*Expanding the Stille Coupling*

# Ligands for Palladium-Catalyzed Cross-Couplings of Alkyl Halides: Use of an Alkyldiaminophosphane Expands the Scope of the Stille Reaction**

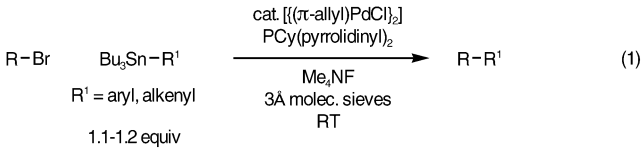
*Haifeng Tang, Karsten Menzel, and Gregory C. Fu**

*Dedicated to Professor Manfred T. Reetz on the occasion of his 60th birthday*

Whereas nickel- and palladium-catalyzed methods for cross-coupling aryl and vinyl halides and sulfonates with a range of organometallic reagents have reached a fairly high level of sophistication,[1] comparable progress has not yet been achieved for reactions of alkyl halides and sulfonates.[2] Recently, we and others have begun to address this shortcoming by describing catalysts for certain Suzuki,[3] Negishi,[4,5] Kumada,[6,7] Stille,[8] and Hiyama[9] couplings of primary alkyl electrophiles. With the exception of Suzuki's observation that $[Pd(PPh_3)_4]$ effects cross-couplings of alkyl iodides with R-(9-BBN),[3a] the palladium-based catalysts that were reported for coupling alkyl electrophiles have all employed a hindered trialkylphosphane ($PCy_3$ or $P(t\mathrm{Bu})_2\mathrm{Me}$) as the ligand.

To increase the likelihood of expanding the still-limited scope of cross-couplings of alkyl electrophiles, we have been exploring the use of new classes of ligands for these processes. Herein, we establish that, in the presence of alkyldiaminophosphanes ($PR(NR'_2)_2$), we can accomplish palladium-catalyzed Stille cross-couplings of alkyl bromides and iodides not only with vinyl stannanes, but also with aryl stannanes [Eq. (1)], a class of reaction partners that are not efficiently coupled by $Pd/PR_3$ ($PR_3$ = trialkylphosphane).

As a consequence of the electron-richness and the ready accessibility of alkyldiaminophosphanes ($PR(NR'_2)_2$),[10] we

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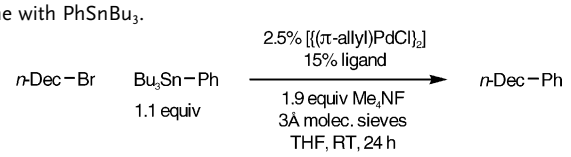
[**] We thank Johnson Matthey for supplying palladium compounds. Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, R01-GM62871), Merck, and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by NSF CHE-9808061 and NSF DBI-9729592.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200352668  

decided to examine the utility of this family of ligands in palladium-catalyzed couplings of alkyl electrophiles. In earlier work, we determined that $P(tBu)_2Me$ is useful for Stille cross-couplings of alkyl bromides with vinyl-, but not with aryl-, stannanes.[11] Thus, as illustrated in Table 1, neither $P(tBu)_2Me$ nor $PCy_3$ is effective for the palladium-catalyzed Stille reaction of 1-bromodecane with $PhSnBu_3$ under our previously reported conditions (entries 1 and 2, respectively).[12]

***Table 1:*** Effect of ligand structure on the cross-coupling of 1-bromodecane with $PhSnBu_3$.




| Entry | Ligand | Yield [%][a] |
|---|---|---|
| 1 | $P(tBu)_2Me$ | 12 |
| 2 | $PCy_3$ | 22 |
| 3 | $PMe(pyrrolidinyl)_2$ | 9 |
| 4 | $PEt(pyrrolidinyl)_2$ | 32 |
| 5 | $PCy(pyrrolidinyl)_2$ | 45 |
| 6 | $P(tBu)(pyrrolidinyl)_2$ | 4 |
| 7 | $PPh(pyrrolidinyl)_2$ | 7 |
| 8 | $P(iBuNCH_2CH_2)_3N$ | $<2$ |
| 9 | $PPh_3$ | $<2$ |
| 10 | no ligand | $<2$ |

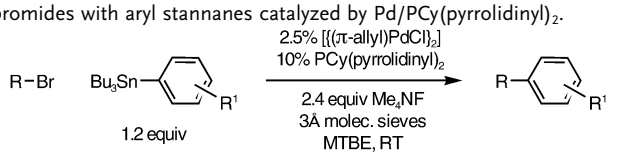
[a] Determined by GC versus a calibrated internal standard (average of two runs).

We therefore synthesized a sterically diverse set of alkyldiaminophosphanes, and we explored their use in this Stille cross-coupling process. Although Pd/PMe(pyrrolidinyl)$_2$ (pyrrolidinyl = 1-pyrrolidinyl) furnishes very little of the desired product (9%; Table 1, entry 3), an increase in the steric demand of the alkyl group can provide an improvement in yield (Me→Et→Cy: 9%→32%→45%; entries 3–5). As we have observed for couplings catalyzed by Pd/$PR_3$,[3b–d,5,8,9] there is a window of maximum reactivity for alkyldiaminophosphane ligands—thus, if the alkyl group, R, of $PR(NR'_2)_2$ becomes too large (e.g., *t*Bu), the yield decreases (4%; entry 5 versus entry 6). In the presence of an aryldiaminophosphane (entry 7), a bicyclic triaminophosphane (entry 8),[13] and $PPh_3$ (entry 9), almost no cross-coupling occurs.

Additional optimization of the most effective catalyst system, Pd/PCy(pyrrolidinyl)$_2$ (45%; Table 1, entry 5), produced an enhancement in yield (72%; Table 2, entry 1; MTBE = *t*BuOMe).[14] As illustrated in Table 2, under a standard set of conditions, an array of functionalized alkyl bromides can be coupled at room temperature with a variety of aryl stannanes.[15,16] Thus, the catalyst tolerates esters (entries 2–6), nitriles (entry 7), ethers (entry 8), and olefins (entry 9). In addition, both electron-rich and electron-poor aryl stannanes (entries 2–8), as well as a heteroaryl stannane (entry 9), are suitable cross-coupling partners.

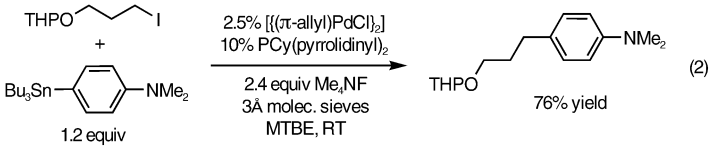
We have determined that the conditions that we have developed for Stille reactions of alkyl bromides (Table 2) can be applied without modification to couplings of alkyl iodides [Eq. (2)]. To the best of our knowledge, this is the first example of a Stille cross-coupling of a simple alkyl iodide that bears β hydrogen atoms.[17,18]

***Table 2:*** Room-temperature Stille cross-couplings of functionalized alkyl bromides with aryl stannanes catalyzed by Pd/PCy(pyrrolidinyl)$_2$.




| Entry | R−Br | Aryl stannane | Yield [%][a] |
|---|---|---|---|
| 1 | *n*-Dec−Br | $Bu_3Sn$ | 72 |
| 2 | EtO(C=O)$(CH_2)_4$Br | $Bu_3Sn$-Me | 63 |
| 3 | EtO(C=O)$(CH_2)_4$Br | $Bu_3Sn$-OMe | 71 |
| 4 | EtO(C=O)$(CH_2)_4$Br | $Bu_3Sn$-$CF_3$ | 57 |
| 5 | EtO(C=O)$(CH_2)_4$Br | OMe, $Bu_3Sn$ | 61 |
| 6 | EtO(C=O)$(CH_2)_4$Br | Me, $Bu_3Sn$ | 62 |
| 7 | NC$(CH_2)_4$Br | $Bu_3Sn$-$NMe_2$ | 68 |
| 8[b] | THPO$(CH_2)_3$Br | $Bu_3Sn$-F | 64 |
| 9 | $(CH_2)_3$Br | $Bu_3Sn$-N | 53 |

[a] Yield of isolated product (except for entry 1, which is a yield by GC versus a calibrated internal standard), average of two runs. [b] THP = tetrahydropyran.



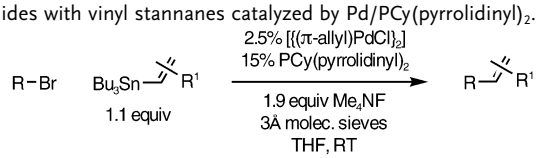

(2)

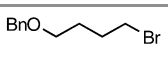
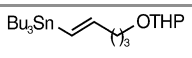
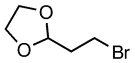
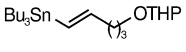
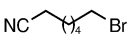
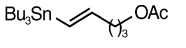
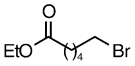
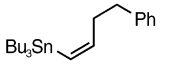
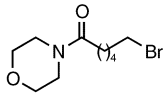
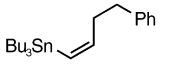
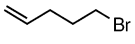
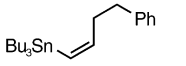
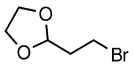
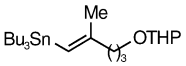
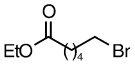
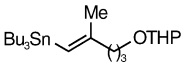
In addition to aryl stannanes, Pd/PCy(pyrrolidinyl)$_2$ can be employed for cross-couplings of vinyl stannanes. Thus, under the conditions that we previously reported for Pd/$P(tBu)_2Me$-catalyzed processes,[8,19] Pd/PCy(pyrrolidinyl)$_2$ catalyzes room-temperature couplings of functionalized alkyl bromides with a range of vinyl stannanes (Table 3).[20] Groups such as ethers, acetals, nitriles, esters, amides, and olefins may be present, and a variety of substitution patterns for the vinyl stannane are tolerated.

Finally, we can apply the same Pd/PCy(pyrrolidinyl)$_2$ catalyst system to room-temperature Stille cross-couplings of alkyl iodides with vinyl stannanes (90% yield; [Eq. (3)]).[21]

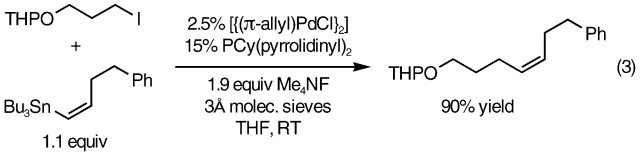
  

***Table 3:*** Room-temperature Stille cross-couplings of functionalized alkyl bromides with vinyl stannanes catalyzed by Pd/PCy(pyrrolidinyl)$_2$.




| Entry | R–Br | Vinyl stannane | Yield [%][a] |
|---|---|---|---|
| 1 |  |  | 74 |
| 2 |  |  | 60 |
| 3 |  |  | 68 |
| 4 |  |  | 89 |
| 5 |  |  | 79 |
| 6 |  |  | 78 |
| 7 |  |  | 54 |
| 8 |  |  | 73 |

[a] Yield of the isolated product, average of two runs.




In conclusion, we have identified a new class of ligands (alkyldiaminophosphanes, PR(NR′$_2$)$_2$) that are effective in palladium-catalyzed cross-couplings of alkyl electrophiles. In comparison with trialkylphosphanes, alkyldiaminophosphanes furnish more versatile catalysts for Stille reactions of alkyl halides, thus achieving, for example, efficient couplings with aryl stannanes. In view of the ready accessibility of a range of alkyldiaminophosphanes, as well as the potential for chiral variants, we anticipate that our observations will add a significant new dimension to the development of broadly applicable catalysts for cross-couplings of alkyl electrophiles.

Received: August 18, 2003 [Z52668]
Published Online: October 14, 2003

**Keywords:** cross-coupling · homogeneous catalysis · palladium · phosphane ligands · Stille reaction

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[11] See reference [8], including footnote [15].

[12] Among the large array of trialkylphosphanes that we have examined, P(*t*Bu)$_2$Me and PCy$_3$ are the most effective.

[13] a) Verkade has established that certain triaminophosphanes provide reactive catalysts for palladium-catalyzed Suzuki and Buchwald–Hartwig cross-couplings of aryl halides. See: S. Urgaonkar, M. Nagarajan, J. G. Verkade, *Tetrahedron Lett.* **2002**, *43*, 8921 – 8924; S. Urgaonkar, M. Nagarajan, J. G. Verkade, *Org. Lett.* **2003**, *5*, 815 – 818; S. Urgaonkar, M. Nagarajan, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 452 – 459; b) With acyclic triaminophosphanes, we have obtained small amounts of Stille cross-coupling products.

[14] Notes: 1) The increased yield is primarily due to the change of solvent (to MTBE). $CH_3CN$, *tert*-amyl alcohol, and $CH_2Cl_2$ are not suitable solvents for this process. 2) For the cross-coupling illustrated in entry 1 of Table 2, use of P(*t*Bu)$_2$Me, rather than PCy(pyrrolidinyl)$_2$, under the conditions of Table 2 leads to a poor yield (< 40%) of the desired product. 3) In the absence of $Me_4NF$, no coupling is observed. 4) $PdBr_2$ and $PdCl_2(PhCN)_2$ provide yields that are comparable with [{(π-allyl)PdCl}$_2$], whereas Pd(OAc)$_2$ is ineffective.

  

[15] Notes: 1) Reactions of (*o*-tolyl)$SnBu_3$ and (*p*-nitrophenyl)$SnBu_3$ proceed in more modest yield. 2) Allylstannanes, alkynylstannanes, alkyl chlorides, alkyl tosylates, and certain (tertiary, secondary, and β-branched primary) alkyl bromides are not useful coupling partners, furnishing at best a poor yield of the desired product.

[16] After the completion of a cross-coupling reaction, if $Cy_2PCH_2CH_2PCy_2$ is added, then a substantial amount of PCy(pyrrolidinyl)$_2$ is observed by $^{31}P$ NMR.

[17] For a discussion and leading references, see Reference [8].

[18] The use of P(*t*Bu)$_2$Me, rather than PCy(pyrrolidinyl)$_2$, leads to a significant loss in yield ($< 50\,\%$).

[19] The only modification: the cross-couplings catalyzed by Pd/PCy(pyrrolidinyl)$_2$ are conducted at an alkyl-halide concentration of 0.2 M, versus 0.1 M for Pd/P(*t*Bu)$_2$Me (for Pd/P(*t*Bu)$_2$Me, reactions run at higher concentration lead to the precipitation of a black solid, presumably Pd).

[20] Notes: 1) The stereochemistry of the vinyl stannane is retained in the cross-coupling product. 2) For entries 1, 4, and 5 of Table 3, the isolated yields for Pd/PCy(pyrrolidinyl)$_2$ are 14–24 % higher than for Pd/P(*t*Bu)$_2$Me (see Reference [8]); for entry 7, the yields are essentially identical, and for entry 2 the yield is 11 % lower for Pd/PCy(pyrrolidinyl)$_2$.

[21] Under these conditions, we have also efficiently coupled 1-iododecane with tributyl(vinyl)tin (93 % yield by GC versus a calibrated internal standard).

  