Large-Scale One-Pot Synthesis of N-Heterocyclic Carbene–Pd(allyl)Cl Complexes

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Abstract: Improved one-pot syntheses of (IPr)Pd(allyl)Cl {IPr = [N,N'-bis(2,6-diisopropylphenyl)imidazol]-2-ylidene} and (SIPr)Pd(allyl)Cl {SIPr = [N,N'-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol]-2-ylidene} complexes are described. This simple method utilizes technical grade isopropanol and water as solvents, affording gram quantities of the cross-coupling pre-catalysts.

Key words: N-heterocyclic carbene, palladium, homogeneous catalysis

N-Heterocyclic carbenes (NHCs) have become increasingly popular in the last few years as an attractive alternative to tertiary phosphines in homogeneous catalysis. This group of ligands has been shown to be better electronic donors than the best donating phosphines, without the disadvantages associated with most common phosphines: (1) phosphines are often sensitive to air oxidation and therefore require air-free handling to minimize ligand oxidation, (2) when phosphine ligands are subjected to higher temperatures significant P–C bond degradation occurs, which then requires the use of excess ligand, and (3) phosphines often react with Pd precursors such as Pd(OAc)_2 in a redox process leading to the formation of Pd(0)Ln (a desired outcome, as it is the catalytically relevant species) and phosphine oxide (a not-so-desirable outcome as this is difficult to separate from organic products).

Our group recently reported the synthesis of a series of complexes with the general formula (NHC)Pd(allyl)Cl. Complexes (IPr)Pd(allyl)Cl (1) and (SIPr)Pd(allyl)Cl (2) have been shown to display excellent activity as pre-catalysts in a variety of cross-coupling reactions (Suzuki–Miyaura, Buchwald–Hartwig, and α-ketone arylation). They have also been successfully employed in telomerization reactions, in dehalogenation of aryl halides, and as precursors for the preparation of other (NHC)Pd(II) complexes. An added advantage is that 1 and 2 are indefinitely air- and moisture-stable. Complex 1 is commercially available and 2 will soon become available.

The initial synthesis of these complexes are straightforward and involve the simple fragmentation of [Pd(allyl)Cl]_2 by NHC in an anhydrous solvent. The NHC used in the original protocol was generated from the corresponding imidazolium salt by action of a base and was isolated prior to its addition to a solution of the dimer. Recently, this step was circumvented in a simplified protocol leading to 1 by following a one-pot protocol in anhydrous THF that yielded nearly quantitative amounts (reaction was performed on >20g scale) of the complex without the need for prior isolation of the carbene. A similar protocol has been described by Jensen and Sigman and was carried out on a half mmol scale in anhydrous solvents. Here, we describe a variation on this one-pot protocol for the synthesis of 1 and 2 that requires neither isolation of the carbene nor the use of anhydrous solvents (Scheme 1).

Scheme 1 One-pot synthesis of 1 and 2

NHC HCl + KOtBu → NHC + KOH

a) tech. iPrOH, 80 °C, 2 h

b) 1.4 equiv 1.2 equiv

0.5 equiv r.t., 2 h

NHC = IPr (1) and SIPr (2)

Figure 1 Complexes (IPr)Pd(allyl)Cl (1) and (SIPr)Pd(allyl)Cl (2)
The deprotonation of the imidazolium salt is carried out in technical grade isopropanol, followed by the addition of the palladium dimer. When the reaction is complete, the complex is precipitated by addition of water to the reaction mixture. Filtration in air affords the desired product in excellent yield. This procedure also allows for recovery of excess imidazolium salt from the aqueous solution by simple extraction.

In summary, a very straightforward and convenient high-yielding one-pot synthesis leading to 1 and 2 has been described. Studies aimed at expanding the application scope of this simple methodology to other (NHC)Pd(allyl)Cl complexes are currently underway in our laboratories.

(Pr)Pd(allyl)Cl (1)
A Schlenk flask equipped with a magnetic bar was charged with imidazolium salt Pr·HCl16 (11.94 g, 28 mmol) and t-BuOK (2.68 g, 24 mmol). The flask was purged on a vacuum line by applying vacuum and refluxing with argon three times. Under a flow of argon, the flask was opened and technical grade i-ProOH (250 mL) was added by syringe; the mixture was stirred for 2 h at 80 °C. After allowing the mixture to cool to r.t. (ca. 45 min with stirring), the flask was charged with [Pd(allyl)Cl]3 (3.66 g, 10 mmol) under a flow of argon. The reaction mixture was then stirred for 2 h at r.t. The flask was subsequently opened and the reaction stirred in open air for 10–15 min to degrade the remaining free carbene. H2O (750 mL) was added and a white solid precipitated. The solution was filtered in air yielding a white solid, which was washed with copious amounts of H2O (300 mL). The solid was dissolved in CH2Cl2 (50 mL), the solution dried over MgSO4, and filtered. The solvent was removed in vacuo and the solid washed with hexanes (3 × 10 mL). The procedure afforded 10.5 grams (92% yield) of (IPr)Pd(allyl)Cl as a white powder. From the hexanes washings, 2.6 grams of product were further recovered after removal of the solvent in vacuo; overall yield: 82%.

1H NMR (400 MHz, CDCl3): δ = 7.604 (t, J = 7.6 Hz, 2 H), 7.261 (d, J = 5.2 Hz, 2 H), 7.204 (s, 2 H), 4.749 (pentet, J = 7.2 Hz, 1 H), 4.0–4.07 (m, 4 H), 3.878 (dd, J = 7.6 Hz, J = 1.6 Hz, 1 H), 3.394–3.536 (m, 4 H), 3.019 (d, J = 6 Hz, 1 H), 2.743 (d, J = 13.6 Hz, 1 H), 1.548 (d, J = 1 Hz, 1 H), 1.465 (d, J = 6.8 Hz, 6 H), 1.366 (d, J = 6.8 Hz, 6 H), 1.291 (d, J = 6.8 Hz, 6 H), 1.251 (d, J = 6.8 Hz, 6 H).

13C NMR (100 MHz, CDCl3): δ = 133.458, 130.544, 136.871, 146.854, 147.021, 188.531.

In summary, a very straightforward and convenient high-yielding one-pot synthesis leading to 1 and 2 has been described. Studies aimed at expanding the application scope of this simple methodology to other (NHC)Pd(allyl)Cl complexes are currently underway in our laboratories.

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References


(3) Jafarpour, L.; Nolan, S. P. Adv. Organomet. Chem. 2001, 46, 181; Pr-Bu) was not included in this study.


(15) (IPr)Pd(allyl)Cl is commercially available from Strem Chemicals in small quantities (hundreds of mg) and from Umicore AG in larger quantities. For more references on uses of this pre-catalyst, see: (a) Marion, N.; Navarro, O.; Kelly, R. A. III; Nolan, S. P. Synthesis 2003, 2590. (b) Scott, N. M.; Navarro, O.; Briel, O.; Nolan, S. P. Chem. Today 2005, 23, 25.

(16) IPr·HCl and SIPr·HCl are commercially available from Strem Chemicals.