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Palladium-Catalyzed Sonogashira Coupling of Aryl Mesylates and Tosylates

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Dedicated to Professor Albert S. C. Chan on his occasion of 60th birthday

Aryl alkynes are important synthetic precursors and subunits for a range of pharmaceutically attractive and valued materials science organic compounds.[1] One of the most straightforward and versatile protocols for the construction of C_{sp^2}–C_{sp} bond is the palladium-catalyzed cross-coupling of aryl halides/sulfonates and terminal alkynes, namely, Sonogashira coupling.[2] This methodology features a modular approach to assemble an array of diversified compounds from commonly available electrophilic and nucleophilic partners.[3]

A number of palladium catalyst systems have been developed for facilitating the Sonogashira coupling to proceed even without Cu^I cocatalyst and at room temperature,[4,5] as well as showing the applicability of aryl chloride substrates.[6] Although the alkyne coupling of aryl halides has been extensively established, the popularity of aryl triflates has been limited. These constraints are possibly due to the high cost of the triflating agent (e.g., Tf_2O),[7] and the low hydrolytic stability of aryl triflates under basic coupling reaction conditions. In fact, it is worth developing methods for phenolic compound derivatives to be used as electrophiles. Since they usually offer different or unique substituted groups in the aromatic ring, in which the corresponding aryl halides are not commonly available, or require additional synthetic steps to manipulate the pattern of complementary substitution. Thus, the exploration of less expensive, yet more stable, aryl arenesulfonates in Sonogashira coupling is highly favorable. Nevertheless, the higher stability of aryl arenesulfonate (e.g., aryl tosylate) makes this less reactive when used for oxidative addition under palladium catalytic system. Thus, the use of C_{sp^2}-tosylates as coupling partners in C_{sp^2}–C_{sp} bond-forming reaction has seldom been reported. Only vinyl tosylates were successful in this transformation.[8] Recently, the Sonogashira coupling of strongly activated and electron-deficient *para*- and *meta*-substituted aryl tosylates was disclosed using the Pd/X-Phos (X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) complex in propionitrile at reflux.[9] These pioneering examples required the slow addition of diluted alkyne substrates for 8 h over the course of reaction. Moreover, it was found that a high purity of the aryl tosylates was a prerequisite for these successful couplings. To the best of our knowledge, an operationally simple and general procedures for Sonogashira coupling of nonactivated aryl and heteraryl tosylates remains sporadically reported to date. A European patent described the application of a $Pd(TFA)_2$/Josiphos-type (Josiphos = 1-[2-(dicyclohexylphosphino)ferrocenyl]ethyldiphenylphosphine) ligand system for this reaction.[10] Herein, we report a general and efficient catalyst system for aryl tosylates in C_{sp^2}–C_{sp} couplings. In particular, we also uncover the first examples of more difficult, but more atom-economical aryl mesylate couplings with alkynes.

We embarked on developing a general protocol for Sonogashira coupling of aryl tosylates by using an unactivated 4-*tert*-butylphenyl tosylate and 1-heptyne as the model substrates (Table 1). Alcoholic solvents such as *t*BuOH were our preference instead of nitrile solvents. Commonly well-recognized and commercially available phosphine ligands,[11] such as Di*t*BuPF, cataCXium A, cataCXium PCy, and X-Phos, were initially screened to test the feasibility of the aryl tosylate–alkyne coupling (Table 1, entries 1–4). Moderate substrate conversions and fair product yields were afforded by using biaryl-type monodentate phosphines as the supporting ligands (Table 1, entries 3 and 4). A combination of $Pd(OAc)_2$ with CM-phos[12] was found to be the best catalyst system for this tosylate coupling (Table 1, entry 5). A survey of often used inorganic bases revealed that K_3PO_4 and $K_3PO_4{\cdot}H_2O$ were equally efficient (Table 1, entries 5–8). The best Pd/CM-phos ratio was found to be 1:3 (Table 1, entries 5, 10, and 11).

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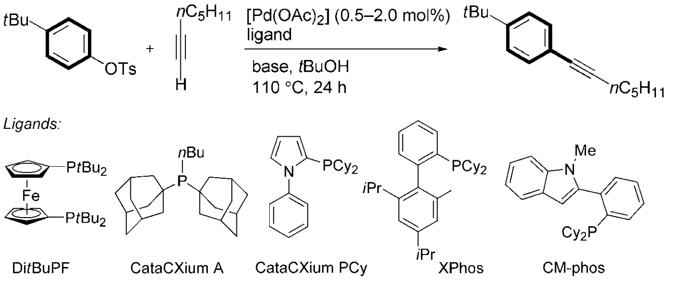
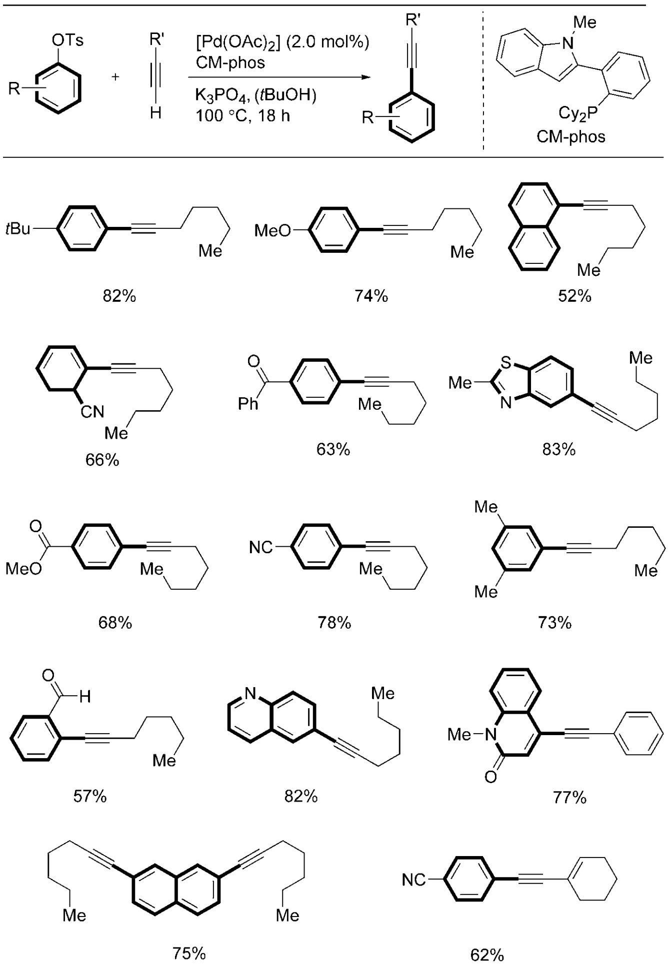
Table 1. Initial screenings of Pd-catalyzed Sonogashira couplings of aryl tosylates.[a]



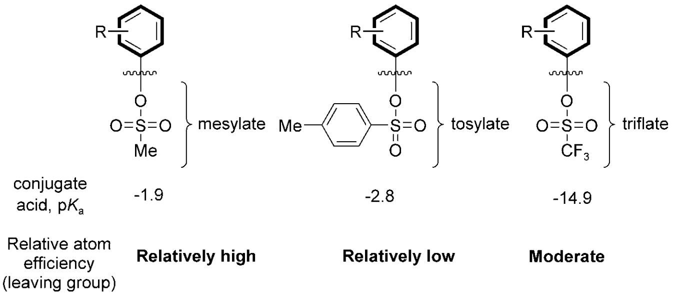
Entry	Ligand[b]	Base	Yield[c] [%]
1	ditBuPF	K_3PO_4	4
2	cataCXium A	K_3PO_4	0
3	cataCXium PCy	K_3PO_4	30
4	X-Phos	K_3PO_4	39
5	CM-phos	K_3PO_4	90
6	CM-phos	$K_3PO_4\cdot H_2O$	89
7	CM-phos	Cs_2CO_3	59
8	CM-phos	K_2CO_3	trace
9[d]	CM-phos	K_3PO_4	32
10[e]	CM-phos	K_3PO_4	93
11[f]	CM-phos	K_3PO_4	62
12[g]	CM-phos	K_3PO_4	59

[a] Reaction conditions: ArOTs (0.5 mmol), alkyne (1.0 mmol), Pd-$(OAc)_2$ (2.0 mol%), (Pd/ligand = 1:4), base (1.5 mmol), and tBuOH (2.0 mL) under N_2 at 110°C for 24 h (reaction time was not optimized). [b] cataCXium A = di(1-adamantyl)-*n*-butylphosphine, cataCXium PCy = 2-(dicyclohexylphosphino)-1-phenyl-1*H*-pyrrole, CM-phos = *N*-methyl-2-(2′-dicyclohexylphosphinophenyl)indole. [c] GC yields were reported. [d] 0.5 mol% of $Pd(OAc)_2$ was used. [e] A ratio of Pd/CM-phos = 1:3 was used. [f] A ratio of Pd/CM-phos = 1:2 was used. [g] 0.6 mmol of the corresponding alkyne was used.

Table 2. Palladium-catalyzed Sonogashira coupling of aryl and heteroaryl tosylates.[a]



[a] Reaction conditions: ArOTs (1.0 mmol), alkyne (2.0 mmol), Pd-$(OAc)_2$ (2.0 mol%), (Pd/CM-phos = 1:3), K_3PO_4 (3.0 mmol), and tBuOH (2.0 mL) under N_2 at 100°C for 18 h (reaction time for each substrate was not optimized). Isolated yields were reported.



Scheme 1. A comparison of aryl mesylate, tosylate, and triflate leaving groups.

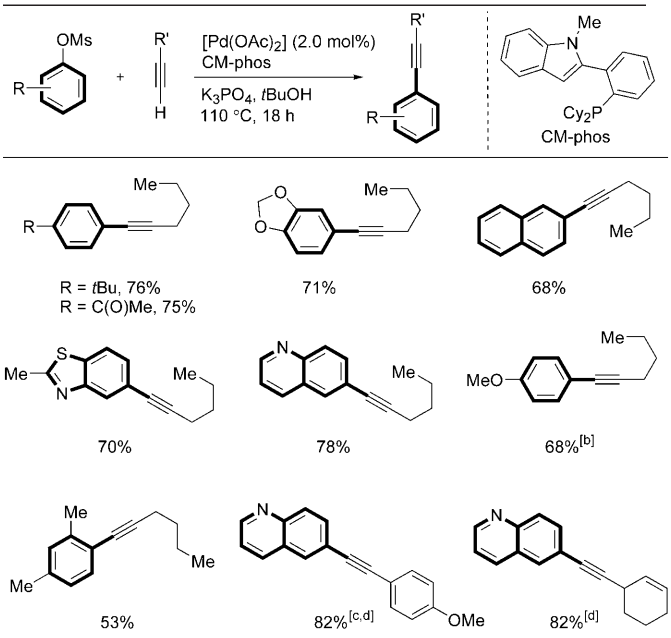
Having the optimized reaction conditions in hand, we examined a variety of aryl tosylate coupling partners with 1-heptyne (Table 2). Common functional groups such as methoxy, cyano, keto, ester, and aldehyde were compatible under the stated reaction conditions. Heterocyclic benzothiazolyl and quinolinyl tosylates furnished the corresponding coupling products smoothly. Alkenyl tosylate coupled with phenylacetylene to afford the product in good yield. 1-Ethynylcyclohex-1-ene could serve as an effective nucleophile for tosylate coupling (Table 2).

In view of commonly used sulfonate leaving groups, the mesylate can be regarded as the most inert group, since the pK_a of the corresponding conjugate acid is the highest among the others (Scheme 1). Nevertheless, mesylate provides the best atom efficiency when compared with tosylate and triflate. Inspired by its intrinsic attractiveness, we turned to examine the possibility of using more difficult, yet more beneficial aryl mesylates as the electrophilic partners in Sonogashira coupling.

Gratifyingly, the Pd/CM-phos catalytic system was found to be effective in promoting the Sonogashira coupling of aryl mesylates (Table 3). An array of aryl mesylates were examined in this coupling reaction using 1-hexyne as the nucleophile. Heteroaryl mesylates were also compatible in this system. Aryl alkyne and conjugated alkyne were found to be capable coupling partners (Table 3). These examples represent the first aryl mesylate–alkyne coupling reaction.

To further show the application of this coupling process, a tandem reaction was investigated. The tosylate Sonogashira approach provided a facile access to nitrogen heterocycles,

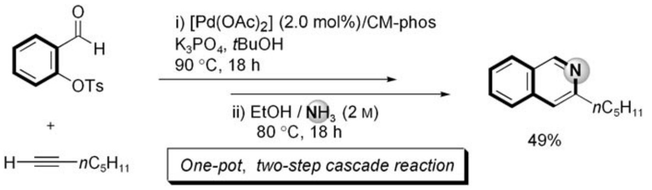
Table 3. Palladium-catalyzed Sonogashira coupling of aryl and heteroaryl mesylates.[a]



[a] Reaction conditions: ArOMs (1.0 mmol), alkyne (2.0 mmol), Pd(OAc)$_2$ (2.0 mol %), (Pd/CM-phos = 1:3), K$_3$PO$_4$ (3.0 mmol), and *t*BuOH (2.0 mL) under N$_2$ at 110 °C for 18 h (reaction time for each substrate was not optimized). Isolated yields were reported. [b] 5 mol % of Pd(OAc)$_2$ was used. [c] K$_2$CO$_3$ was used instead of K$_3$PO$_4$. [d] 3.0 mmol of alkyne was used.

such as isoqinoline scaffold (Scheme 2). To the best of our knowledge, this is the first example to target isoquinoline using a phenolic derivative (tosylate) precursor. The formylphenyl tosylate and 1-heptyne was directly transformed to 2-substituted isoquinoline effectively by an operationally simple one-pot, two-step cascade process (Scheme 2).

In summary, we have established a general Sonogashira coupling of aryl and heteroaryl tosylates. This finding is of high significance because this procedure enables difficult phenolic derivatives to be used as the electrophilic partners, which offer different substitution patterns with respect to aryl halides, for aromatic alkyne synthesis. Notably, we have also succeeded in showing the first examples of even more difficult, yet more atom-economical aryl mesylate couplings using Sonogashira methodology. Indeed, the inertness of the mesylate group would mean that aryl mesylates could be used as protecting groups during a multistep synthesis, allowing a number of orthogonal organic transformations and performing modular C$_{sp^2}$–C$_{sp}$ bond constructions at appropriate stages in the whole synthetic sequence. Particularly noteworthy is that this versatile alkyne-tosylate/mesylate coupling also provides a facile access to 2-substituted isoquinoline by a one-pot cascade process. Further complementary syntheses of unique nitrogen heterocycles (other than from aryl halide patterns) using this catalytic system are currently underway and will be reported in due course.[13]



Scheme 2. One pot synthesis of substituted isoquinoline from aryl tosylate. Reaction conditions: i) ArOTs (2.0 mmol), alkyne (4.0 mmol), Pd(OAc)$_2$ (2.0 mol %), (Pd/CM-phos = 1:3), K$_3$PO$_4$ (6.0 mmol), and *t*BuOH (4.0 mL) under N$_2$ at 110 °C for 18 h. ii) Without purification/isolation processes, ethanolic ammonia was directly added to the reaction mixture and stirred at 80 °C for 18 h. Isolated yield is given over two steps.

Acknowledgements

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Keywords: alkynes · cross-coupling · palladium · phosphanes · Sonogashira coupling

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[1] F. Diederich, P. Stang, R. R. Tykwinski, *Acetylene Chemistry: Chemistry, Biology and Material Science*, Wiley-VCH: Weinheim, **2005**.

[2] For a Highlight and reviews, see: a) H. Plenio, *Angew. Chem.* **2008**, *120*, 7060; *Angew. Chem. Int. Ed.* **2008**, *47*, 6954; b) H. Doucet, J.-C. Hierso, *Angew. Chem.* **2007**, *119*, 850; *Angew. Chem. Int. Ed.* **2007**, *46*, 834; c) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874; d) M. S. Viciu, S. P. Nolan, *Arylation Reactions of Alkynes: The Sonogashira Reaction in Modern Arylation Methods* (Ed.: L. Ackermann), Wiley-VCH, Weinheim, **2009**, pp. 183–220.

[3] For a review describing modular/coupling approaches in total synthesis, see: K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.

[4] For examples of Sonogashira coupling without Cu cocatalyst, see: a) A. Tougerti, S. Negri, A. Jutand, *Chem. Eur. J.* **2007**, *13*, 666; b) M. Ahlquist, P. O. Norrby, *Organometallics* **2007**, *26*, 550; c) Y. Liang, Y.-X. Xie, J.-H. Li, *J. Org. Chem.* **2006**, *71*, 379; d) C. Yi, R. Hua, *J. Org. Chem.* **2006**, *71*, 2535; e) B. Liang, M. Dai, J. Chen, Z. Yang, *J. Org. Chem.* **2005**, *70*, 391; f) S. Urgaonkar, J. G. Verkade, *J. Org. Chem.* **2004**, *69*, 5752.

[5] For examples at room-temperature conditions, see: a) A. Soheili, J. Albaneze-Walker, J. A. Murry, P. G. Dormer, D. L. Hughes, *Org. Lett.* **2003**, *5*, 4191; b) T. Hundertmark, A. F. Littke, S. L. Buchwald, G. C. Fu, *Org. Lett.* **2000**, *2*, 1729; c) V. P. W. Böhm, W. A. Herrmann, *Eur. J. Org. Chem.* **2000**, 3679.

[6] For recent selected references, see: a) C. Torborg, J. Huang, T. Schulz, B. Schaeffner, A. Zapf, A. Spannenberg, A. Borner, M. Beller, *Chem. Eur. J.* **2009**, *15*, 1329; b) A. Komáromi, Z. Novak, *Chem. Commun.* **2008**, 4968; c) C. A. Fleckenstein, H. Plenio, *Chem. Eur. J.* **2007**, *13*, 2701; d) K. W. Anderson, S. L. Buchwald, *Angew. Chem.* **2005**, *117*, 6329; *Angew. Chem. Int. Ed.* **2005**, *44*, 6173; e) A. Köllhofer, T. Pullmann, H. Plenio, *Angew. Chem.* **2003**, *115*, 1086; *Angew. Chem. Int. Ed.* **2003**, *42*, 1056.

[7] The prices of the sulfonating agent are the following: TsCl, approx. 0.05 USD g^{-1}; Tf$_2$O, approx. 5 USD g^{-1}, from commercial suppliers in 2005–2006. Note: TsCl is a solid form and sold in ordinary reagent bottle, whereas Tf$_2$O is a highly moisture sensitive liquid and usually sold in an ampule.

[8] For activated vinyl tosylates, see: a) D. Steinhuebel, J. M. Baxter, M. Palucki, I. W. Davies, *J. Org. Chem.* **2005**, *70*, 10124; b) X. Fu, S.

Zhang, J. Yin, D. P. Schumacher, *Tetrahedron Lett.* **2002**, *43*, 6673; c) J. Wu, Y. Liao, Z. Yang, *J. Org. Chem.* **2001**, *66*, 3642.

[9] D. Gelman, S. L. Buchwald, *Angew. Chem.* **2003**, *115*, 6175; *Angew. Chem. Int. Ed.* **2003**, *42*, 5993.

[10] O. R'Kyek, M. Nazare, A. Lindenschmidt, M. Urmann, N. Halland, J. Alonso, WO2009003589, **2009**.

[11] From Strem chemicals catalogue 2008–2010.

[12] For our previous developments on CM-phos and related indolylphosphines, see: a) C. M. So, C. P. Lau, A. S. C. Chan, F. Y. Kwong, *J. Org. Chem.* **2008**, *73*, 7731; b) C. M. So, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2007**, *9*, 2795; c) C. M. So, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 8179; *Angew. Chem. Int. Ed.* **2008**, *47*, 8059; d) C. M. So, Z. Zhou, C. P. Lau, F. Y. Kwong, *Angew. Chem.* **2008**, *120*, 6502; *Angew. Chem. Int. Ed.* **2008**, *47*, 6402; e) C. M. So, H. W. Lee, C. P. Lau, F. Y. Kwong, *Org. Lett.* **2009**, *11*, 317; f) F. Y. Kwong, C. M. So, US patent 2009/0326243A1, **2009**; for a related indolylphosphine developed by Beller and co-workers, see: g) F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen, M. Beller, *Chem. Eur. J.* **2004**, *10*, 2983.

[13] Editorial note: for a similar paper on this subject, see: O. R'kyek, N. Halland, A. Lindenschmidt, J. Alonso, P. Lindemann, M. Urmann, M. Nazaré, *Chem. Eur. J.* **2010**, DOI: 10.1002/chem.201001524.

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