Palladium-Catalyzed Cross-Coupling of (Hetero)Aryl or Alkenyl Sulfonates with Aryl Titanium as the Multi-Functional Reagent

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The first palladium-catalyzed cross-coupling reaction of aryl/heteroaryl and alkenyl mesylates and tosylates with aryl titanium as the multi-functional reagent is reported. Using the catalyst system of Pd(OAc)$_2$ associated with the new NMe$_2$-CM-Phos (**L14**), a broad range of electron-rich, -neutral, -deficient, and sterically hindered aryl/ heteroaryl and alkenyl mesylates and tosylates are well-coupled with aryl titanium reagents to give the corresponding products in good-to-excellent yields. The catalyst loading down to 0.2 mol% Pd and the reaction time shortening to 10 min can be achieved. The reaction can be easily scaled up to gram scale without diminishing in product yield.

Palladium-catalyzed cross-coupling reactions are the most powerful methods in accessing divergent organic molecules via formation of carbon-carbon or carbon-heteroatom bonds from corresponding electrophilic and organometallic fragments.[1] Recent developments of highly efficient catalyst systems[2] allow them to utilize relatively inert electrophiles, such as aryl chlorides,[3] tosylates,[4] mesylates,[5] pivalates,[6] and even aromatic ethers.[6] Organometallic reagents, such as organomagnesium,[7] organotin,[8] organogermanium,[9] organoboron,[10] organozirconium,[11] organozinc,[11] organoaluminium,[12] organoindium,[13] organobismuth,[14] and others,[15] have been well studied as nucleophilic partners in these cross-coupling reactions. With regard to the necessity of having inorganic bases or additives in common cross-coupling reaction medium (i.e. heterogeneous conditions), it would be attractive to seek a homogeneous coupling condition which does not require additional inorganic base and/or additive, complementary. Indeed, the use of large excess of base/additive for the coupling reactions come with a heavy cost to our environment.[16] Thus, the exclusion of the use of solvent and base/additive would significantly reduce the waste production.[16,17] Moreover, the homogeneous condition would even enable the possible microchannel reaction and flow systems. However, to our best knowledge, transition metal-catalyzed both solvent-free and base/additive-free biaryl cross-coupling reactions have not yet been reported. Specifically, only solvent-free biaryl cross-coupling reactions were sporadically studied, for instance solvent-free Suzuki coupling,[18] ball mill,[19] and solvent-free Hiyama coupling reactions.[20] Most recently, a direct coupling of organolithium compounds with no additional solvents was reported.[21]

We believe the organotitanium nucleophile may act as a multi-functional reagent to realize the solvent-free and base/additive-free palladium-catalyzed cross-coupling reaction. The relatively low melting point of the aryl titanium reagents (e.g. PhTi(O*i*-Pr)$_3$, 88–90 ^{o}C) allows the organometallic reagents to work as a reaction medium in the coupling reaction which permits the absence of organic solvent. In addition, the enhanced nucleophilicity of Ar'Ti(O*i*-Pr)$_3$ facilitates the transmetalation step better, even without the need of additional and excess amount of base/additive to activate the reagent.[22] Nevertheless, the application of organotitanium reagents in the cross-coupling reactions has received relatively less attention than the aforementioned organometallic reagents. The pioneering works from Hayashi and co-workers demonstrated that Ar'Ti(O*i*-Pr)$_3$ were applicable for palladium and nickel-catalyzed cross-coupling reactions.[23] There were only three literature reports on the application of organotitanium reagents in palladium-catalyzed biaryl synthesis to-date.[22, 23b, 24] The exploration of (hetero)aryl mesylates and tosylates coupling reaction under solvent-free conditions have been challenging,[25] because common organometallic reagents are unable to allow efficient transformation under these reaction conditions.[26] Hence, we are interested to establish a new catalytic system for possible solvent-free and base/additive free coupling reaction.

In the presence of Pd(OAc)$_2$/CM-Phos **L1** as a catalyst, the reaction of 4-*tert*-butylphenylmesylate with different nucleophiles were carried out in the absence of base/additive and solvent. Essentially no or trace amount of product yield was observed with popular organometallic reagents such as organolithium, magnesium, zinc, boron, silicon and tin (Table 1, entries 1-8). For the trials of organolithium and magnesium reagents, significant amount of phenolic side products were observed which likely caused by the strong nucleophilicity and

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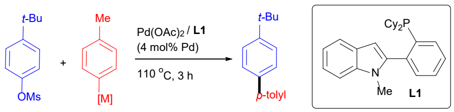
Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data for all compounds (PDF) and X-ray crystallographic data of **L14** (CIF). See DOI: 10.1039/x0xx00000x basicity of the reagents in hydrolyzing the aryl sulfonate. For the zinc, boron, silicon, and tin reagents, 4-*tert*-butylphenylmesylate remained intact during the course of the reaction (Table 1, entries 3-8). Aryl titanium reagents can be easily synthesized from the commercially available chlorotriisopropoxytitanium(IV) with the corresponding aryl magnesium halides or aryl lithium. Aryl titanium reagent was then tested. Delightfully, it was able to allow the cross-coupling reaction to proceed under the base/additive- and solvent-free reaction conditions which demonstrated the uniqueness of this coupling partner (Table 1, entry 9). Pd_2dba_3 as Pd source was screened (Table 1, entry 10). The corresponding product was obtained in 8%, which indicates that AcO^- from $Pd(OAc)_2$ is not necessary for this reaction. To probe the moisture sensitivity of the reaction, one equivalence of water was added in the reaction and showed no detrimental effect on this reaction (Table 1, entry 11). However, the addition of five equivalence of water added suppressed the reaction (Table 1, entry 12).

Table 1 Investigation of Nucleophiles for Base/Additive-free and Solvent-free Cross-Coupling Reaction[a]

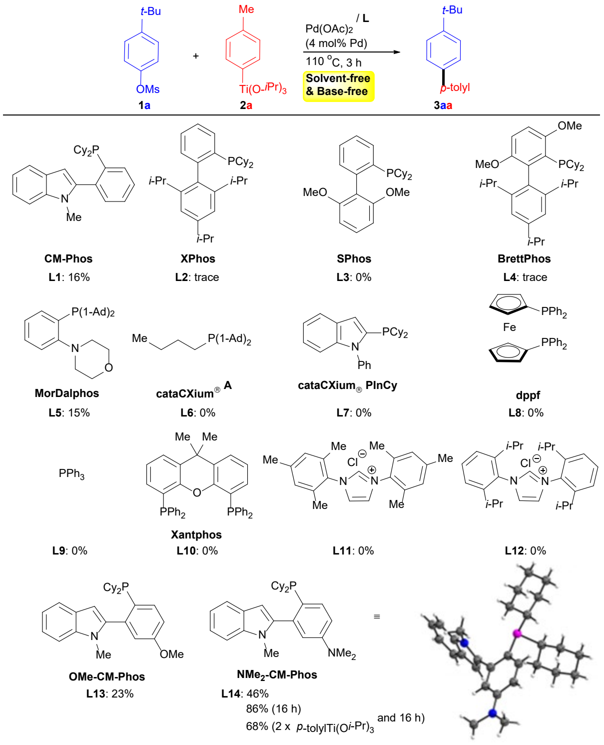


Entry	[M]	%Yield[b]	% Yield of remained ArOMs[b]
1	-Li[c]	0	11
2	-MgBr	0	0
3	-ZnCl	0	93
4	$-B(OH)_2$	0	95
5	-Bpin	0	89
6	$-BF_3K$	trace	89
7	$-Si(OMe)_3$	0	87
8	-Sn(*n*-Bu)$_3$	trace	99
9	-Ti(O-*i*-Pr)$_3$	16	66
10	-Ti(O-*i*-Pr)$_3$[d]	8	73
11	-Ti(O-*i*-Pr)$_3$[e]	20	65
12	-Ti(O-*i*-Pr)$_3$[f]	trace	72

[a] Reaction conditions: ArOMs (0.5 mmol), Ar'-[M] (2.5 mmol), $Pd(OAc)_2$ (4 mol%), **L1** (16 mol%) were stirred at 110 °C for 3 h under nitrogen atmosphere. [b] The yields were calibrated by GC-FID using dodecane as the internal standard. [c] PhLi was used. [d] Pd_2dba_3 was used. [e] 1 equiv. H_2O was added. [f] 5 equiv. H_2O was added.

With this inspiring result, a series of well-recognized and superior supporting ligands for palladium-catalyzed cross-coupling reactions of aryl sulfonates were tested (Table 2).[5] XPhos (**L2**), SPhos (**L3**), BrettPhos (**L4**), and MorDalphos (**L5**) failed to promote this solvent-free and base/additive-free coupling reaction of aryl mesylate with aryl titanium reagent. Other commercially available phosphines, such as cataCXium® A (**L6**), cataCXium® PInCy (**L7**), dppf (**L8**), PPh_3 (**L9**), Xantphos (**L10**), and NHC-carbene ligands (**L11** and **L12**) were also screened but did not show any catalytic performance. We believe further introducing electron-donating group at the *para*-position to the $-PCy_2$-containing arene (based on CM-Phos scaffold) would enhance more towards the oxidative addition of inert $C_{(Ar)}$-O bond. The more electron-rich ligand OMe-CM-Phos (**L13**) gave a better product yield (23%). The even more electron-donating $-NMe_2$ group on NMe_2-CM-Phos (**L14**) showed even higher product yield (46%). Using $Pd(OAc)_2$/newly developed NMe_2-CM-Phos (**L14**) catalyst, completed conversion of 4-*tert*-butylphenyl mesylate and excellent product yield (86%) were achieved in 16 h. It should be noted that the desired product yield was not strongly influenced by using two equivalent of *p*-tolylTi(O*i*-Pr)$_3$.

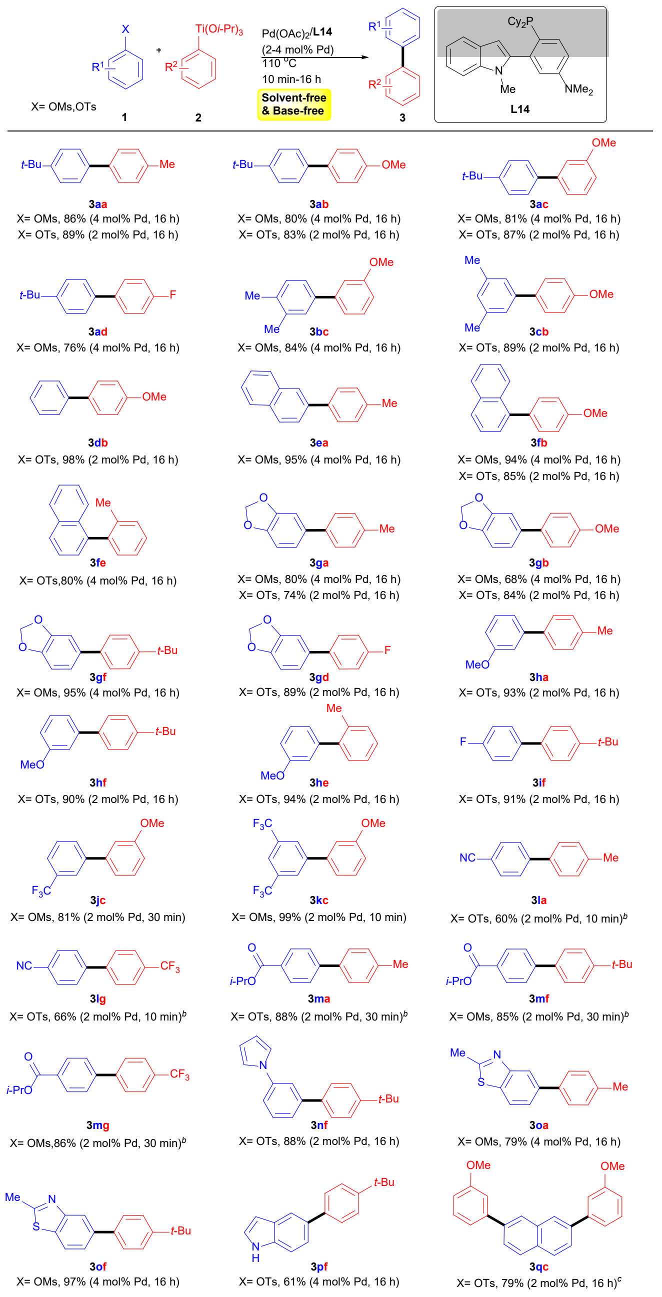
Table 2 Ligand screening in the palladium-catalyzed cross-coupling reaction of ArOMs with Ar'Ti(O*i*-Pr)$_3$[a]



[a] Reaction conditions: ArOMs (0.5 mmol), Ar'Ti(O*i*-Pr)$_3$ (2.5 mmol), $Pd(OAc)_2$ (4 mol%), **L** (16 mol%) were stirred at 110 °C for 3 h under nitrogen atmosphere. The yields were calibrated by GC-FID using dodecane as the internal standard.

The scope of the cross-coupling reaction of aryl mesylates or tosylates with organotitanium nucleophiles was then investigated. Most reactions generally completed within 16 h in the presence of 2-4 mol% Pd/**L14** catalyst (Table 3). It was noteworthy that the aryl titanium reagent worked as a good reaction medium and showed excellent compatibility to the aryl sulfonates. Electron-rich (-4-OMe), -neutral (-4-Me, -4-*tert*-Bu, -3-OMe) and -poor (-4-F, $-4-CF_3$) aryl titanium reagents provided good to excellent product yields (Table 3, compounds **3aa**, **3ab**, **3ac**, **3ad**, **3gf** and **3mg**). Particularly noteworthy was that the sterically hindered 1-naphthyl mesylate and tosylate were successfully coupled with *p*-anisylTi(O*i*-Pr)$_3$ and *o*-tolylTi(O*i*-Pr)$_3$ and generated mono- and di-*ortho*-substituted biaryl compounds respectively, under the same reaction conditions (Table 3, compounds **3fb** and **3fe**). The mono- and di- CF_3 substituted electron-deficient aryl mesylates were converted to the corresponding products with shorter timeframes (30 and 10 min) (Table 3, compounds **3jc** and **3kc**). Aryl mesylates/tosylates bearing functional groups such as ester and nitrile were also compatible and afforded the corresponding products in excellent yields in 30 min (Table 3, compounds **3la**, **3lg**, **3ma**, **3mf** and **3mg**). Heteroaryl mesylates and tosylates, such as benzothiazolyl mesylates, pyrrolylphenyl tosylate and indolyl tosylate, gave the desired products in good-to-excellent yields (Table 3, compounds **3nf**, **3oa**, **3of**, and **3pf**). The free N-H group remained intact under these reaction conditions (Table 3, compound **3pf**). 1,6-Naphthyl ditosylate coupling reaction also proceeded smoothly (Table 3, compound **3qc**).

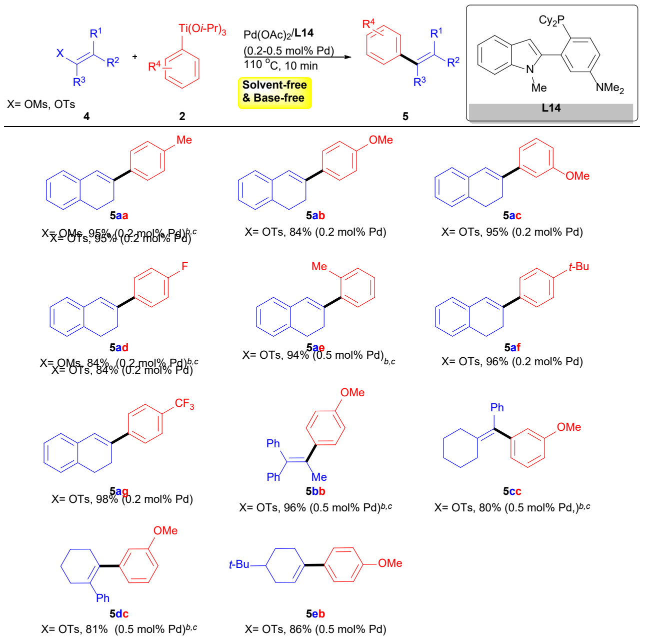
Table 3 Palladium-Catalyzed Cross-Coupling Reaction of ArOMs/OTs with Ar'Ti(O*i*-Pr)$_3$[a]



[a] Reaction conditions: ArOMs/OTs (0.5 mmol), Ar'Ti(O*i*-Pr)$_3$ (2.5 mmol), Pd(OAc)$_2$, **L14** (Pd:L = 1:4) were stirred at 110 °C for the indicated time under nitrogen atmosphere. Isolated yields. [b] Ar'Ti(O*i*-Pr)$_3$ (1.0 mmol) was used. [c] Ar'Ti(O*i*-Pr)$_3$ (5.0 mmol) was used.

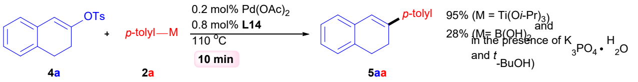
Alkenyl sulfonates, which are essential complements to limited availability of alkenyl halides, reacted smoothly to give excellent yields of desired products within 30 min using Pd(OAc)$_2$/**L14** catalytic system (Table 4). For some of the alkenyl tosylates, the reactions were completed in 10 min with only 0.2 mol% Pd. Tetralone- (Table 4, compounds **5aa**, **5ab**, **5ac**, **5ad**, **5ae**, **5af**, and **5ag**) and cycloalkanone-derived alkenyl tosylates (Table 4, compounds **5dc** and **5eb**) were converted to the corresponding cross-coupled products in excellent yields. Sterically congested *o*-aryl-substituted alkenyl tosylate afforded the desired product in an 81% yield (Table 4, compound **5dc**). Arylacetone-derived alkenyl tosylates were also coupled effectively (Table 4, compounds **5bb, and 5cc**).

Table 4 Palladium-Catalyzed Cross-Coupling Reaction of Alkenyl OMs/OTs with Ar'Ti(O*i*-Pr)$_3$[a]



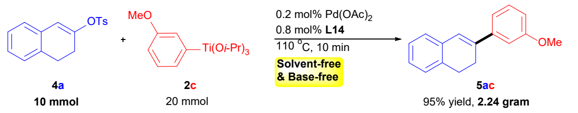
[a] Reaction condition: alkenyl OMs/OTs (0.5 mmol), Ar'Ti(O*i*-Pr)$_3$ (1.0 mmol), Pd(OAc)$_2$, **L14** (Pd:L = 1:4) were stirred at 110 °C for 10 min under nitrogen atmosphere. Isolated yields. [b] Ar'Ti(O*i*-Pr)$_3$ (2.5 mmol) was used. [c] 30 min.

To spotlight the advantages of the solvent-free reaction condition enabled by aryl titanium reagents, a direct comparison experiment between Suzuki reagent and titanium reagent was performed (Scheme 1). When the Suzuki reaction was performed using the optimal reaction conditions, only a 28% product yield was obtained. On the other hand, the reaction using *p*-tolylTi(O*i*-Pr)$_3$ reagent underwent smoothly and gave a 95% yield within 10 min.

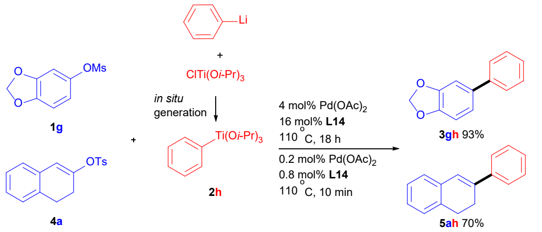


Scheme 1 A Set of Parallel Experiments between Suzuki-Type Organoboron and Organotitanium Nucleophiles.

One of the challenges for the solvent-free reaction is the feasibility of scaling up the reaction which may be hindered by the formation of hot spots and the possibility of runaway reactions. Here the reaction between organotitanium nucleophile and alkenyl tosylate was scaled up 20 times using a simple reflux setup. The coupling product was afforded in gram-scale without reducing the percentage yield (Table 4 and Scheme 2, compound **5ac**). Notably, even the PhTi(O*i*-Pr)$_3$ was prepared *in situ* (by adding PhLi to ClTi(O*i*-Pr)$_3$), the coupling of this titanium reagent with sesamol mesylate or dihydronaphthalenyl tosylate were also performed smoothly and afforded corresponding product yields of 93% and 70%, respectively (Scheme 3, compounds **3gh** and **5ah**).



Scheme 2 The Gram-Scale Cross-Coupling Reaction in a Simple Reflux Setup.



Scheme 3 The base/additive-free and solvent-free cross-coupling reaction of ArOMs and alkenyl OTs using the in situ preparation PhTi(O*i*-Pr)$_3$.

To summarize, palladium-catalyzed cross-coupling reaction of a wide range of (hetero)aryl and alkenyl mesylates and tosylates with aryl titanium reagents has been developed for the first time. Aryl titanium acted as the multi-functional reagent which can provide aryl fragment and act as base/additive and reaction medium at the same time. The new and electron-enriched NMe$_2$-CM-Phos (**L14**) ligand in combination with Pd(OAc)$_2$ was found highly effective in tackling this reaction. Good functional group tolerance was demonstrated where nitrile, ester and unprotected indole, remained compatible under these reaction conditions. Particular noteworthy is that the catalyst loading can be as low as 0.2 mol% Pd and the reaction time can be shortened to 10 min. The reaction can be easily scaled up to the gram scale without diminishing the product yield. We anticipate this finding would open up a new platform of organotitanium nucleophile development in targeting flow reaction technology under base and additive-free homogeneous conditions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) Metal-Catalyzed Cross-Coupling Reactions, Vol. 1–2, 2nd ed. (Eds.: A. de Meijere and F. Diederich), Wiley-VCH, Weinheim, 2004; (*b*) M. Beller and C. Bolm, Transition Metals for Organic Synthesis Building Blocks and Fine Chemicals, Vol. 1–2, 2nd ed., Wiley-VCH, Weinheim, 2004; (*c*) Handbook of Organopalladium for Organic Synthesis, Vol. 1–2 (Ed.: E. Negishi), Wiley- Interscience, New York, 2002.

2 For recent reviews, see, (*a*) R. Martin and S. L. Buchwald, Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands, *Acc. Chem. Res.* 2008, **41**, 1461; (*b*) J. F. Hartwig, Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides, *Acc. Chem. Res.* 2008, **41**, 1534; (*c*) S. M. Wong, C. M. So and F. Y. Kwong, The Recent Development of Phosphine Lligands Derived from 2-Phosphino-Substituted Heterocycles and Their Applications in Palladium-Catalyzed Cross-Coupling Reactions, *Synlett* 2012, **23**, 1132; (*d*) R. J. Lundgren and M. Stradiotto, Addressing Challenges in Palladium-Catalyzed Cross-Coupling Reactions Through Ligand Design, *Chem. Eur. J.* 2012, **18**, 9758; (*e*) S. M. Wong, O. Y. Yuen, P. Y. Choy and F. Y. Kwong, When Cross-Coupling Partners Meet Indolylphosphines, *Coord. Chem. Rev.* 2015, **293-294**, 158-186; (*f*) P. G. Gildner and T. J. Colacot, Reactions of the 21st Century: Two Decades of Innovative Catalyst Design for Palladium-Catalyzed Cross-Couplings, *Organometallics* 2015, **34**, 5497; (*g*) C. Li, D. Chen, W. Tang, Addressing the Challenges in Suzuki–Miyaura Cross-Couplings by Ligand Design, *Synlett* 2016, **27**, 2183.

3 A. F. Littke and G. C. Fu, Palladium-Catalyzed Coupling Reactions of Aryl Chlorides, *Angew. Chem. Int. Ed.* 2002, **41**, 4176.

4 For selected examples, see (*a*) A. H. Roy and J. F. Hartwig, Oxidative Addition of Aryl Tosylates to Palladium(0) and Coupling of Unactivated Aryl Tosylates at Room Temperature, *J. Am. Chem. Soc.* 2003, **125**, 8704; (*b*) H. N. Nguyen, X. Huang and S. L. Buchwald, The First General Palladium Catalyst for the Suzuki–Miyaura and Carbonyl Enolate Coupling of Aryl Arenesulfonates, *J. Am. Chem. Soc.* 2003, **125**, 11818; (*c*) A. L. Hansen, J.-P. Ebran, M. Ahlquist, P.-O. Norrby and T. Skrydstrup, Heck Coupling with Nonactivated Alkenyl Tosylates and Phosphates: Examples of Effective 1,2-Migrations of the Alkenyl Palladium(II) Intermediates, *Angew. Chem. Int. Ed.* 2006, **45**, 3349; (*d*) T. Ogata and J. F. Hartwig, Palladium-Catalyzed Amination of Aryl and Heteroaryl Tosylates at Room Temperature, *J. Am. Chem. Soc.* 2008, **130**, 13848; (*e*) C. M. So, C. P. Lau, A. S. C. Chan and F. Y. Kwong, Suzuki–Miyaura Coupling of Aryl Tosylates Catalyzed by an Array of Indolyl Phosphine–Palladium Catalysts, *J. Org. Chem.* 2008, **73**, 7731; (*f*) R. J. Lundgren and M. Stradiotto, Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Tosylates with Hydrazine, *Angew. Chem. Int. Ed.* 2010, **49**, 8686.

5 For a review, see (*a*) C. M. So and F. Y. Kwong, Palladium-Catalyzed Cross-Coupling Reactions of Aryl Mesylates, *Chem. Soc. Rev.* 2011, **40**, 4963; for selected references, see (*b*) P. G. Alsabeh and M. Stradiotto, Addressing Challenges in

Palladium-Catalyzed Cross-Couplings of Aryl Mesylates: Monoarylation of Ketones and Primary Alkyl Amines, *Angew. Chem. Int. Ed.* 2013, **52**, 7242; (*c*) W. C. Fu, C. M. So and F. Y. Kwong, Palladium-Catalyzed Phosphorylation of Aryl Mesylates and Tosylates, *Org. Lett.* 2015, **17**, 5906.

6 B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A. Remerita, N. K. Garg and V. Percec, Nickel-Catalyzed Cross-Couplings Involving Carbon−Oxygen Bonds, *Chem. Rev.* 2011, **111**, 1346.

7 For selected references, see (*a*) K. Tamao, K. Sumitani and M. Kumada, Selective Carbon-Carbon Bond Formation by Cross-Coupling of Grignard Reagents with Organic Halides. Catalysis by Nickel-Phosphine Complexes, *J. Am. Chem. Soc.* 1972, **94**, 4374; (*b*) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II): An Effective Catalyst for Cross-Coupling of Secondary and Primary Alkyl Grignard and Alkylzinc Reagents with Organic Halides, *J. Am. Chem. Soc.* 1984, **106**, 158; (*c*) T. Nagano and T. Hayashi, Iron-Catalyzed Grignard Cross-Coupling with Alkyl Halides Possessing β-Hydrogens, *Org. Lett.* 2004, **6**, 1297; (*d*) N. Yoshikai, H. Mashima and E. Nakamura, Nickel-Catalyzed Cross-Coupling Reaction of Aryl Fluorides and Chlorides with Grignard Reagents under Nickel/Magnesium Bimetallic Cooperation, *J. Am. Chem. Soc.* 2005, **127**, 17978; (*e*) G. Manolikakes and P. Knochel, Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents, *Angew. Chem. Int. Ed.* 2009, **48**, 205.

8 For selected references, see (*a*) P. Espinet, A. M. Echavarren, The Mechanisms of the Stille Reaction, *Angew. Chem. Int. Ed.* 2004, **43**, 4704; (*b*) W. Su, S. Urgaonkar, P. A. McLaughlin and J. G. Verkade, Highly Active Palladium Catalysts Supported by Bulky Proazaphosphatrane Ligands for Stille Cross-Coupling: Coupling of Aryl and Vinyl Chlorides, Room Temperature Coupling of Aryl Bromides, Coupling of Aryl Triflates, and Synthesis of Sterically Hindered Biaryls, *J. Am. Chem. Soc.* 2004, **126**, 16433; (*c*) D. A. Powell, T. Maki and G. C. Fu, Stille Cross-Couplings of Unactivated Secondary Alkyl Halides Using Monoorganotin Reagents, *J. Am. Chem. Soc.* 2005, **127**, 510; (*d*) C. Chiappe, D. Pieraccini, D. Zhao, Z. Fei and P. J. Dyson, Remarkable Anion and Cation Effects on Stille Reactions in Functionalised Ionic Liquids, *Adv. Synth. Catal.* 2006, **348**, 68.

9 For selected references, see (*a*) A. C. Spivey, C. J. G. Gripton and J. P. Hannah, Recent Advances in Group 14 Cross-Coupling: Si and Ge-Based Alternatives to the Stille Reaction, *Curr. Org. Synth.* 2004, **1**, 211; (*b*) H. -J. Song, W. -T. Jiang, Q. -L. Zhou, M. -Y. Xu and B. Xiao, Structure-Modified Germatranes for Pd-Catalyzed Biaryl Synthesis, *ACS Catal.* 2018, **8**, 9287; (*c*) M. -Y. Xu, W. -T. Jiang, Y. Li, Q. -H. Xu, Q. -L. Zhou, S. Yang and B. Xiao, Alkyl Carbagermatranes Enable Practical Palladium-Catalyzed sp2–sp3 Cross-Coupling, *J. Am. Chem. Soc*. 2019, **141**, 7582; (*d*) C. Fricke, A. Dahiya, W. B. Reid and F. Schoenebeck, Gold-Catalyzed C–H Functionalization with Aryl Germanes, *ACS Catal.* 2019, **9**, 9231; (*e*) C. Fricke, G. J. Sherborne, I. Funes-Ardoiz, E. Senol, S. Guven and F. Schoenebeck, Orthogonal Nanoparticle Catalysis with Organogermanes, *Angew. Chem. Int. Ed.* 2019, **58**, 17788; (f) W. -T. Jiang, S. Yang, M. -Y. Xu, X. -Y. Xie and B. Xiao, Zn-Mediated Decarboxylative Carbagermatranation of Aliphatic N-Hydroxyphthalimide Esters: Evidence for an Alkylzinc Intermediate, *Chem. Sci.* 2020, **11**, 488.

10 For selected references, see (*a*) O. Navarro, R. A. Kelly and S. P. Nolan, A General Method for the Suzuki−Miyaura Cross-Coupling of Sterically Hindered Aryl Chlorides: Synthesis of Di- and Tri-*ortho*-substituted Biaryls in 2-Propanol at Room Temperature, *J. Am. Chem. Soc.* 2003, **125**, 16194; (*b*) C.-G. Dong and Q.-S. Hu, Preferential Oxidative Addition in Palladium(0)-Catalyzed Suzuki Cross-Coupling Reactions of Dihaloarenes with Arylboronic Acids, *J. Am. Chem. Soc.* 2005, **127**, 10006; (*c*) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, Catalysts for Suzuki−Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure, *J. Am. Chem. Soc.* 2005, **127**, 4685; (*d*) F. González-Bobes and G. C. Fu, Amino Alcohols as Ligands for Nickel-Catalyzed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids, *J. Am. Chem. Soc.* 2006, **128**, 5360; (*e*) D. Imao, B. W. Glasspoole, V. S. Laberge and C. M. Crudden, Cross Coupling Reactions of Chiral Secondary Organoboronic Esters with Retention of Configuration, *J. Am. Chem. Soc.* 2009, **131**, 5024.

11 Selected references for organozirconium, see (*a*) S. L. Wiskur, A. Korte and G. C. Fu, Cross-Couplings of Alkyl Electrophiles under "Ligandless" Conditions: Negishi Reactions of Organozirconium Reagents, *J. Am. Chem. Soc.* 2004, **126**, 82; for organozinc, see (*b*) P. Stanetty, G. Hattinger, M. Schn€urch and M. D. Mihovilovic, Novel and Efficient Access to Phenylamino-pyrimidine Type Protein Kinase C Inhibitors Utilizing a Negishi Cross-Coupling Strategy, *J. Org. Chem.* 2005, **70**, 5215; (*c*) Z. Huang, M. Qian, D. J. Babinski and E. I. Negishi, Palladium-Catalyzed Cross-Coupling Reactions with Zinc, Boron, and Indium Exhibiting High Turnover Numbers (TONs): Use of Bidentate Phosphines and Other Critical Factors in Achieving High TONs, *Organometallics* 2005, **24**, 475; (*d*) H. Xu, K. Ekoue-Kovi and C. Wolf, Palladium−Phosphinous Acid-Catalyzed Cross-Coupling of Aryl and Acyl Halides with Aryl-, Alkyl-, and Vinylzinc Reagents, *J. Org. Chem.* 2008, **73**, 7638.

12 For selected references, see (*a*) S. L. Ku, X. P. Hui, C. A. Chen, Y. Y. Kuo and H. M. Gau, AlAr3(THF): Highly Efficient Reagents for Cross-Couplings with Aryl Bromides and Chlorides Catalyzed by the Economic Palladium Complex of PCy_3, *Chem. Commun.* 2007, 3847; (*b*) H. Minami, T. Saito, C. Wang and M. Uchiyama, Organoaluminum-Mediated Direct Cross-Coupling Reactions, *Angew. Chem. Int. Ed.* 2015, **54**, 4665.

13 For selected examples, see (*a*) V. Papoian and T. Minehan, Palladium-Catalyzed Reactions of Arylindium Reagents Prepared Directly from Aryl Iodides and Indium Metal, *J. Org. Chem.* 2008, **73**, 7376; (*b*) Y. H. Chen and P. Knochel, Preparation of Aryl and Heteroaryl Indium(III) Reagents by the Direct Insertion of Indium in the Presence of LiCl, *Angew. Chem. Int. Ed.* 2008, **47**, 7648.

14 For selected examples, see (*a*) M. L. N. Rao, S. Shimada and M. Tanaka, Palladium Complex-Catalyzed Cross-Coupling Reaction of Organobismuth Dialkoxides with Triflates, *Org. Lett.* 1999, **1**, 1271; (*b*) M. L. N. Rao, O. Yamazaki, S. Shimada, T. Tanaka, Y. Suzuki and M. Tanaka, Palladium-Catalyzed Cross-Coupling Reaction of Triarylbismuths with Aryl Halides and Triflates, *Org. Lett.* 2001, **3**, 4103.

15 For selected references, see (*a*) A. K. Sahoo, T. Oda, Y. Nakao and T. Hiyama, Cross-Coupling of Triallyl(aryl)silanes with Aryl Bromides and Chlorides: An Alternative Convenient Biaryl Synthesis, *Adv. Synth. Catal.* 2004, **346**, 1715; (*b*) C. Wolf and R. Lerebours, Palladium−Phosphinous Acid-Catalyzed NaOH-Promoted Cross-Coupling Reactions of Arylsiloxanes with Aryl Chlorides and Bromides in Water, *Org. Lett.* 2004, **6** 1147; (*c*) S. E. Denmark, R. C. Smith, W.-T. T. Chang and J. M. Muhuhi, Cross-Coupling Reactions of Aromatic and Heteroaromatic Silanolates with Aromatic and Heteroaromatic Halides, *J. Am. Chem. Soc.* 2009, **131**, 3104.

16 B. H. Lipshutz, N. A. Isley, J. C. Fennewald and E. D. Slack, On the Way Towards Greener Transition-Metal-Catalyzed Processes as Quantified by E Factors, *Angew. Chem. Int. Ed.* 2013, **52**, 10952.

17 (*a*) Handbook of Green Chemistry, Vol. 5, 1st ed. (Eds.: P. T. Anastas and C. J. Li), Wiley-VCH, 2010; (*b*) M. S. Singh and S. Chowdhury, Recent Developments in Solvent-Free

Multicomponent Reactions: A Perfect Synergy for Eco-compatible Organic Synthesis *RSC Adv.* 2012, **2**, 4547.

18 (*a*) P. Nun, J. Martinez and F. Lamaty, Solvent-Free Microwave-Assisted Suzuki-Miyaura Coupling Catalyzed by PEPPSI-iPr, *Synlett* 2009, 1761; (*b*) K. Mandai, T. Korenaga, T. Ema, T. Sakai, M. Furutani, H. Hashimoto and J. Takada, Biogenous Iron Oxide-Immobilized Palladium Catalyst for the Solvent-Free Suzuki–Miyaura Coupling Reaction, *Tetrahedron Lett.* 2012, **53**, 329; (*c*) A. F. Asachenko, K. R. Sorochkina, P. B. Dzhevakov, M. A. Topchiy and M. S. Nechaev, Suzuki–Miyaura Cross-Coupling under Solvent-Free Conditions, *Adv. Synth. Catal.* 2013, **355**, 3553; (*d*) N. Y. Baran, T. Baran and A. Mentes, Fabrication and Application of Cellulose Schiff Base Supported Pd(II) Catalyst for Fast and Simple Synthesis of Biaryls via Suzuki Coupling Reaction, *Appl. Catal. A- Gen.* 2017, **531**, 36.

19 F. Schneider and B. Ondruschka, Mechanochemical Solid-State Suzuki Reactions Using an In Situ Generated Base, *ChemSusChem.* 2008, **1**, 622.

20 (*a*) E. Alacid and C. Nájera, Solvent-Less and Fluoride-Free Hiyama Reaction of Arylsiloxanes with Aryl Bromides and Chlorides Promoted by Sodium Hydroxide: A Useful Protocol for Palladium Recycling and Product Isolation, *Adv. Synth. Catal.* 2006, **348**, 945; (*b*) O. Y. Yuen, C. M. So, H. W. Man and F. Y. Kwong, A General Palladium-Catalyzed Hiyama Cross-Coupling Reaction of Aryl and Heteroaryl Chlorides, *Chem. Eur. J.* 2016, **22**, 6471.

21 Storage solvents (e.g. heptane, hexane, tetrahydrofuran, and dibutyl-ether) were used as the reaction medium, see (*a*) E. B. Pinxterhuis, M. Giannerini, V. Hornillos and B. L. Feringa, Fast, Greener and Scalable Direct Coupling of Organolithium Compounds with No Additional Solvents, *Nat. Commun.* 2016, **7**, 11698; (*b*) E. B. Pinxterhuis, P. Visser, I. Esser, J. Gualtierotti and B. L. Feringa, Fast, Efficient and Low E-Factor One-Pot Palladium-Catalyzed Cross-Coupling of (Hetero)Arenes, *Angew. Chem. Int. Ed.* 2018, **57**, 9452.

22 H. W. Lee, F. L. Lam, C. M. So, C. P. Lau, A. S. C. Chan and F. Y. Kwong, Palladium-Catalyzed Cross-Coupling of Aryl Halides Using Organotitanium Nucleophiles, *Angew. Chem. Int. Ed.* 2009, **48**, 7436.

23 (*a*) T. Hayashi, N. Tokunaga, K. Yoshida and J. W. Han, Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryltitanium Reagents Generating Chiral Titanium Enolates: Isolation as Silyl Enol Ethers, *J. Am. Chem. Soc.* 2002, **124**, 12102; (*b*) J. W. Han, N. Tokunaga and T. Hayashi, Palladium- or Nickel-Catalyzed Cross-Coupling of Organotitanium Reagents with Aryl Triflates and Halides, *Synlett* 2002, 871; (*c*) K. Yoshida and T. Hayashi, A New cine-Substitution of Alkenyl Sulfones with Aryltitanium Reagents Catalyzed by Rhodium: Mechanistic Studies and Catalytic Asymmetric Synthesis of Allylarenes, *J. Am. Chem. Soc.* 2003, **125**, 2872; (*d*) N. Tokunaga, K. Yoshida and T. Hayashi, Mechanistic Studies on the Catalytic Cycle of Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryltitanate Reagents to α,β-Unsaturated Ketones, *PNAS* 2004, **101**, 5445; (*e*) T. Hayashi, S. Yamamoto and N. Tokunaga, Rhodium-Catalyzed Asymmetric 1,6-Addition of Aryl Zinc Reagents to Dienones, *Angew. Chem. Int. Ed.* 2005, **44**, 4224.

24 H. T. Yang, S. Zhou, F. S. Chang, C. R. Chen and H. M. Gau, Synthesis, Structures, and Characterizations of $[ArTi(O\text{-}i\text{-}Pr)_3]_2$ and Efficient Room-Temperature Aryl−Aryl Coupling of Aryl Bromides with $[ArTi(O\text{-}i\text{-}Pr)_3]_2$ Catalyzed by the Economic $Pd(OAc)_2/PCy_3$ System, *Organometallics* 2009, **28**, 5715.

25 Aryl mesylates and tosylates (commonly in solid state) are more de-manding in the solvent-free reaction condition than the corresponding aryl chlorides and bromides (commonly in liquid state).

26 To our best knowledge, there are no reports about palladium-catalyzed cross-coupling reactions of aryl mesylates using Grignard, organozinc or organolithium reagents.