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$Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ – a Powerful Catalyst System for Pd(0)-Mediated C–C-Bond Formation

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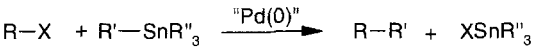
Among the many transition metals that mediate CC bond formation, palladium is by far the most prominent one [1]. Palladium catalysis in cross coupling reactions between aryl, hetaryl or alkenyl halides (or pseudohalides) and organostannanes as pioneered by the late J. K. Stille [2] proved to be an extremely versatile tool for synthetic chemists and has opened new venues in the fields of natural and nonnatural product synthesis (Scheme 1).

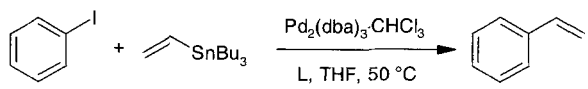


X = halide or pseudohalide
R, R' = alkyl, alkenyl, alkynyl, aryl or hetaryl
R" = Me, Bu

Scheme 1

The active species involved in these coupling reactions is palladium(0), which may be either generated *in situ* from Pd(II) complexes like $PdCl_2(PPh_3)_2$, or, more directly, from the palladium(0) sources $Pd(PPh_3)_4$ or $Pd_2(dba)_3 \cdot CHCl_3$ (**1**, dba = dibenzylidene acetone). Especially the use of the latter complex has important advantages over the light- and air-sensitive $Pd(PPh_3)_4$: The dinuclear, so-called "ligandless" Pd-complex **1** is stable to the ambient and is readily prepared as purple needles from $PdCl_2$ and dba in hot methanol followed by recrystallisation from $CHCl_3$ [3]. In addition to its superior stability, the weakly coordinating dba ligands are easily displaced by external auxiliary ligands (phosphanes, arsanes, etc.) thereby allowing to fine-tune the catalytic activity of the generated Pd-complex to the specific needs of a given substrate.

In a comprehensive study of the influence of various ligands on the reactivity of palladium(0) catalysts generated from $Pd_2(dba)_3 \cdot CHCl_3$, Farina and Krishnan [4] have identified $AsPh_3$ as the most efficient auxiliary ligand in terms of yield, reactivity, and turnover rates in CC bond forming reactions of the Stille type (Scheme 2). It is found that the rate of the transmetallation of stannane **3** to Pd, which is thought to be the rate-determining step of the catalytic cycle, is increased by a factor of 1100 using $AsPh_3$ instead of PPh_3. In fact, it was demonstrated that excess PPh_3 has an inhibitory effect on the catalytic activity of $Pd(PPh_3)_4$ [5], whereas no such effect exists



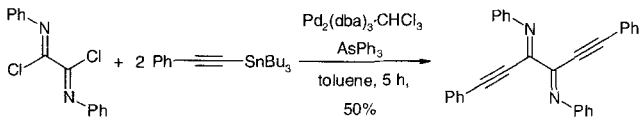
2 **3** **4**

auxiliary ligand L	rel. rate of transmetallation	isolated yield of **4** (%)
PPh_3	1	15.2
$P(2\text{-furyl})_3$	105	95
$AsPh_3$	1100	95

Scheme 2

in case of the bulkier $AsPh_3$ [4]. Hence, the combination of $Pd_2(dba)_3 \cdot CHCl_3$ with $AsPh_3$ is a convenient and efficient "off-the-shelve" catalyst system whose recent applications are highlighted in the following.

The necessity to obtain high turnover rates at relatively low temperatures prompted us to employ $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ in the construction of the first dialkynylated 1,4-diazabuta-1,3-dienes **6** (Scheme 3) [6]. These compounds are promising building blocks for the construction of NIR chromophores, for heterocycles with ene-diyne substructure, and for catalyst systems involved in olefin polymerisation.

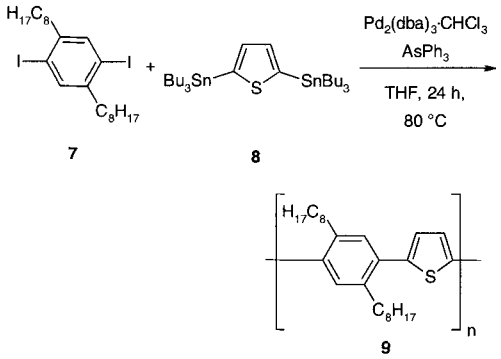


5 **6**

Scheme 3

Standard palladium sources such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ or $Pd(PhCN)_2(PPh_3)_2$ failed to give the desired coupling product. A possible explanation for this failure lies in the known propensity of 1,4-diazabuta-1,3-dienes to displace PPh_3 from the coordination sphere of palladium. This does not appear to happen in case of $AsPh_3$ auxiliary ligands at temperatures below 60 °C. Raising the temperature above 70 °C leads to products derived from the fragmentation of the central CC bond of **5**.

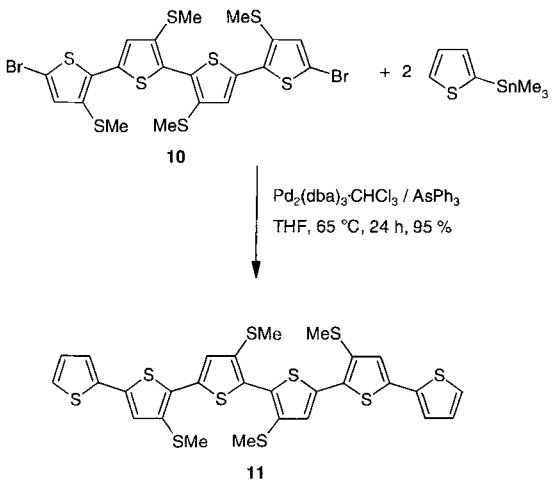
Similar observations have been made in the synthesis of aryl-thiophene polymers that are of interest for their liquid crystalline and photorefractive properties (Scheme 4).



Scheme 4

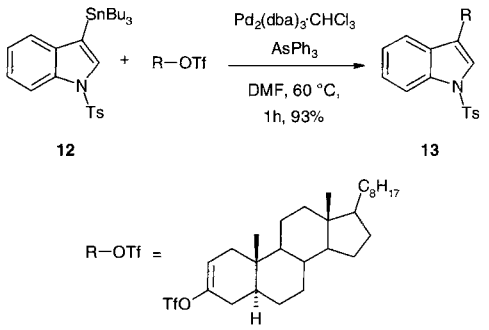
The Stille cross-coupling between **7** and **8** leads to polymer **9** in satisfactory yield only if Farina's catalyst system $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ is employed [7]. In this case the reaction was found to go to completion much faster than with phosphane auxiliary ligands, reducing the reaction time from 7 days to 24 h. The resulting polymer has an average molecular weight of 56 000 g/mol, *i.e.* 2.5 times higher than that achieved by polymerizing **7** and **8** with $Pd_2(dba)_3 \cdot CHCl_3/PPh_3$.

A related example in the field of thiophene chemistry is the construction of the sexithiophene **11** [8] (Scheme 5). The Pd-catalyzed coupling of compound **10** with trimethyl-(2-thienyl)tin was studied in the presence of three different ligands, namely PPh_3, P(2-furyl)$_3$ and $AsPh_3$ using $Pd_2(dba)_3 \cdot CHCl_3$ as the Pd(0) source. The lowest yield was obtained with PPh_3, while $AsPh_3$ functions as the best of all ligands in this series.



Scheme 5

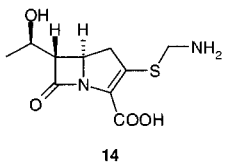
Other heterocyclic structures may be assembled by this catalyst system as well. This is exemplified by the synthesis of the indolyl-steroid **13** starting from 3-(tributylstannyl)indole **12** [9] (Scheme 6). Unsatisfactory yields of **13** (below 50%) were obtained when the reaction was performed using



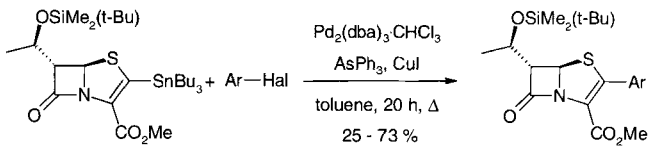
Scheme 6

$Pd_2(dba)_3 \cdot CHCl_3$ in conjunction with PPh_3. Prolonged heating was required resulting in substantial destannylation of **12**. A dramatic improvement was achieved upon changing the auxiliary ligand from PPh_3 to $AsPh_3$. The reaction went to completion in 1 h and **13** could be isolated in 93% yield.

Farina's catalyst system also found its application in the synthesis of natural products, especially in cases where the standard Pd–phoshane catalysts failed to deliver.



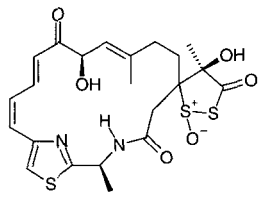
In 1976 the discovery of thienamycin **14** as an antibiotic initiated a flurry of synthetic activity in this field [10]. A key step in preparing derivatives of this class of compounds is the functionalization of the 2-position of penems like **15** [11]. A variety of aryl-substituents can be introduced in moderate to good yields using $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$.



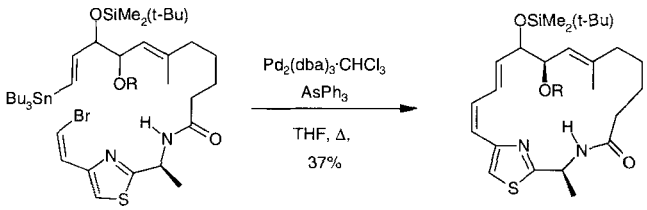
Ar = pyridyl, substituted phenyl

Scheme 7

Pattenden and Thom examined a new approach towards polyene macrolactam construction based on intramolecular Pd-catalyzed vinyl–vinyl cross coupling reactions [12]. In a quest for model compounds of the novel antitumor antibiotic leinamycin **16**, the vinyltin derivative **17** was cyclized intramolecularly under $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ catalysis in 37% yield (Scheme 8). Interestingly, a less functionalized macrolactam precurser could be cyclized using $Pd(PPh_3)_4$. In con-



16

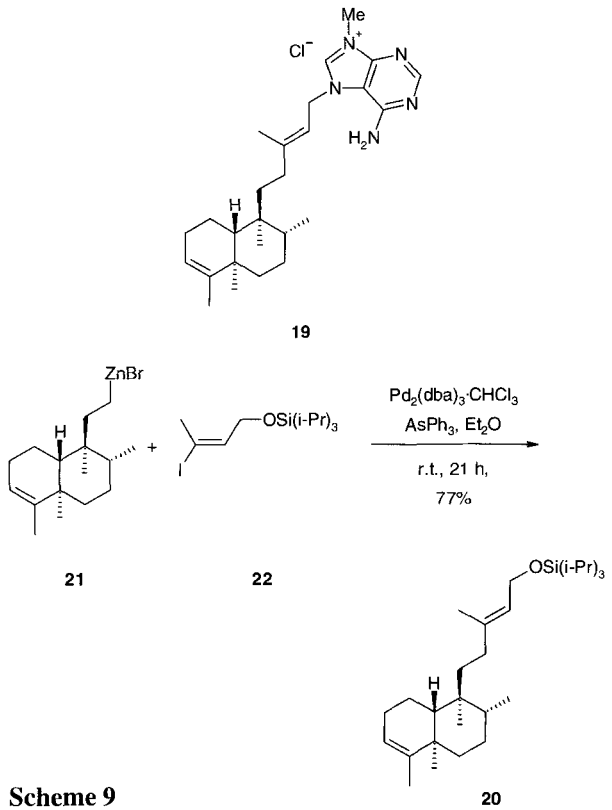


17 18

Scheme 8

trast, the higher functionalized macrolactam **18** could only be prepared with Farina's catalyst system [12].

A rare example for an alkyl–vinyl bond formation can be found in the total synthesis of the diterpenoid (–)-aglasine B **19** [13], isolated from the Okinawan marine sponge *Agelas nakamurai*. This compound has been shown to possess a variety of biological activities, including antimicrobial activity and inhibitory effects on Na, K-ATPase.

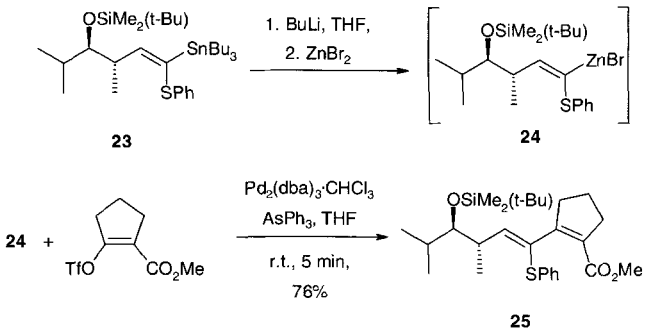


19 21 22 20

Scheme 9

(–)-Aglasine B **19** contains an adeninium moiety attached to C-15 of a *trans*-clerodane diterpenoid skeleton. A key step for the assembly of these two substructures is the preparation of **20**, which is formed by reacting the zinc-functionalized decalin derivative **21** with vinyl iodide **22** using $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ in diethylether at room temperature (Scheme 9).

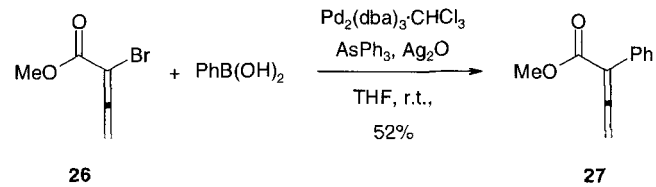
Organozinc compounds are also used in the work by Kocienski *et al.* who investigated vinyl–vinyl bond formation in order to synthesize trisubstituted alkenes in a model study for their synthesis of polyketide chains [14] (Scheme 10). While stannane **23** was reluctant to undergo the Stille coupling, the more reactive organozinc derivative **24**, prepared *in situ* from **23**, was successfully employed. The use of $AsPh_3$ instead of PPh_3 with $Pd_2(dba)_3 \cdot CHCl_3$ reduces the reaction time dramatically from 6 h at 60 °C to 5 min at room temperature for the preparation of **25**.



23 24 25

Scheme 10

The use of $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ is, however, not limited to variations of the Stille coupling reaction. Also Suzuki coupling of arylboronic acids and vinyl halides are efficiently catalyzed by this catalyst system. This was demonstrated by the reaction of 2-halo-2,3-butadienoate **26** with arylboronic acids to the allenic ester **27** [15] (Scheme 11).



26 27

Scheme 11

Once again, using $Pd(PPh_3)_4$ at room temperature for 14 h furnished product **27** only in 32% and the by-product biphenyl in 13% yield. Attempts to improve this process by increasing the temperature were unsuccessful, leading mostly to decomposition of starting material with a concomitant increase of biphenyl formation. The mild conditions required for the formation of **27** could be achieved using $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ catalysis, which furnished **27** in 52% yield in a reaction time of only 1.5 h at room temperature.

These examples may serve to demonstrate the widespread applications of the Farina catalyst system $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ in various types of CC bond formation. As opposed to more traditional phosphane-ligated Pd complexes, $Pd_2(dba)_3 \cdot CHCl_3/AsPh_3$ stands out by showing a higher catalytic activity under milder reaction conditions, by having higher turnover rates and by giving higher yields. The Farina catalyst system also makes possible some reactions, in which Pd–phosphane catalysts failed to give the desired product.

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