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Palladium–Indolylphosphine-Catalyzed Hiyama Cross-Coupling of Aryl Mesylates

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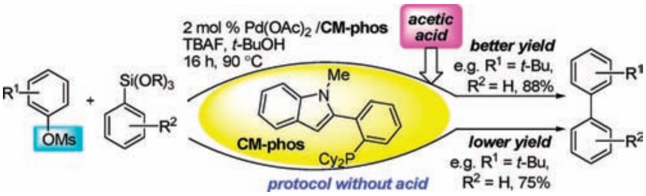
ABSTRACT



Aryl mesylates are found to be applicable as electrophiles in organosilicon-mediated coupling reactions. The catalyst system comprising 2 mol % of $Pd(OAc)_2$ and CM-phos supporting ligand is highly effective in catalyzing Hiyama cross-coupling of various aryl and heteroaryl mesylates. Interesting acid additive effects show that the presence of 0.25–0.50 equiv of acetic acid efficiently suppresses the mesylate decomposition and generally promotes the coupling product yields.

The exploration and development of new and general catalytic methods for organic synthesis remains at the center of modern day organic chemistry since they empower scientists working in areas as diverse as the total synthesis of natural products[1] to the preparation of analogues of lead compounds for drug discovery.[2] In fact, transition-metal-catalyzed cross-coupling represents a versatile protocol in organic synthesis for the connection of two different fragments together via the formation of carbon–carbon and/or carbon–heteroatom bonds.[3] Aryl halides, of course, are the most commonly used electrophiles in these reactions.[4]

However, aryl sulfonates such as tosylates and mesylates are less effective than triflates in the application of this class of catalysis, mainly due to their relative inertness toward oxidative addition by palladium complexes.[5,6] Appropriate ligand choice in these processes is recognized to have a significant impact on the outcome of such reactions.[7] Recently, synthetic chemists have been remarkably adept at

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(1) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis. Targets, Strategies, and Methods*; VCH: Weinheim, 1996.

(2) For selected examples, see: (a) Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527. (b) Suzuki, T.; Tanaka, S.; Yamada, I.; Koashi, Y.; Yamada, K.; Chida, N. *Org. Lett.* **2000**, *2*, 1137. (c) Zhang, X. X.; Sadighi, J. P.; Mackewitz, T. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 7606. (d) Harwood, E. A.; Hopkins, P. B.; Sigurdsson, S. T. *J. Org. Chem.* **2000**, *65*, 2959. (e) Tanoury, G. J.; Senanayake, C. H.; Hett, R.; Kuhn, A. M.; Kessler, D. W.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 6845. (f) Morita, S.; Kitano, K.; Matsubara, J.; Ohtani, T.; Kawano, Y.; Otsubo, K.; Uchida, M. *Tetrahedron* **1998**, *54*, 4811. For a recent book chapter, see: (g) King, A. O.; Yasuda, N. In *Organometallics in Process Chemistry*; Larsen, R. D., Ed.; Springer-Verlag: Berlin, Heidelberg, 2004; pp 205–245.

(3) (a) de Meijere, A., Diederich, F., Ed. *Metal-Catalyzed Cross-Coupling Reactions*; 2nd ed.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (b) Beller, M.; Bolm, C., *Transition Metals for Organic Synthesis, Building Blocks and Fine Chemicals*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (c) Nigeshi, E., Ed. *Handbook of Organopalladium for Organic Synthesis*; Wiley-Interscience: New York, 2002; Vols. 1 and 2. (d) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, 2004. (e) Yin, L. X.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (f) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (g) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622. (h) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (i) Kwong, F. Y.; Chan, A. S. C. *Synlett.* **2008**, 1440. (j) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (k) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (l) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.

(4) For a pertinent review focused on aryl chloride couplings, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

10.1021/ol802493z CCC: $40.75

devising effective ligands for specific bond constructions under palladium catalysis (Figure 1), and the extension of these reactions to aryl tosylates[8] and mesylates[9] couplings is highly noteworthy.[10]

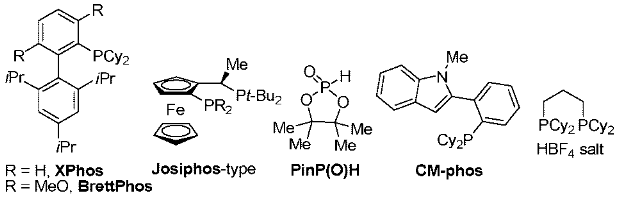
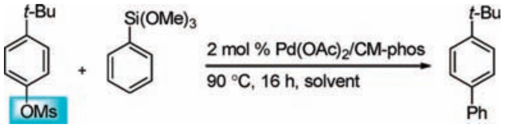


Figure 1. Effective ligand examples for Pd-catalyzed cross-coupling of aryl benzensulfonates, tosylates, and mesylates.

As part of our continuing interest in the use of easily accessible indolylphosphine ligands for mediating C−C bond-forming reactions,[9c,11] we herein report our efforts at expanding the scope of the Hiyama cross-coupling[12] to aryl mesylates.[13] Additionally, a beneficial additive effect on this coupling process will also be described.

Table 1. Initial Screening on the Feasibility of Hiyama Cross-Coupling of Aryl Mesylate[a]



entry	promotor/base	solvent	% yield[b]
1	TBAF	toluene	23
2	TBAF	THF	14
3	TBAF	DMF	4
4	TBAF	THF/*t*-BuOH (1:1)	58
5	TBAF	*t*-BuOH	81
6	TBAF	toluene/*t*-BuOH (1:1)	83
7	CsF	*t*-BuOH	0
8	KF	*t*-BuOH	trace
9	K_2CO_3	*t*-BuOH	0
10	K_3PO_4	*t*-BuOH	0
11	Cs_2CO_3	*t*-BuOH	0
12[c]	TBAF	*t*-BuOH	8

[a] Reaction conditions: ArOMs (0.5 mmol), ArOMs/PhSi(OMe)$_3$/TBAF = 1:2:2; Pd(OAc)$_2$/CM-phos = 1:4; 90 °C for 16 h in the specified solvent (1.0 mL, total solvent volume) under N_2. [b] Calibrated GC yields were reported using tetradecane as the internal standard. [c] 4 mol % of Pd(OAc)$_2$ was used at 60 °C.

In order to probe the feasibility of a Hiyama cross-coupling of an aryl mesylate, a series of screening experiments were carried out (Table 1). 4-*tert*-Butylphenyl mesylate and PhSi(OMe)$_3$ were used as the model substrates, and 2 mol % of Pd(OAc)$_2$ with CM-phos ligand were used as the initial catalytic system for our prototypical reaction. Since the transmetalation of organosilanes proceeds smoothly after the activation by fluoride anion,[14] we initially applied TBAF as the promoter. Among the commonly used organic solvents we examined, *t*-BuOH and toluene/*t*-BuOH mixtures gave

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(5) For mechanistic studies on Pd-mediated oxidative addition of aryl tosylates, see: Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194, and references therein.

(6) Ni-catalyzed cross-coupling of aryl tosylates/mesylates are precedented; see: (a) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049. (b) Tang, Z. Y.; Hu, Q. S. *J. Am. Chem. Soc.* **2004**, *126*, 3058. (c) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447. (d) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060. (e) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1066. (f) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895. (g) Ueda, M.; Saitoh, A.; Oh-tani, S.; Miyaura, N. *Tetrahedron* **1998**, *54*, 13079. (h) Kobayashi, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 8531. (i) Tang, Z.-Y.; Spinella, S.; Hu, Q.-S. *Tetrahedron Lett.* **2006**, *47*, 2427. (j) Lipshutz, B. H.; Butler, T.; Swift, E. *Org. Lett.* **2008**, *10*, 697. (k) Wilson, D. A.; Wilson, C. J.; Rosen, B. M.; Percec, V. *Org. Lett.* **2008**, *10*, 4879. (l) Gao, C.-Y.; Yang, L.-M *J. Org. Chem.* **2008**, *73*, 1624. For a related reference on homocoupling of aryl mesylates, see: (m) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176.

(7) For a review, see: Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431, and references therein.

(8) For ArOTs substrates and Suzuki coupling, see: (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (b) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346. (c) So, C. M.; Lau, C. P.; Chan, A. S. C.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7731. For Kumada coupling, see: (d) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (e) Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364. (f) Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457. For Buchwald−Hartwig C−N bond coupling, see: (g) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (h) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (i) Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848. For Sonogashira coupling using activated ArOTs, see: (j) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993. For Hiyama coupling, see: (k) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250. For C−S bond formation (one example), see: (l) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. For carbonylation, see: (m) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754. For alkenyl-OTs substrates and Suzuki coupling, see: (n) Steinhuebel, D.; Baxter, J. M.; Palucki, M.; Davies, I. W. *J. Org. Chem.* **2005**, *70*, 10124. For Buchwald−Hartwig amidation, see: (o) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185. For Heck coupling, see: (p) Hansen, A. L.; Skrydstrup, T. *Org. Lett.* **2005**, *7*, 5585. (q) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349.

(9) For ArOMs substrates and C−N bond formation, see: (a) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402. (b) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. For ArOMs Suzuki coupling, see: (c) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059. (d) For carbonylation, see ref 8m.

(10) Ar-OMs is more inert than Ar-OTs. For reference, usually the lower the pK_a of the conjugate acid, the better the leaving group (cf. methanesulfonic acid, pK_a = −1.9; *p*-toluenesulfonic acid, pK_a = −2.8; benzenesulfonic acid, pK_a = −6.5; triflic acid, pK_a = −14.9). Serjeant, E. P., Dempsey, B., Eds. *Ionization Constants of Organic Acids in Solution*; IUPAC Chemical Data Series No. 23; Pergamon Press: Oxford, UK, 1979.

(11) (a) So, C. M.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 2795. (b) So, C. M.; Yeung, C. C.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7803. (c) Reference 8c.

(12) For reviews and examples of the Hiyama couplings, see: (a) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 10. (b) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58. (c) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (d) Denmark, S. E.; Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 4. (e) Denmark, S. E.; Baird, J. D. *Chem.—Eur. J.* **2006**, *12*, 4954. (f) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556. (g) Denmark, S. E.; Butler, C. R. *Org. Lett.* **2006**, *8*, 63.

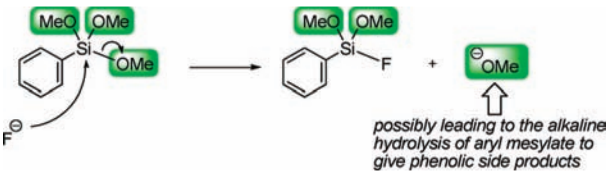
(13) Hiyama coupling of ArOMs remains sporadically studied, and there is only one publication to date. During the completion of our experimental work, a closely related paper on Hiyama coupling appeared. Zhang, L.; Qing, J.; Yang, P.; Wu, J. *Org. Lett.* **2008**, *10*, 4971. The authors used 4 mol % of Pd(OAc)$_2$ with Xphos ligand at 90 °C as the optimized catalytic system.

(14) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

the best results (entries 1−6). We next tested other fluoride salts. However, neither CsF nor KF provided the desired product (entries 7 and 8). General inorganic bases such as K_2CO_3, K_3PO_4, and Cs_2CO_3 were found to be inferior in the reaction (entries 9−11). Lowering the reaction temperature to 60 °C significantly retarded the rate of reaction (entry 12).

In fact, we routinely observed ~10−15% of problematical phenolic side products being formed during the course of the initial screenings as judged by GC−MS analyses. We wondered whether the formation of this phenolic side product might be triggered by the alkaline hydrolysis of the aryl mesylate in the presence of the methoxide, which was generated by the nucleophilic cleavage of silyl ether using TBAF (Scheme 1).[15] In order to reduce side product formation, as well as to further increase the desired product yield, we introduced an acid additive to the reaction mixture (Table 2).

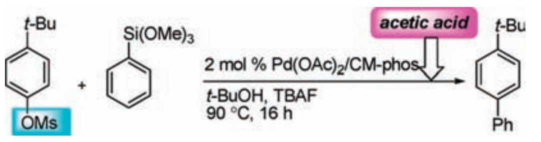
Scheme 1. Silyl Ether Cleavage by TBAF



possibly leading to the alkaline hydrolysis of aryl mesylate to give phenolic side products

Our rationale for adding acetic acid to the reaction mixtures was to neutralize the methoxide anion, and thus to reduce the possibility of alkaline hydrolysis of the aryl mesylate. Gratifyingly, when 0.25 equiv of acetic acid was introduced, the desired product yield was enhanced (Table 2, entry 1 vs 2). In general, the addition of 0.25−0.50 equiv of acetic acid is sufficient to suppress the phenolic side product formation

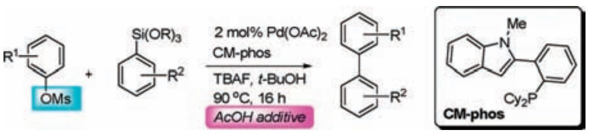
Table 2. Acid Additive Effect in Hiyama Coupling of ArOMs[a]

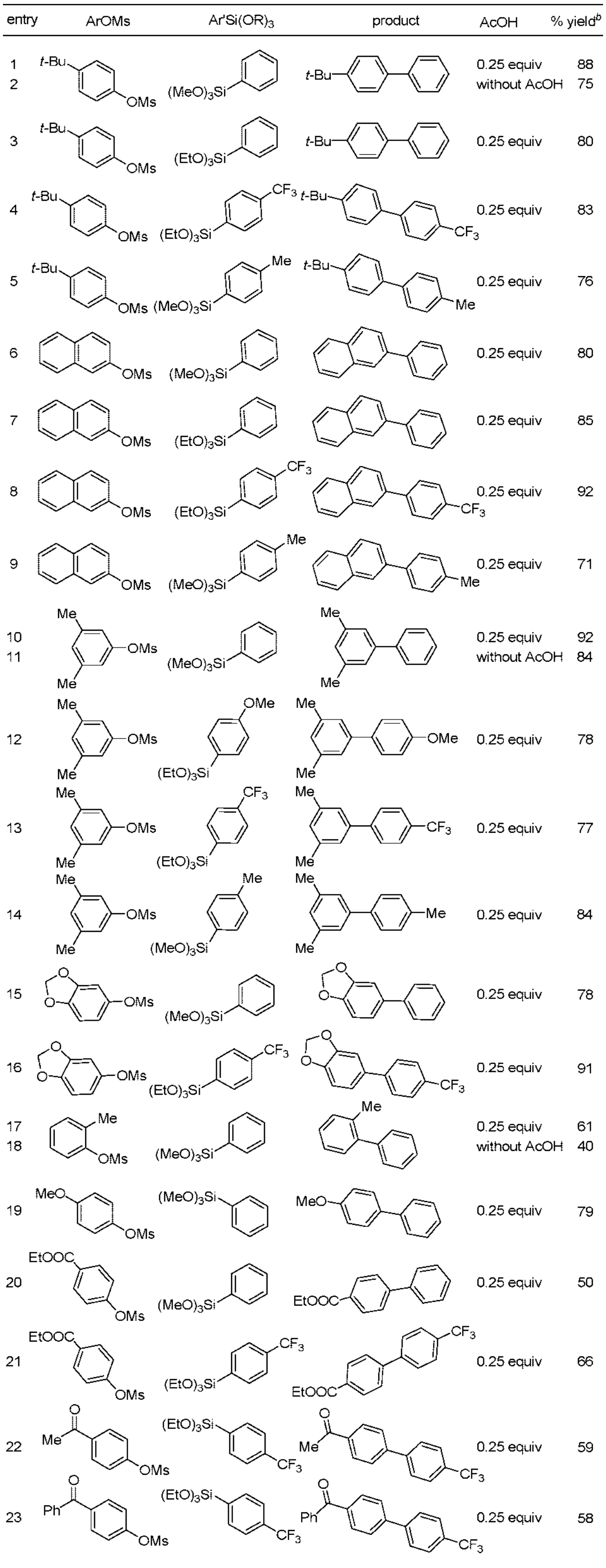


entry	acid additive[b]	% yield[c]
1	no AcOH added	75
2	0.25 equiv AcOH	88 (94)[d]
3	0.50 equiv AcOH	85
4[e]	1.00 equiv AcOH	(65)[d]
5[e]	2.00 equiv AcOH	(27)[d]

[a] Reaction conditions: as in Table 1. [b] Equivalence with respected to TBAF. [c] Isolated yields. [d] Calibrated GC yield in parentheses. [e] 4 mol % of $Pd(OAc)_2$ was used, at 90 °C for 8 h.

Table 3. Pd-Catalyzed Hiyama Cross-Coupling of ArOMs[a]





entry	AcOH	% yield[b]
1	0.25 equiv	88
2	without AcOH	75
3	0.25 equiv	80
4	0.25 equiv	83
5	0.25 equiv	76
6	0.25 equiv	80
7	0.25 equiv	85
8	0.25 equiv	92
9	0.25 equiv	71
10	0.25 equiv	92
11	without AcOH	84
12	0.25 equiv	78
13	0.25 equiv	77
14	0.25 equiv	84
15	0.25 equiv	78
16	0.25 equiv	91
17	0.25 equiv	61
18	without AcOH	40
19	0.25 equiv	79
20	0.25 equiv	50
21	0.25 equiv	66
22	0.25 equiv	59
23	0.25 equiv	58

[a] Reaction conditions: see Tables 1 and 2. [b] Isolated yields.

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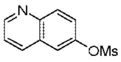
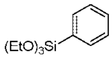
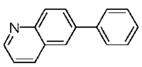
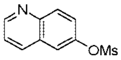
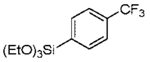
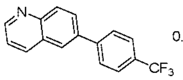
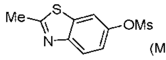
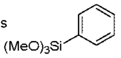
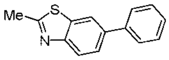
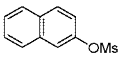
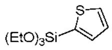
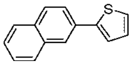
(15) For references on nucleophilic attack of fluoride anion to cleave silyl ether in generating alkoxide, see: Thomas, S. E. *Organic Synthesis − The Roles of Boron and Silicon*; Oxford University Press: Oxford, 1991.

(Table 2, entries 2 and 3). However, excess acetic acid added reduced the rate of reaction (Table 2, entries 4 and 5).

To evaluate the effectiveness of our new catalytic system, a range of aryl mesylates was examined using the preliminary optimized reaction conditions (Table 3). Complete conversions of aryl mesylates were normally observed between 6−16 h at 90 °C.[16] Beneficial effects of the acid additive were generally found (Table 3, e.g., entries 1 vs 2, 10 vs 11, 17 vs 18). Both $PhSi(OMe)_3$ and $PhSi(OEt)_3$ provided similar yields of the desired product (entries 1 and 3). Electron-deficient nucleophiles furnished the coupling product in good yield (entry 4). Essentially no electronic effect on both electrophilic and nucleophilic partners was observed in this coupling process, which is in contrast to Wu's recent report.[13] Sterically hindered substrates also coupled smoothly to give the desired product (entry 17).[17] Deactivated 4-methoxyphenyl mesylate was found to be a feasible substrate in this reaction (entry 19). Functional groups such as ester and ketone were compatible under these reaction conditions (entries 20−23). For instance, we also further examined the relative activity between the chloro and mesylate group (not shown in Table 3). 4-Chlorophenyl mesylate was used as the model substrate for this investigation. Almost complete selectivity (>99%) on the coupling of the chloro group was observed (i.e., no 4-chlorobiphenyl was formed as monitored by GC−MS analysis).

Apart from a variety of aryl mesylates, heteroaryl mesylates were effective substrates for Hiyama coupling (Table 4). Quinolyl and benzothiazolyl substrates provided moderate to good yields of the corresponding coupling products (Table 4, entries 1−3). However, when the heterocyclic substrate was used as the nucleophilic partner, only 29% of the desired product was obtained (entry 4).

Table 4. Pd-Catalyzed Hiyama Coupling of Heteroaryl Mesylates[a]

entry	ArOMs	Ar'Si(OR)$_3$	product	AcOH	% yield[b]
1				0.25 equiv	62
2				0.25 equiv	76
3				0.25 equiv	68
4				0.25 equiv	29

[a] Reaction conditions: see Tables 1 and 2. [b] Isolated yields.

In summary, we have succeeded in devising an effective system for performing Hiyama cross-couplings on aryl and heteroaryl mesylates. In the presence of CM-phos ligand, 2 mol % of Pd is generally sufficient to catalyze this coupling process. Particularly noteworthy is that we have also demonstrated the beneficial effect of acid additives which very effectively suppress phenolic side product formation. These findings may prove of relevance for improving Si-based cross-couplings of aryl sulfonates (e.g., mesylate/tosylate/triflate) and open up the possibility of expanding the scope to other related types of catalysis.

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Supporting Information Available: General considerations, detailed experimental procedures, references of known compounds, product characterization data, and copies of ^1H NMR, ^{13}C NMR, and MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The reaction time for each substrate has not been optimized. In general, 16 h is sufficient for complete conversion of all aryl mesylates.

(17) In ref 13, Wu and co-workers reported that ~5% yield of the coupled product was observed when ortho-substituted aryl mesylate was used.