bond between P(V) centre and O atom (in C=O) to accelerate the carbonylation (CO insertion) step (from **A** to **B**), while the therein phosphine site was in charge of the coordination to Pd-center for catalyst protection, in Pd/**L**-catalyzed carbonylative Sonogashira couplings. Certainly, besides of the effect of the phosphenium cation to accelerate the carbonylation step, the CO pressure was another important factor to influence the reversible steps of the oxidative addition (from Pd(0)-**L** to **A**) and the subsequent carbonylation. The increase of CO pressure reasonably propelled the oxidative addition of PhI and CO insert proceeding forward to favour the carbonylative Sonogashira reaction over Sonogashira reaction, which was consistent to the results observed in Table 1 (Entries 3 *vs* 12).

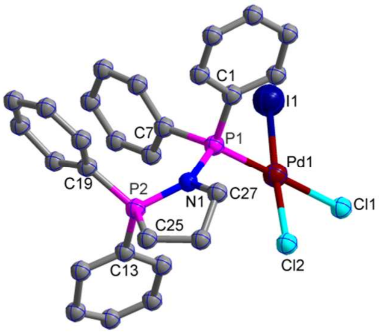


Fig. 1 The single crystal structure of **L4-Pd** (all H-atoms have been omitted for clarity). Selected bond distances (Å) and angles (o): Pd1–P1 2.240(3), Pd1–Cl1 2.487(2), Pd1-Cl1 2.382(3), Pd1-I1 2.5523(1); P1-Pd1-Cl1 177.8291), I1-Pd1-Cl2 176.28(9).

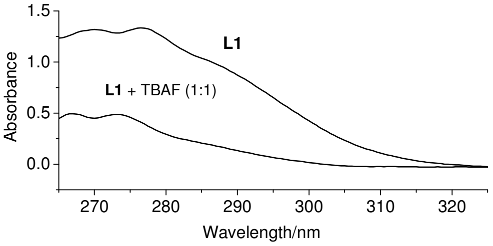


Fig. 2 The UV-vis. spectra of **L1** and **L1**+TBAF (1:1 molar ratio) [2.0×10^{-4} M in CH_2Cl_2].

In order to explore the existence of the secondary bonding interaction between phosphenium and O-atom (acid-base pair interaction in nature), the selected **L1** (or **L3**) has to be firstly coordinated to a metal centre to rule out the competitive interference of the neighboured phosphine site as a soft base. Then we had tried our best to prepare the Pd(II) complexes ligated by **L1** and **L3** respectively. Unfortunately the obtained Pd(II)-complexes were not stable enough under the ambient conditions to afford the corresponding single crystals suitable for the single crystal X-ray analysis, due to the steric hindrance

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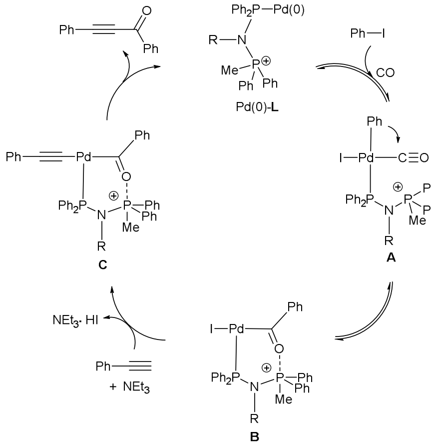
for the square-planar Pd(II)-complexes coordinated by two bulky **L** ligands. Then, the typical linear configuration for Au(I)-complexes with less steric hindrance highlighted us to prepare the corresponding Au-complexes (**L1-Au** and **L3-Au**) and use their single crystal structures to explore the P…O secondary bonding interaction instead.



Scheme 2 Proposed mechanism for Pd-catalyzed carbonylative Sonogashira reaction with the involvement of phosphino-phosphenium salts (**L**).

The single-crystal X-ray diffraction analysis (Fig. 3) shows that the conformation of C(26)-C(27) bond in **L1-Au** (gauche) is completely different to that in **L3-Au** (skew). Moreover, the O-atom in **L1-Au** is projecting inward towards the P-atom, and the P(2)-O(1) distance (3.19 Å) is significantly shorter than the sum of the van der Waals radii of P and O (~3.34 Å) [15]. Such information indicates that the strong secondary bond in P…O linkage [4,16] is formed due to the available Lewis acidity-basicity interaction between the phosphenium(V) centre and O-atom of ether group in **L1-Au**. The absence of the Lewis basic counterpart in **L3-Au** led to the outward projection of phenethyl group. The crystal structure of **L1-Au** confirmed that the Lewis acidic phosphenium site [P(V)$^+$] could develop a secondary bonding interaction with a weak base of O-atom in ether group at the ambient temperature. It was then very rational to support the proposed mechanism that such Lewis acidic phosphenium in **L** indeed could stabilize the Pd-acyl intermediates (Scheme **2-B** and **C**) through forming the secondary bond between P(V)$^+$ centre and O atom (in C=O) to accelerate the carbonylation step (from **A** to **B**) in carbonylative Sonogashira reaction. It should be noted that, under the applied reaction conditions (90 °C, 1.0 MPa), the intramolecular P…O secondary bonding interaction in **L1** was doomed to vanish due to thermodynamic instability at high temperature and the completive coordination of a large amount of CO molecules in the surroundings, and then the intermolecular P…O (in CO) secondary bonding interaction was able to exhibit its function for stabilizing the Pd-acyl intermediates, making **L1** exhibit the same activity as **L3** as observed in Table 1 (Entries 3 vs 7).

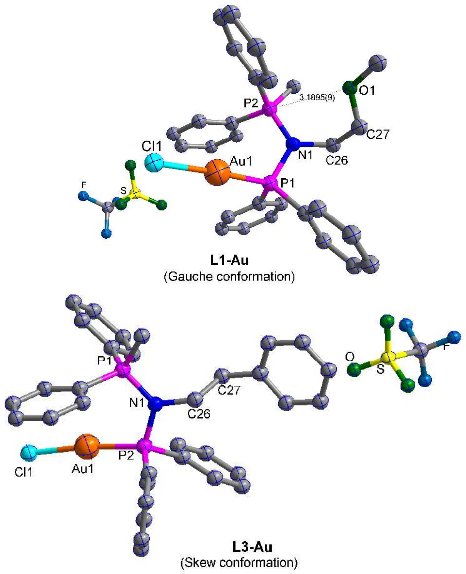


Fig. 3 The single crystal structures of Au(I)-complexes of **L1-Au** and **L3-Au** (all H-atoms have been omitted for clarity).

Moreover, as the cationic ligands, **L1** can be applied together with room temperature ionic liquid (RTIL) solvents as the efficient alternative to immobilize the Pd catalysts for recovery and recycling [17]. Herein Pd(CH_3CN)$_2$Cl$_2$ and **L1** were dissolved in [Bmim]BF$_4$ (1-butyl-3-methylimidazolium tetrafloruoborate) for the recycling uses. Under CO pressure of 1.0 MPa as applied to the homogeneous reactions (in DMF, Table 1), over Pd(CH_3CN)$_2$Cl$_2$-**L1** system, only 72% conversion of PhI was obtained with 93% selectivity to 1,3-diphenylprop-2-yn-1-one due to the mass transfer limitation in the IL-organic biphasic reaction system. When CO pressure was increased to 2.0 MPa, the carbonylative reaction was obviously improved along with 84% conversion of PhI and 96% selectivity. Hence the recycling experiments were performed at 2.0 MPa (see S. Fig. 1 in SI). After 5 runs, the yields of 1,3-diphenylprop-2-yn-1-one decreased from 81% to 60% mainly due to the encapsulation of the Pd-catalyst in the formed slurry Et$_3$N·HI salt, along with the well maintained selectivity from 96% to 100%. The ICP-AES analysis indicated that the leaching of Pd in the combined organic phase was non-detectable (below the detection limit of <0.1 μg/g).

At last, the scope of the reaction was explored (see S. Table 2 in SI). The electron density and steric hindrance of the aryl substituents have influence on the catalytic activity. In addition, when an aliphatic alkyne was used, the yield of the product was very low (See Supplementary Information). It was suggested that the kinetic characteristic of this reaction varies considerably among the substituents. The repetition of the reaction with PhBr instead of PhI did not produce the desired carbonylative product under the same conditions, which also indicated the developed **L1** was only responsible for the stabilization of Pd-acyl intermediates (Scheme 2-**B** and **C**), but had no positive effect on the oxidative addition step of aryl halides.

In summary, a series of bifunctional ligands in combination with the phosphines and the Lewis acidic phosphenium [P(V)$^+$] cations

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were synthesized and characterized. It was found that in the catalytic cycle the Lewis acidity of phosphenium site play an important role in cooperatively activating CO through forming the secondary bond between acidic $P(V)^+$ and O-atom (in C=O) to stabilize the Pd-acyl intermediates, while the phosphine sites were in charge of the coordination to Pd-center for catalyst protection. When strong Lewis base F^- was added to the reaction system, the catalytic activity was depressed due to the quenching of the $P(V)^+$ acidic centres with strong fluorophilicities. The secondary $P(V)^+$-O bond with distance of 3.19 Å was observed in the **L1**-ligated Au(I)-complex (**L1-Au**), in which even the weak basic O-atom in ether group could develop the chemical interaction with the acidic phosphenium site. Moreover, the $PdCl_2(CH_3CN)$-**L1** system with the wide substrate generality could be applied as a recoverable and recyclable catalyst in RTIL of $[Bmim]BF_4$.

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