

## SYNLETT Spotlight 113

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

### Tri-*tert*-butylphosphine [P(*t*-Bu)<sub>3</sub>]: An Electron-Rich Ligand for Palladium in Cross-Coupling Reactions

Compiled by Srinivas Reddy Dubbaka

Srinivas Reddy Dubbaka was born in 1979 in MachiReddy Pally, Andhra Pradesh, India. He received his B.Sc. from the Kakatiya University in 1999 and M.Sc. from the Central University of Hyderabad, India in 2001. He is doing Ph.D. studies under the supervision of Prof. Pierre Vogel at the Swiss Federal Institute of Technology (EPFL) in Lausanne, Switzerland since 2001. His research focuses on the development of new organic chemistry based on sulfur dioxide. He has demonstrated that inexpensive sulfonyl chlorides are excellent electrophilic partners in carbon-carbon cross-coupling reactions, including those catalyzed by palladium or rhodium complexes.

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#### Introduction

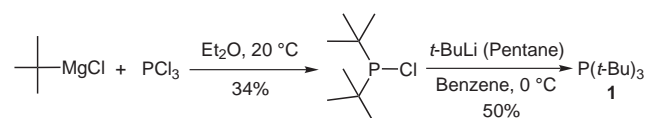
Transition-metal-catalyzed cross-couplings are recognized to be the most powerful carbon-carbon bond forming reactions.<sup>1</sup> The palladium-catalyzed coupling of aryl halides, arylsulfonates with aryl/alkyl metals (such as M = B, Sn, Zn, Si, Mg) are very often employed in the synthesis of compounds, the skeletons of which are found in a wide range of important natural products and analogues of biological interest.<sup>2,3</sup> Before 1990, the insertion of palladium into C-Br and C-I bonds was well exploited. However, the same reaction with C-Cl bonds proved to be very difficult. Organochloride compounds are less expensive than the other organohalides, and would thus be most interesting partners in cross-coupling reactions. Fu and co-workers have shown that electron-rich ligands such as tri-*tert*-butyl phosphine [P(*t*-Bu)<sub>3</sub>] allow the metal insertion into C-Cl bonds at or above room temperature. Subsequent transmetalations with organoboron, organotin, organozinc, organocopper and organosilicon reagents and final reductive elimination give the corresponding products of C-C cross-couplings.<sup>4</sup> Littke and Fu showed that arylation of olefins can be catalyzed by the same Pd/P(*t*-Bu)<sub>3</sub> system.

Other convenient ligands have been proposed to promote the palladium oxidative addition of aryl chlorides. Most common today are bulky, electron-rich chelating bisphosphines as those proposed by Milstein,<sup>5</sup> bulky and electron-rich phosphines proposed by Buchwald,<sup>6</sup> the palladacy-

cles and N-heterocyclic carbenes proposed by Herrmann,<sup>7</sup> as well as the phosphites proposed by Beller.<sup>8</sup>

#### Preparation

P(*t*-Bu)<sub>3</sub> **1** can be easily prepared by a two-step sequence starting with addition of *tert*-butylmagnesium chloride to PCl<sub>3</sub> (Scheme 1). Chloro-di-*tert*-butylphosphine thus obtained is then reacted with 1.2 equiv of *tert*-butyl lithium to produce desired product **1**.<sup>4c</sup> The *pK*<sub>a</sub> of P(*t*-Bu)<sub>3</sub> was found to be 11.4. Thus, P(*t*-Bu)<sub>3</sub> appears to be one of the most basic phosphines, leading to a particular behaviour as ligand in numerous catalyzed reactions.<sup>4a,b</sup>



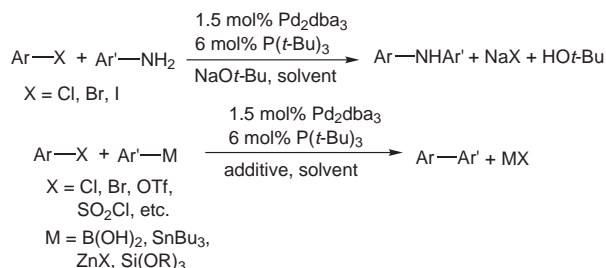
Scheme 1

This ligand is available from Strem company as a 10% solution (w/w) in hexane or in dioxane. Although it is also available in pure form from other commercial sources, it is conveniently used as a solution, since only a small amount of ligand is usually needed and also because it is most air sensitive in its pure form. The reagent can be stored at low temperature and must be manipulated in a glove box or under a nitrogen flow.

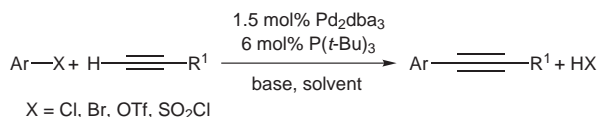
## Abstracts

(A) The Buchwald–Hartwig amination of aryl halides was realized for the first time in 1998 using  $P(t\text{-Bu})_3$  as ligand to the palladium catalyst.<sup>9</sup> Fu and co-workers extended the scope of  $P(t\text{-Bu})_3$  as ligand for other types of palladium-catalyzed coupling reactions of aryl chlorides. These authors reported the reactions of triflates and aryl chlorides in Suzuki–Miyaura,<sup>10</sup> Stille,<sup>11</sup> Negishi,<sup>12a</sup> Hiyama<sup>12b</sup> and other C–C cross-coupling reactions.

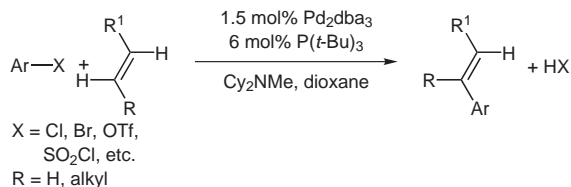
Recently, we found that arenesulfonyl chlorides can be used in the desulfurative Suzuki–Miyaura<sup>13</sup> and Stille<sup>14</sup> cross-coupling reactions. In these cases, good results were also obtained using  $P(t\text{-Bu})_3$  as ligand to the palladium catalyst.



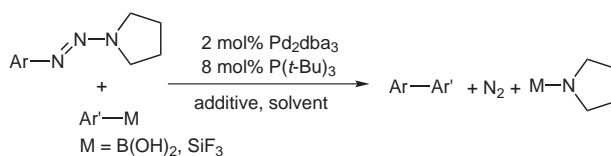
(B) Typical reaction conditions for the Sonogashira–Hagihara cross-coupling of terminal acetylenes and aryl bromides require high temperatures and CuI as a co-catalyst. Using  $P(t\text{-Bu})_3$  ligand, Fu and Buchwald showed that electron-rich aryl bromides can react already at room temperature.<sup>15a</sup> Herrmann and co-workers,<sup>15b</sup> as well as chemists of Merck company,<sup>15c</sup> showed that the use of CuI can be avoided in these reactions. Aryl chlorides can be reacted at higher temperature using the same ligand.<sup>15d</sup> We have shown that the desulfurative Sonogashira–Hagihara reactions with arenesulfonyl chlorides can be carried out in the presence of CuI, with 3 mol% Pd<sub>2</sub>(dba)<sub>3</sub> and 10 mol% P(*t*-Bu)<sub>3</sub>.<sup>16</sup>



(C) Littke and Fu have shown the Heck–Mizoroki reactions can couple aryl chlorides with mono- or disubstituted olefins giving the corresponding arylated products with high stereoselectivity. This requires the use of  $P(t\text{-Bu})_3$  ligand to the palladium and Cy<sub>2</sub>NMe as base.<sup>17</sup> The Pd/ $P(t\text{-Bu})_3$  system is also a good catalyst in the desulfurative Heck–Mizoroki arylation reactions with arenesulfonyl chlorides.<sup>18</sup>



(D) Recently, Sakei and co-workers have used 1-aryltriazines as electrophilic partners in cross-coupling reactions. For instance, the reaction of aryltriazines and areneboronic acids in the presence of a catalytic amount of Pd<sub>2</sub>(dba)<sub>3</sub> and P(*t*-Bu)<sub>3</sub> give the corresponding biaryls.<sup>19a</sup> Similarly, the 1-aryltriazines can be cross-coupled with aryl- and alkenyltrifluorosilanes under the same conditions.<sup>19b</sup>



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