Cross-Coupling

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Palladium-Catalyzed Cross-Coupling of Aryl Halides Using Organotitanium Nucleophiles**

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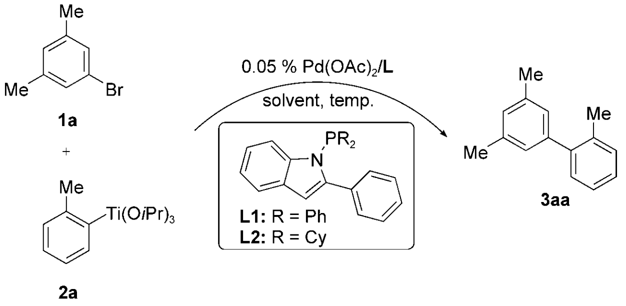
Palladium-catalyzed cross-coupling reactions constitute an extremely versatile protocol in organic synthesis for the connection of electrophilic to organometallic fragments through the formation of either carbon–carbon or carbon–heteroatom bonds.[1] During the past decade, enormous effort has been undertaken, especially in ligand design,[2] to enhance the capability of utilizing relatively inert electrophiles, such as aryl chlorides,[3] tosylates,[4] mesylates,[5] and pivalates,[6] as coupling partners. Yet, investigations on the development and application of new nucleophilic partners in cross-coupling reactions remain limited. The construction of $C(sp^2)-C(sp^2)$ bonds through the use of nucleophilic transmetalating agents, such as organotin,[7] -boron,[8] -zinc,[9] -magnesium,[10] -silicon,[11] and -aluminum,[12] is well-known. However, there is need for a versatile nucleophilic partner to realize the potential benefits of these methodologies and to tackle current difficulties in cross-coupling reactions. Such a nucleophilic partner would allow the development of a protocol that eliminates the need to add a solid inorganic base to the reactions and would hence enable the effective application of such reactions in microchannel reactors and flow systems.

The pioneering studies by Hayashi and co-workers[13] demonstrated that $MeTi(OiPr)_3$ and $PhTi(OiPr)_3$ could be used for the methylation and phenylation, respectively, of 2-naphthyl triflate. Knochel and co-workers also reported a similar arylation using nickel complexes of N-heterocylic carbenes.[14] However, a general palladium system suitable for the reaction of aryl titanium nucleophiles with aryl halides is not yet available. To our knowledge, there is only one publication regarding the palladium-catalyzed coupling of an aryl triflate with an organotitanium reagent, and this is only of limited scope.[15] We report herein the first general palladium-catalyzed cross-coupling of aryl titanium reagents with a variety of aryl halides. In addition, we disclose here the use of readily available aminophosphanes in the coupling of aryl bromides, as well as the new indolyl ligands for the successful coupling of aryl chlorides.

The palladium-catalyzed coupling of aryl bromides/chlorides with aryl titanium nucleophiles has not yet been reported. The feasibility of coupling aryl halides with aryl titanium reagents was investigated by using a series of indolylaminophosphanes.[16] The most readily accessible aminophosphanes, with either a diphenylphosphano or dicyclohexylphosphano group (one step from commercially available 2-phenylindole), were initially employed in the study. Electronically neutral 5-bromo-*m*-xylene and sterically hindered *o*-tolyltitanium derivative **2a** were used as the model substrates in our benchmark reaction (Table 1). In particular, we chose the *o*-tolyl derivative (instead of phenyl) as the prototypical substrate since the unsubstituted phenyl ring is generally regarded as the substrate that undergoes cross-coupling reactions easiest. We thus did not use the phenyl

Table 1: Initial screening of the palladium-catalyzed cross-coupling of aryl bromide **1a** with the aryl titanium nucleophilic partner **2a**.[a]



Entry	Ligand	Solvent	*T*, *t*	Yield[b] [%]
1	**L1**	toluene	90°C, 1 h	98
2	**L2**	toluene	90°C, 1 h	99
3	Ph_3P	toluene	90°C, 1 h	18
4	**L2**	toluene	RT, 18 h	89
5	**L1**	dioxane	90°C, 1 h	33
6	**L1**	THF	90°C, 1 h	45
7[c]	**L1**	toluene	90°C, 1 h	58
8[d]	**L1**	toluene	90°C, 1 h	99
9[e]	**L1**	toluene	90°C, 1 h	79

[a] Reaction conditions: ArBr (0.2 mmol), $Ar'Ti(OiPr)_3$ (0.3 mmol), $Pd(OAc)_2$ (0.05 mol%, with respect to ArBr), **L** (0.1 mol%), solvent (0.6 mL), under N_2 for the specified time. [b] Calibrated GC yields were reported using dodecane as the internal standard. [c] Pd/L = 1:1. [d] Pd/L = 1:3. [e] $Ar'Ti(OiPr)_3$ (0.2 mmol) was used.

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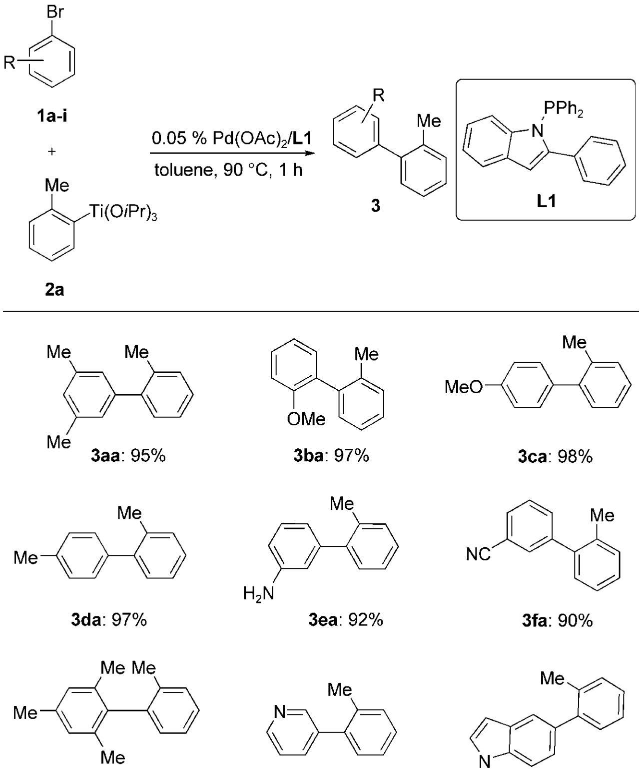
derivative in our initial exploration into establishing the scope of the procedure. Notably, a survey of the reaction conditions indicated this titanium-mediated protocol did not require the addition of solid inorganic bases. This feature possibly provides a new opportunity and has the advantage of avoiding the need to agitate the solid-base suspension, as is necessary in common cross-coupling processes.

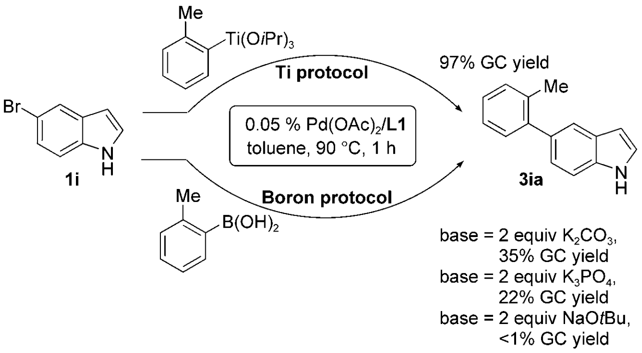
Aminophosphanes **L1** and **L2** with PPh_2 or PCy_2 (Cy = cyclohexyl) groups, respectively, proved to be efficient ligands and provided the coupling products in excellent yields; in contrast, the commonly used Ph_3P resulted in poor conversion of the substrate (Table 1, entries 1–3). The coupling reactions could be performed at room temperature by employing ligand **L2** (Table 1, entry 4). Toluene was the solvent of choice, while dioxane and THF afforded only moderate yields (Table 1, entries 5 and 6). A Pd/L ratio of 1:1 resulted in poor conversion of the substrate,[17] while a ratio greater than 1:2 provided essentially complete conversion (Table 1, entries 1, 7, and 8). Since **L1** (with a PPh_2 group) is considerably much less expensive to make than **L2** (with a PCy_2 group), we therefore used the optimized reaction conditions depicted in entry 1 for our further investigations.

To test the effectiveness of the Pd/**L1** catalyst system, a range of aryl bromides was examined under the preliminary optimized reaction conditions (Scheme 1). In general, complete conversion was observed within 1 hour when 0.05 mol % Pd was used. Particularly noteworthy was that the coupling of a sterically hindered substrate (with 2,6-dimethyl substituents) with the *o*-tolyl nucleophile generated a tri-*ortho*-substituted biaryl (Scheme 1, **3ga**). This catalyst loading is the lowest achieved so far for the synthesis of tri-*ortho*-substituted compounds by coupling reactions involving a phosphane ligand with a PPh_2 group. Moreover, heterocycles such as pyridine and indole (with a free NH group) could be coupled effectively to furnish the corresponding products **3ha** and **3ia**, respectively.



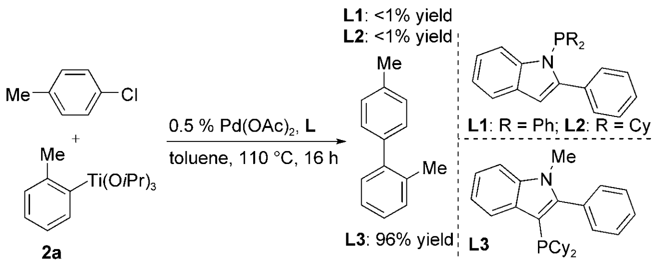
Scheme 1. Palladium-catalyzed cross-coupling of aryl bromides **1** with *o*-tolyltitanium nucleophile **2a**. Reaction conditions: ArBr (0.2 mmol), $Ar'Ti(OiPr)_3$ (0.3 mmol), $Pd(OAc)_2$ (0.05 mol%, with respect to ArBr), **L1** (0.1 mol%), toluene (0.6 mL, total volume), at 90°C under N_2 for 1 h, (see the Supporting Information for experimental details), yields of isolated products are given in all cases. [a] 0.5 mol% of $Pd(OAc)_2$ was used.

The efficacy of the organotitanium-mediated coupling reaction can be further highlighted by a series of parallel competitive experiments. The pharmaceutically useful 5-bromoindole (**1i**) was chosen as the electrophile. The use of the Suzuki-type nucleophile (*o*-tolylboronic acid) and an *o*-tolyltitanium reagent were compared (Scheme 2). Under the same reaction conditions, the titanium-based protocol showed complete conversion of 5-bromoindole and afforded the desired product in 97% yield. However, the parallel experiments using the organoboron nucleophile resulted in poor conversion of the substrate and provided the product in 22–35% yield when K_2CO_3 or K_3PO_4 was added (Scheme 2). It is noteworthy that different aryl metal nucleophiles have corresponding specific windows in cross-coupling processes.



Scheme 2. A set of parallel experiments between Suzuki-type organoboron and organotitanium nucleophiles.

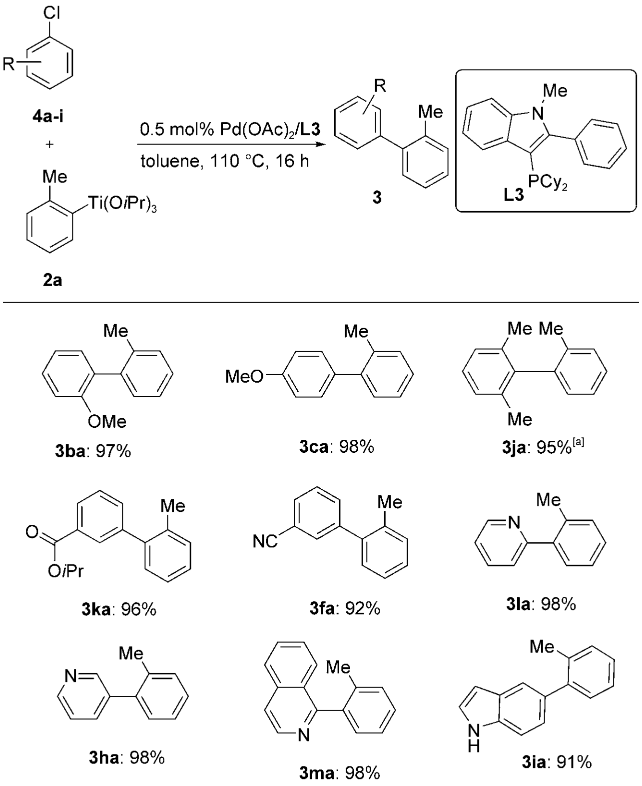
The Pd/**L1** catalyst system was investigated in the coupling reactions of aryl chlorides. However, the aminophosphanes **L1** and **L2** were found to be inferior in this process (Scheme 3). We wondered if the aminophosphane was not



Scheme 3. Efficiency of the coupling of an aryl chloride with **2a** in the presence of aminophosphane and phosphane ligands.

able to donate sufficient electron density to the palladium center for oxidative addition to occur. Hence, we took advantage of the ligand scaffold and modified the phosphane ligand by introducing a phosphano group on the opposite side (3-position) of the indole skeleton to generate ligand **L3**. This ligand gave a significantly better result in the coupling reaction compared to **L1** and **L2** (Scheme 3).[18]

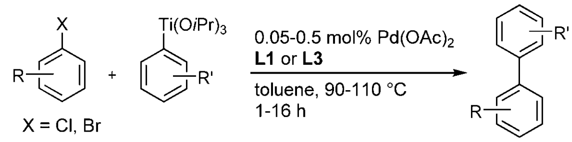
We then set out to explore a range of aryl chloride coupling reactions under our optimized reaction conditions (Scheme 4). In general, a 0.5 mol% loading of the Pd catalyst was sufficient to promote this reaction. Deactivated 4-chloroanisole could be effectively coupled with an *o*-tolyl nucleophilic partner (Scheme 4, **3ca**). Sterically hindered 2-chloro-*m*-xylene was also found to act as a substrate in this reaction (Scheme 4, **3fa**). Nitrogen heterocycles such as pyridine, quinoline, and indole proved to be proficient and afforded their corresponding products in excellent yields.

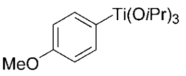
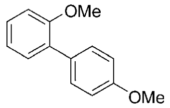
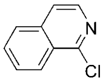
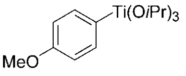
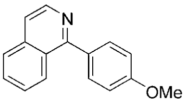
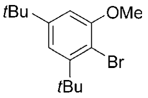
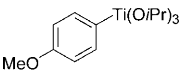
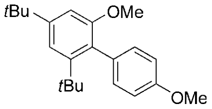
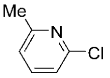
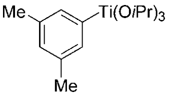
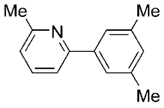
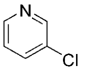
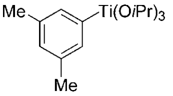
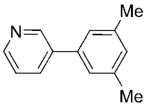
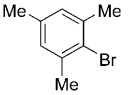
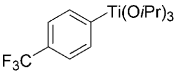
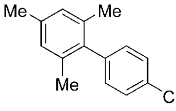
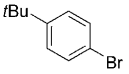
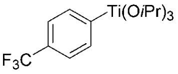
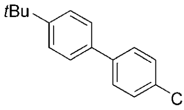


Scheme 4. Palladium-catalyzed cross-coupling of different aryl chlorides with *o*-tolyltitanium nucleophile **2a**. Reaction conditions: ArCl (0.2 mmol), Ar'Ti(O*i*Pr)$_3$ (0.3 mmol), Pd(OAc)$_2$ (0.5 mol%, with respect to ArCl), **L3** (1 mol%), toluene (0.6 mL, total volume), at 110°C under N$_2$ for 16 h, yields of isolated products are given in all cases. [a] 2.0 mol% of Pd(OAc)$_2$ was used.

The scope of the aryl titanium reagents was then examined (Table 2). Titanium nucleophiles bearing either electron-donating or electron-withdrawing groups could be used in this coupling reaction. Exceedingly hindered 6-methoxy-2,4-di-*tert*-butylbromobenzene could be coupled effectively to afford the desired product in excellent yield (Table 2, entry 3).

Table 2: Palladium-catalyzed cross-coupling of different aryl halides with aryl titanium nucleophiles.[a]

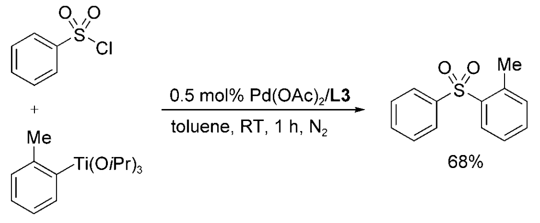


Entry	ArX	Ar'-Ti	Product	Yield[b] [%]
1				98
2				88
3				91
4				89
5				91
6				92
7				93

[a] Reaction conditions: see Schemes 1 and 4 for ArBr and ArCl coupling reactions, respectively. [b] Yields of isolated product.

Organosulfones are highly attractive intermediates in organic synthesis because of their chemical properties and biological activities.[19] Vogel and Dabbaka reported the palladium-catalyzed Suzuki-type coupling of sulfonyl chlorides with aryl boronic acids,[20] as well as the Stille-type coupling of sulfonyl chlorides with organostannanes.[21] Interestingly, the coupling products were biaryls instead of the desired diaryl sulfones. This desulfonyl coupling possibly results from the extrusion of SO$_2$ at the high reaction temperatures and the long reaction times. To probe the effectiveness of the titanium nucleophile, we coupled the aryl titainium reagent to benzenesulfonyl chloride (Scheme 5). Under our mild reaction conditions, the SO$_2$ moiety can be retained in the product, and thus the desired unsymmetrical sulfone was obtained in good yield.

In conclusion, we have succeeded in establishing the first palladium-catalyzed titanium-mediated cross-coupling of aryl halides. The catalyst system derived from 0.05 mol% Pd and aminophosphane **L1** or from 0.5 mol% Pd and phosphane **L3** proved general and sufficient to promote the coupling of aryl bromides and chlorides, respectively. Particularly noteworthy



Scheme 5. Palladium-catalyzed coupling of benzenesulfonyl chloride with the *o*-tolyltitanium nucleophile.

is the versatility of the organotitanium nucleophiles, which can offer higher efficiency than organoboron derivatives in the coupling of bromoindole which contains an NH group. In addition to aryl halides, this titanium-mediated coupling also allowed, for the first time, an aryl sulfonyl chloride to be coupled. This protocol has the beneficial feature that additional solid inorganic bases are not required, and thus the homogeneous medium would offer advantages for performing reactions in a flow system or microchannel reactor. Efforts to expand the reaction scope and a mechanistic study are currently underway.

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Keywords: cross-coupling · palladium · phosphanes · sulfones · titanium

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[1] a) *Metal-Catalyzed Cross-Coupling Reactions, 2nd* ed., *Vol 1–2* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis Building Blocks and Fine Chemicals*, 2nd ed., Vol. 1–2, Wiley-VCH, Weinheim, **2004**; c) L. Yin, J. Liebscher, *Chem. Rev.* **2007**, *107*, 133; d) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; e) A. Roglans, A. Pla-Quintana, M. Moreno-Manas, *Chem. Rev.* **2006**, *106*, 4622; f) L. Ackermann, *Modern Arylation Methods*, Wiley-VCH, Weinheim, **2009**.

[2] For recent reviews on the development of phosphane ligands, see a) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534; c) F. Y. Kwong, A. S. C. Chan, *Synlett* **2008**, 1440.

[3] For a pertinent review on coupling reactions of aryl chlorides, see A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

[4] For the use of ArOTs in palladium-catalyzed C–C coupling reactions, see a) H. N. Nguyen, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 11818; b) C. M. So, C. P. Lau, A. S. C. Chan, F. Y. Kwong, *J. Org. Chem.* **2008**, *73*, 7734; c) L. Zhang, T. Meng, J. Wu, *J. Org. Chem.* **2007**, *72*, 9346; d) A. H. Roy, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 8704; e) M. E. Limmert, A. H. Roy, J. F. Hartwig, *J. Org. Chem.* **2005**, *70*, 9364; f) L. Ackermann, A. Althammer, *Org. Lett.* **2006**, *8*, 3457; g) A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby, T. Skrydstrup, *Angew. Chem.* **2006**, *118*, 3427; *Angew. Chem. Int. Ed.* **2006**, *45*, 3349; for nickel-catalyzed coupling reactions of ArOTs, see h) D. Zim, V. R. Lando, J. Dupont, A. L. Monteiro, *Org. Lett.* **2001**, *3*, 3049; i) Z. Y. Tang, Q. S. Hu, *J. Am. Chem. Soc.* **2004**, *126*, 3058; j) V. Percec, G. M. Golding, J. Smidrkal, O. Weichold, *J. Org. Chem.* **2004**, *69*, 3447.

[5] For the use of ArOMs in palladium-catalyzed C–C coupling reactions, see a) C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 8179; *Angew. Chem. Int. Ed.* **2008**, *47*, 8059; b) C. M. So, Z. Zhou, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 6502; *Angew. Chem. Int. Ed.* **2008**, *47*, 6402; c) L. Zhang, J. Qing, P. Yang, J. Wu, *Org. Lett.* **2008**, *10*, 4971; d) C. M. So, H. W. Lee, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2009**, *11*, 317; for nickel-catalyzed ArOMs coupling reactions, see e) V. Percec, J.-Y. Bae, D. H. Hill, *J. Org. Chem.* **1995**, *60*, 1060.

[6] a) B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu, Z.-J. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 14468; b) K. W. Quasdorf, X. Tian, N. K. Garg, *J. Am. Chem. Soc.* **2008**, *130*, 14422.

[7] For selected references and reviews, see a) P. Espinet, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 4808; *Angew. Chem. Int. Ed.* **2004**, *43*, 4704; b) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.

[8] For selected references and reviews, see a) N. Miyaura, *Top. Curr. Chem.* **2002**, *219*, 11; b) A. Suzuki in *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, **2002**, pp. 53 – 106.

[9] For selected references and reviews, see a) E.-i. Negishi, X. Zeng, Z. Tan, M. Qian, Q. Hu, Z. Huang in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, chap. 15; b) G. Manolikakes, Z. Dong, H. Mayr, J. Li, P. Knochel, *Chem. Eur. J.* **2009**, *15*, 1324.

[10] For selected references and reviews, see a) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Hirotsu, *J. Am. Chem. Soc.* **1984**, *106*, 158; b) G. Manolikakes, P. Knochel, *Angew. Chem.* **2009**, *121*, 211; *Angew. Chem. Int. Ed.* **2009**, *48*, 205.

[11] For selected references and reviews, see a) T. Hiyama, *J. Organomet. Chem.* **2002**, *653*, 58; b) S. E. Denmark, R. F. Sweis, *Acc. Chem. Res.* **2002**, *35*, 835.

[12] S.-L. Ku, X.-P. Hui, C.-A. Chen, Y.-Y. Kuo, H.-M. Gau, *Chem. Commun.* **2007**, 3847.

[13] J. W. Han, N. Tokunaga, T. Hayashi, *Synlett* **2002**, 871.

[14] G. Manolikakes, N. Dastbaravardeh, P. Knochel, *Synlett* **2007**, 2077.

[15] There is only one reported example with an aryl triflate (Ref. [13]). In fact, no examples of the use of aryl halides and aryl titanium reagents in palladium-catalyzed Ar–Ar′ coupling reactions have been reported so far.

[16] For our recent study on aminophosphanes based on an indolyl scaffold, see C. M. So, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2007**, *9*, 2795. For our related indolylphosphane, see C. M. So, C. C. Yeung, C. P. Lau, F. Y. Kwong, *J. Org. Chem.* **2008**, *73*, 7803

[17] Pd black was observed after heating the reaction for about 10 minutes.

[18] Under the same reaction conditions, the use of the Cy$_3$P ligand resulted in 29% conversion of ArCl and a 26% yield of the desired product (GC yield).

[19] N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon, Oxford, **1993**.

[20] S. R. Dubbaka, P. Vogel, *Org. Lett.* **2004**, *6*, 95.

[21] S. R. Dubbaka, P. Vogel, *J. Am. Chem. Soc.* **2003**, *125*, 15292.