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Bifunctional ligands for Pd-catalyzed selective alkoxycarbonylation of alkynes

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ABSTRACT

Catalytic carbonylations of alkynes represent straightforward and atom-economic synthesis of α,β-unsaturated carbonyl compounds. One of the issues associated with the currently known catalytic systems is insufficient efficiency. In this context, Pd/ligand-catalyzed regioselective and efficient alkoxycarbonylation of terminal alkynes is desirable for the synthesis of α,β-unsaturated esters. Herein, we present the use of a newly designed bifunctional ligand for efficient Pd-catalyzed alkoxycarbonylation of alkynes. Both aliphatic and aromatic alkynes were smoothly transformed to the branched desired products with high selectivity (28 examples, 45–96% yields, 95.0–99.9% selectivity).

1. Introduction

Among different methods for synthesis of α,β-unsaturated esters, alkoxycarbonylation of alkynes is considered as an atom-economic and straightforward route [1]. Historically, the development of this chemistry started since 1930s when Reppe developing the hydroxycarbonylations of acetylene to produce acrylic acid [2]. Carbonylations of alkynes can generate many types of functionalized compounds, such as unsaturated carboxylic acid derivatives and heterocycles, with extensive applications for bulk chemicals and intermediates of bio-active molecules. In the last decades, significant progress in transition metal–ligand catalyzed carbonylation was achieved for both catalyst efficiency and mechanism understanding [3]. Tremendous efforts were devoted in the area and resulted in the development of catalysts based on palladium [4], rhodium [5], nickel [6], copper [7] and cobalt [8] among other metals for carbonylation of alkynes.

Specifically, in 1990s Drent and co-workers with Shell made the breakthrough on the use of 2-pyridyldiphenyl phosphine Ph_2P(2-Py) for Pd-catalyzed methoxycarbonylation of propyne to produce methyl methacrylate (MMA) [9]. After a thorough mechanistic studies, it is accepted that ligand Ph_2P(2-Py) functions both as a bidentate chelating P,N-ligand to control the selectivity, and as a monodentate ligand for proton shuttling accelerating the reaction rate in the catalytic cycle.

Based on this well-known catalytic system, numerous efforts have been pursued to further increase the carbonylation efficiency by developing new ligands, mostly of the type bearing pyridyl groups on the phosphorus atom [10]. Hence, based on the understanding of the mechanism for hemi-labile P,N-ligand systems, the following questions were considered in our design approach: (1) Should pyridyl group be covalently linked to P atoms or not? (2) Could these new ligands be more efficient in carbonylation reaction? (3) Could these new catalysts tolerate allene poisoning?

In this work, we disclose catalytic effect of new ligands based on the carbazole motif. These ligands are also bidentate chelating P,N-ligands with pyridyl ring close in space to the P atoms but not covalently linked. A variety of aliphatic and aromatic alkynes were smoothly transformed to the desired ester products (28 examples, 45–96% yields, 95.0–99.9% branch selectivity) under mild conditions. It is noteworthy to mention that with these new ligands enhanced reactivity was achieved for the tested substrates compared with the use of well-known Ph_2P(2-Py) ligand. Notably, **L3** ligand showed enhanced catalytic activity and the structure of the Pd-**L3** complex was elucidated via single X-ray diffraction analysis. The crystal structure shows a *cis*-P,N-chelation mode suggesting hemi-labile coordination of N atom in the presence of Brønsted acid co-catalysts.

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2. Experimental

2.1. Materials and methods

All materials were purchased from commercial sources and used without further purification. Solvents were dried by solvent purification system from LC Technology Solution Inc. CO (99.95%) was purchased from Messer (Wujiang, China). GC data obtained through Shimadzu GC-2010 Plus. All ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer. HRMS data were obtained on Agilent 6530 spectrometer. X-ray data collection from Bruker SMART APEX diffractometer.

Diffraction intensity for complex Pd(**L3**)Cl_2 is collected on a Bruker SMART APEX diffractometer system equipped with graphite monochromatic Mo Kα radiation (λ = 0.71073 Å) at 296 K. An empirical absorption correction using SADABS [11] was applied for all data. The structure was solved by direct methods using the SHELXS program. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 by the use of the program SHELXL [12]. Crystallographic data are given in Table S1 (see the Supplementary Data). Selected bond distances and angles are given in Table S2. CCDC1821020 contains the supplementary crystallographic data.

2.2. Preparation of ligands (*L1*-*L5*)

Ligands **L1**-**L5** were synthesized by coupling dicyclohexylphosphine or diphenylphosphine with the corresponding carbazole aryl halide. Unless otherwise stated, the synthetic method is similar to the preparation of **L3** shown below in two steps.

Step 1: In 150 mL sealed tube, a stirred mixture of CuI (38.1 mg, 0.2 mmol), 1-methylimidazole (41.7 μL, 0.4 mmol), *t*-BuOLi (2.401 g, 30 mmol), 1-bromo-*9H*-carbazole (4.922 g, 20 mmol) and 2-bromopyridine (2.1 mL, 22 mmol) in toluene (70 mL) was heated to 130 °C. After 12 h, the reaction mixture was allowed to cool to room temperature, and upon evaporation of solvent a brownish yellow solid was obtained (1-bromo-9-(pyridin-2-yl)-*9H*-carbazole, 95% yield).

Step 2: $Pd(OAc)_2$ (44.9 mg, 0.2 mmol), 1,1′-bis(di-*i*-propylphosphino)ferrocene (100.4 mg, 0.24 mmol), Cs_2CO_3 (3.909 g, 12.0 mmol) and 1-bromo-9-(pyridin-2-yl)-*9H*-carbazole (4.406 g, 10.0 mmol) were added to an oven dried 75 mL sealed tube containing 20 mL toluene in the glove box. After stirring for 1 h at room temperature, a reddish-brown solution was obtained. Then dicyclohexylphosphine (12 mmol) were added under a nitrogen atmosphere, and the mixture was heated to 130 °C, and stirred for 20 h. After cooling, dichloromethane (30 mL) and water (30 mL) were added and the layers were separated. The aqueous layer was extracted three times with dichloromethane, the combined organic extracts were washed with water (three times) and brine. Then the organic phase was dried with $MgSO_4$ and the solvent was concentrated to afford a yellow solid. The crude product was purified by flash column chromatography on silica gel to afford the desired **L3** as a pale yellow solid (89% yield).

2.3. Preparation of crystals of complex (Pd(*L3*)Cl_2)

In an oven dried one necked 100 mL round bottom flask, $Pd(PhCN)_2Cl_2$ (44 mg, 0.11 mmol), **L3** (52 mg, 0.12 mmol) and toluene were added under N_2. After stirring for 3 h at room temperature, a light yellow solution was obtained. Then, the solvent is evaporated under reduced pressure and resulted in a pale yellow solid (yield 85%). The crystals of this complex were obtained by slow evaporation from a 2:1 DCM/MeCN solvent mixture at room temperature.

2.4. Catalytic carbonylations of alkynes using ligand *L3* or complex Pd(*L3*)Cl_2

In the glove box, a 4 mL screw-cap vial was charged with Pd-catalyst (1.0 mol%), ligand **L3** (4.0 mol%), methanesulfonic acid (MSA) (6.0 mol%), solvent (1 mL), and an oven-dried stirring bar. After stirring for 15 min, alkyne (0.5 mmol) and alcohols (1.0 mmol) were injected into the vial. The vial was closed by PTFE/white rubber septum (Wheaton 13 mm Septa) and phenolic cap, and connected with atmosphere with a needle, and fixed in an alloy plate, and put into the autoclave (250 mL) under argon atmosphere. At room temperature, the autoclave was flushed with CO gas five times and pressurized with CO gas to 30 bar. The reaction was performed at 80 °C for 12 h. After that, the autoclave was cooled to room temperature and the pressure was carefully released. Hexadecane was added as an internal standard. A sample of the mixture was taken and analyzed by GC-FID (Shimadzu GC-2010) and GC–MS (Agilent GC–MS 7890A-5975C). Pure product could be obtained by column chromatography on silica gel using petroleum ether/ethyl acetate as eluents with a gradient ratio of 100:1–50:1.

3. Results and discussion

3.1. Conditions optimization

We originally investigated methoxycarbonylation of 1-octyne using different metal precursors and ligands with reactions carried out under various conditions. Firstly, using $PdCl_2$ as the metal precursor, the five carbazole-derived ligands were screened. The results showed that only **L3** and **L4** having P atom substitution on 1-position of the carbazole moiety led to good reactivity (83% yield; Table 1, entries 3–4). By contrast, for the other three ligands (**L1**, **L2** and **L5**) having either P atom substitution on 2- and 3-position on the carbazole or the absence of N-pyridyl group substitution, inferior reactivity was observed under the same reaction conditions (8–40% yields; Table 1, entries 1, 2 and 5). This result clearly supports our design strategy and shows the importance of having Py group at close proximity in space to P atom in both reactivity and selectivity in alkyne alkoxycarbonylations.

In addition, different palladium precursors were screened using **L3** as the ligand showing that both Pd(0) or Pd(II) salts give reasonable reactivity with similar branched regioselectivity (Table 1, entries 6–9). The reaction medium was also investigated showing that two polar solvents were suitable with MeCN as medium giving better regioselectivity (98.0%; Table 1, entry 11). Hence, MeCN was chosen as the best reaction medium for these alkyne alkoxycarbonylations. Further investigation of acid co-catalysts, reaction temperature and time, yielded the optimized conditions; 60 °C with 60 bar of CO for 16 h giving the desired branched product in 89% yield and 99.2% selectivity (Table 1, entry 18). Due to the high yield obtained, the *in-situ* formation the catalyst based on ligand **L3** and $PdCl_2$ was chosen for subsequent substrate scope study.

3.2. Crystal structure of complex Pd(*L3*)Cl_2

In order to understand the coordination behavior of **L3** with Pd center in the catalytic cycle, a good quality single crystal of Pd(**L3**)Cl_2 has been prepared and its single-crystal structure has been investigated by the single-crystal X-ray diffraction method. On crystals bulk analysis, the XRD data from simulation result of the single-crystal structure and the experimental data of the crystallized powder were in total agreement. Analysis of the single-crystal X-ray diffraction reveals that Pd(**L3**)Cl_2 crystallizes in monoclinic space group. The asymmetrical unit of Pd(**L3**)Cl_2 consists of