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General and Efficient Route for the Synthesis of 3,4-Disubstituted Coumarins via Pd-Catalyzed Site-Selective Cross-Coupling Reactions

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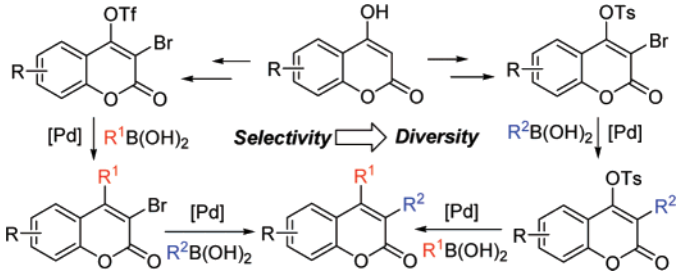

Palladium-catalyzed site-selective cross-coupling reactions of 3-bromo-4-trifloxycoumarin or 3-bromo-4-tosyloxycoumarin provide an efficient and facile route for the synthesis of 3,4-disubstituted coumarins, which include 3,4-diarylcoumarins, 3-amino-4-arylcoumarins, and 3-aryl-4-aminocoumarins. The order of reactivity of the (pseudo)halide substituents in the coumarins was found to be 4-OTf > 3-Br > 4-OTs.

Introduction

The prominence of coumarin in natural products and biologically active molecules[1] has promoted considerable efforts toward their synthesis. As a "privileged" scaffold, coumarins show interesting biological properties, especially for their anti-HIV and antibiotic activities.[2] For example, Novobiocin is a coumarin-derived antibiotic used as a competitive inhibitor of the bacterial ATP binding gyrase B subunit, blocking the negative supercoiling of relaxed DNA.[2a,d] Lamellarin is utilized as a selective inhibitor of HIV-1 integrase.[2i] Recently, we also discovered that 4-substituted coumarins showed good anti-HCV activity.[3] The discovery of promising lead antivirus compounds and their moderate activity warranted the development of efficient and rapid syntheses and evaluations of analogous structures in the search for better inhibitors. Thus, we initiated

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(1) For selected examples, see: (a) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashi, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 59. (b) Maier, W.; Schmidt, J.; Nimtz, M.; Wray, V.; Strack, D. *Phytochemistry* **2000**, *54*, 473. (c) Garcia-Argaez, A. N.; Ramirez, Apan, T. O.; Delgado, H. P.; Velazquez, G.; Martinez-Vazquez, M. *Planta Med.* **2000**, *66*, 279. (d) Zhou, P.; Takaishi, Y.; Duan, H.; Chen, B.; Honda, G.; Itoh, M.; Takeda, Y.; Kodzhimatov, O. K.; Lee, K-H. *Phytochemistry* **2000**, *53*, 689. (e) Khalmuradov, M. A.; Saidkhodzhaev, A. I. *Chem. Nat. Compd.* **1999**, *35*, 364. (f) Kamalam, M.; Jegadeesan, M. *Indian Drugs* **1999**, *36*, 484. (g) Tan, R. X.; Lu, H.; Wolfender, J. L.; Yu, T. T.; Zheng, W. F.; Yang, L.; Gafner, S.; Hostettmann, K. *Planta Med.* **1999**, *65*, 64. (h) Vlietinck, A. J.; De Bruyne, T.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97. (i) Bal-Tembe, S.; Joshi, D. D.; Lakdawala, A. D. *Indian J. Chem., Sect. B*: *Org. Chem. Incl. Med. Chem.* **1996**, *35B*, 518. (j) Silvan, A. M.; Abad, M. J.; Bermejo, P.; Villar, A.; Sollhuber, M. *J. Nat. Prod.* **1996**, *59*, 1183. (k) Yang, Y. M.; Hyun, J. W.; Sung, M. S.; Chung, H. S.; Kim, B. K.; Paik, W. H.; Kang, S. S.; Park, J. G. *Planta Med.* **1996**, *62*, 353.

(2) For selected examples, see: (a) Gellert, M.; O'Dea, M. H.; Itoh, T.; Tomizawa, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4474, 4478. (b) Murray, R. D. H.; Méndez, J.; Brown, S. A. *The Natural Coumarins*: *Occurrence*, *Chemistry*, *and Biochemistry*; Wiley: New York, 1982. (c) Ali, J. A.; Jackson, A. P.; Howells, A. J.; Maxwell, A. *Biochemistry* **1993**, *32*, 2717. (d) Pereira, N. A.; Pereira, B. M. R.; Celia, do Nascimento, M.; Parente, J. P.; Mors, W. B. *Planta Med.* **1994**, *60*, 99. (e) Vlietinck, A. J.; De Bruyne, T.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97. (f) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashi, H. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 59. (g) Xia, Y.; Yang, Z.-Y.; Xia, P.; Hackl, T.; Hamel, E.; Mauger, A.; Wu, J.-H.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 3932. (h) Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2001**, *44*, 2374. (i) Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Lett.* **2006**, *47*, 3755 and references cited therein.

(3) Wu, J.; Yang, Z.; Fathi, R.; Zhu, Q. *U.S. Pat. Appl. Publ.* **2004**, 43. (U.S. Pat. Appl. 2,538, 2004).

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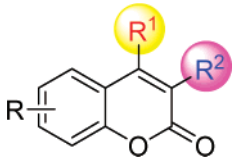


FIGURE 1. Diversified coumarins.

a program to develop efficient methods for the synthesis of diversified coumarin molecules (Figure 1), with the hope of finding more active hits or leads for our particular biological assays.

Although there are classical methods, such as the Perkin and Pechman reactions,[4] for the synthesis of a wide variety of substituted coumarins, these methods often require the use of strong acids and high temperatures. The scope of these transformations is therefore somewhat limited. Recent research has centered on the use of palladium-catalyzed C−C bond formation leading to the 3- or 4-substituted coumarins,[5] and the number of transition-metal-catalyzed approaches for accessing coumarins is increasing.[6] However, most of these approaches are focused on monosubstituted coumarins. Only limited applications of transition-metal-catalyzed reactions for the synthesis of 3,4-disubstituted coumarins have been reported; however, these impose restrictions upon substituent diversity and also suffer from regioselectivity problems.[7] For example, Larock[7i,j] reported a novel synthetic method for the synthesis of a variety of 3,4-disubstituted coumarins by using the palladium-catalyzed coupling of *o*-iodophenols with internal alkynes and carbon monoxide. When a series of phenylalkylacetylenes was employed in the reaction, mixtures of regioisomers were obtained in all cases with modest regioselectivity.[7j] Thus, it is of great interest to develop general protocols for the synthesis of 3,4-disubstituted coumarins under mild reaction conditions.

Transition-metal-catalyzed cross-coupling reactions with multifunctional substrates which proceed stepwise and display site-selectivity are particularly attractive for synthetic chemists. Diversified structures, often containing bioactive scaffolds, could be generated via successive introduction of various substituents in specific positions of the molecular skeleton. A number of compounds bearing two or more leaving groups, especially dihaloheteroarenes, have proven to be suitable partners for this kind of transformation.[8] Inspired by the recent advances of site-selective transition-metal-catalyzed dicoupling reactions,[8k] we conceived that the synthesis of differentially 3,4-disubstituted coumarins could be achieved via Pd-catalyzed regioselective cross-coupling reactions. The key step in our program is installing R^1 and R^2 groups to the C-4 and C-3 positions of the coumarin scaffold. By attaching leaving groups of different reactivities to the electronically different C-3 and C-4 positions, two substituents were expected to be successively installed into the coumarin moiety. This controllable site-selectivity comes from the chemoselectivity. We envisioned this strategy should be particularly useful for the facile and concise synthesis of diversified coumarin derivatives. Herein, we describe our efforts for palladium-catalyzed site-selective dicouplings of 3-bromo-4-trifloxycoumarins or 3-bromo-4-tosyloxycoumarins for the synthesis of differentially 3,4-disubstituted coumarins.

Results and Discussion

Our strategy is based on the decoration of the readily available coumarin core structure using site-selective cross-coupling reactions. The key compound in our overall synthetic route was identified as 4-hydroxycoumain. It is well-known that 4-hydroxycoumarins are useful intermediates for many industrial products and several methods for their preparation have been reported.[9] Prompted by the recent advances of halogenation of 1,3-dicarbonyl compounds,[10] we envisioned that 3-bromo-4-

(4) For selected examples, see: (a) von Pechmann, H.; Duisberg, C. *Chem. Ber.* **1884**, *17*, 929. (b) Johnson, J. R. *Org. React.* **1942**, *1*, 210. (c) Jones, G. *Org. React.* **1967**, *15*, 204. (d) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1996**, *43*, 1257. (e) Shirner, R. L. *Org. React.* **1942**, *1*, 1. (f) Narasimhan, N. S.; Mali, R. S.; Barve, M. V. *Synthesis* **1979**, 906. (g) Yavari, I.; Hekmat-Shoar, R.; Zonouzi, A. *Tetrahedron Lett.* **1998**, *39*, 2391. (h) Cartwright, G. A.; McNab, W. *J. Chem. Res.* (*S*) **1997**, 296. (i) Alexander, V. M.; Bhat, R. P.; Samant, S. D. *Tetrahedron Lett.* **2005**, *46*, 6957 and references cited therein. (j) Sengh, V.; Sengh, J.; Kaur, K. P.; Kad, G. L. *J. Chem. Res.* (*S*) **1997**, 58. (k) Frere, S.; Thiery, V.; Besson, T. *Tetrahedron Lett.* **2001**, *42*, 2791. (l) John, E. V. O.; Israelstam, S. S. *J. Org. Chem.* **1961**, *26*, 240. (m) Hoefnagel, A. J.; Gennewagh, E. A.; Downing, R. S.; Bekkum, H. V. *J. Chem. Soc., Chem. Commun.* **1995**, 225. (n) Wu, J.; Diao, T.-N.; Sun, W.; Li, Y. *Synth. Commun.* **2006**, *36*, 2949. (o) Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R. *Tetrahedron Lett.* **2005**, *46*, 6119.

(5) For examples, see: (a) Tang, Z. Y.; Hu, Q.-S. *Adv. Synth. Catal.* **2004**, *346*, 1635. (b) Wu, J.; Liao, Y.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 3642. (c) Lei, J.-G.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2004**, 2364. (d) Wu, J.; Wang, L.; Fathi, R.; Yang, Z. *Tetrahedron Lett.* **2002**, *43*, 4395. (e) Schio, L.; Chatreaux, F.; Klich, M. *Tetrahedron Lett.* **2000**, *41*, 1543. (f) Yao, M.-L.; Deng, M.-Z. *Heterocycl. Chem.* **2000**, *11*, 380. (g) Wu, J.; Yang, Z. *J. Org. Chem.* **2001**, *66*, 7875.

(6) (a) Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669 and references cited therein. (b) Jia, C. G.; Piao, D. G.; Oyamada, J. Z.; Lu, W. J.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (c) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264. (d) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (e) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581.

(7) (a) Rayabarapu, D. K.; Sambaiah, T.; Cheng, C. -H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286. (b) Yoneda, E.; Sugioka, T.; Hirao, K.; Zhang, S.-W.; Takahashi, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 477. (c) Van, T. N.; Debenedetti, S.; De Kimpe, N. *Tetrahedron Lett.* **2003**, *44*, 4199. (d) Catellani, M.; Chuisoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5919. (e) Catellani, M.; Chiusoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett.* **1994**, *35*, 5923. (f) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1996**, *118*, 6305. (g) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (h) Jia, C.; Piao, D.; Kitamura, T.; Fujiwara, Y. *J. Org. Chem.* **2000**, *65*, 7516. (i) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643. (j) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9423. (k) Kitamura, T.; Yamamoto, K.; Kotani, M.; Oyamada, J.; Jia, C.; Fujiwara, Y. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1889. (l) An, Z.; Catellani, M.; Chiusoli, G. P. *Gazz. Chim. Ital.* **1990**, *120*, 383. (m) Park, K. H.; Jung, G., II; Chung, Y. K. *Synlett* **2004**, 2541.

(8) (a) Review on site-selective cross-coupling reactions of multiple halogenated heterocycles, see: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245. Selected examples: (b) Zezschwitz, P.; Petry, F.; Meijere, A. *Chem. Eur. J.* **2001**, *7*, 4035. (c) Voigt, K.; Zezschwitz, P.; Rosauer, K.; Lansky, A.; Adams, A.; Reiser, O.; Meijere, A. *Eur. J. Org. Chem.* **1998**, 1521. (d) Handy, S. T.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 1537. (e) Duan, X.-F.; Li, X.-H.; Li, F.-Y.; Huang, C.-H. *Synthesis* **2004**, 2614. (f) Kaswasaki, I.; Yamashita, M.; Ohta, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2085. (g) Bellina, F.; Anselmi, A.; Martina, F.; Rossi, R. *Eur. J. Org. Chem.* **2003**, 2290. (h) Bellina, F.; Falchi, E.; Rossi, R. *Tetrahedron* **2003**, *59*, 9091. (i) Christoforou, I. C.; Koutentis, P. A. *Org. Biomol. Chem.* **2007**, *5*, 1381. (j) Cerna, I.; Pohl, R.; Klepetarova, B.; Hocek, M. *Org. Lett.* **2006**, *8*, 5389. (k) Conreaux, D.; Bossharth, E.; Monteiro, N.; Desbordes, P.; Vors, J.; Balme, G. *Org. Lett.* **2007**, *9*, 271. (l) Pereira, R.; Furst, A.; Iglesias, B.; Germain, P.; Gronemeyerb, H.; Lera, A. R. *Org. Biomol. Chem.* **2006**, *4*, 4514. (m) Araujo-Junior, J. X.; Schmitt, M.; Benderittera, P.; Bourguignon, J. *Tetrahedron Lett.* **2006**, *47*, 6125. (n) Dang, T. T.; Rasool, N.; Dang, T. T.; Reinkea, H.; Langer, P. *Tetrahedron Lett.* **2007**, *48*, 845.

(9) Selected examples: (a) Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *Synth. Commun.* **2001**, *31*, 1195. (b) Kalinin, A. V.; Da, S.; Alcides, J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4995. (c) Mizuno, T.; Nishiguchi, I.; Hirashima, T.; Ogawa, A.; Kambe, N.; Sonoda, N. *Synthesis* **1988**, 257.

SCHEME 1. Synthesis of 3-Bromo-4-trifloxycoumarin 2a or 3-Bromo-4-tosyloxycoumarin 3a from 4-Hydroxycoumarin

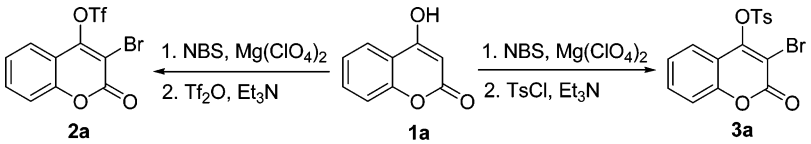
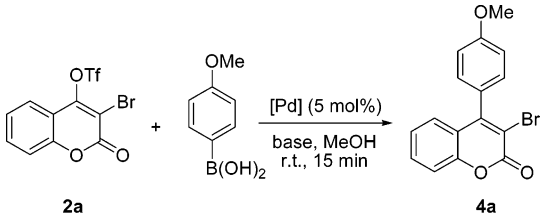


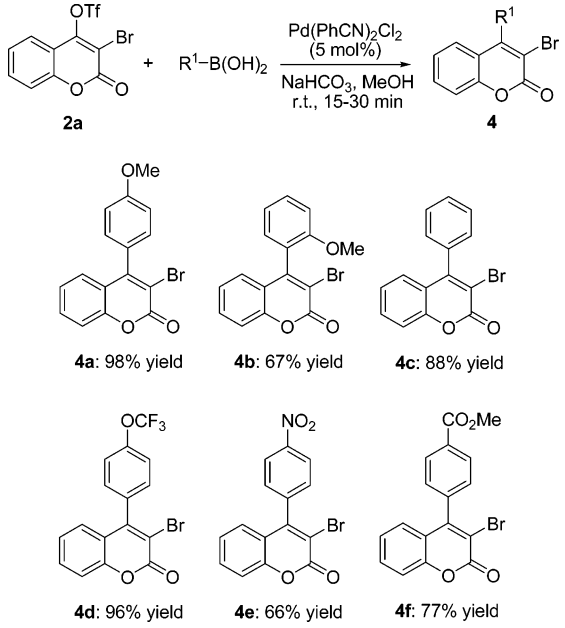
TABLE 1. Monocoupling of 2a with 4-Methoxyphenylboronic Acid[a]



entry	catalyst	base	yield (%)[b]
1	$Pd(OAc)_2$	$K_2HPO_4 \cdot 3H_2O$	72
2	$Pd(OAc)_2$	$K_2HPO_4 \cdot 3H_2O$	70[c]
3	$Pd(OAc)_2$	$K_2HPO_4 \cdot 3H_2O$	68[d]
4	$Pd(PhCN)_2Cl_2$	$K_2HPO_4 \cdot 3H_2O$	75
5	$Pd(PhCN)_2Cl_2$	$KF \cdot 2H_2O$	30
6	$Pd(PhCN)_2Cl_2$	K_3PO_4	40
7	$Pd(PhCN)_2Cl_2$	Na_2CO_3	85
8	$Pd(PhCN)_2Cl_2$	$NaHCO_3$	98
9	$Pd(PhCN)_2Cl_2$	K_2CO_3	38
10	$Pd(PhCN)_2Cl_2$	CsOAc	63

[a] Reaction conditions: substrate (0.30 mmol), arylboronic acid (1.1 equiv), [Pd] (5 mol %), methanol (2.0 mL), base (3.0 equiv), rt, 15 min. [b] Isolated yield. [c] With 10 mol % of PCy_3. [d] At 0 °C, 3 h.

SCHEME 2. Synthesis of 3-Bromo-4-arylcoumarin 4



hydroxycoumarin could be generated by treatment of 4-hydroxycoumarin with NBS/$Mg(ClO_4)_2$. Further treatment with Tf_2O or TsCl in the presence of base afforded the 3-bromo-4-trifloxycoumarin **2a** or 3-bromo-4-tosyloxycoumarin **3a**, respectively (Scheme 1).

Among transition-metal-catalyzed cross-coupling reactions, the Suzuki−Miyaura coupling is probably most widely used in both the laboratory and industry, due to the great functional group tolerance of this transformation and the innocuous nature of boronic acids, which are generally nontoxic and thermally, air, and moisture stable.[11] Thus, initial studies were carried out for the palladium-catalyzed reaction of 3-bromo-4-trifloxycoumarin **2a** with 4-methoxyphenylboronic acid (Table 1). The reactivity of the vinyl trifloxy group is favored over vinyl bromide in cross-coupling reactions,[12] and we reasoned that the electron-withdrawing property of the ester group in compound **2a** may also facilitate the oxidative addition step of the C-4 trifloxy group. As expected, we observed the formation of the 4-arylcoumarin **4a** as the only monocoupled product (72% yield), although combined with a small amount of bis-arylated product as a slight excess of the boronic acid was needed to ensure complete conversion of starting material **2a** (Table 1, entry 1). This result established that the coupling reaction proceeds essentially at C-4 rather than at C-3. The yield of **4a** could not be improved by the addition of a phosphine ligand or changing reaction temperature (Table 1, entries 2 and 3). To our delight, excellent yield was obtained when $Pd(PhCN)_2Cl_2$ was employed as a catalyst and $NaHCO_3$ was used as a base (Table 1, entry 8, 98% yield).

To demonstrate the generality of this strategy, the method was applied to other arylboronic acids. Remarkably, both electron-rich and electron-poor arylboronic acids are suitable partners in this process, affording the corresponding monosubstituted products in good to excellent yields (Scheme 2).

To further diversify the monocoupled coumarins, we then explored the reactivity of the remaining bromide atom at the C-3 position. After screening, $Pd(OAc)_2$ was found to be the best catalyst, and $K_2HPO_4 \cdot 3H_2O$ was the choice of base. The corresponding disubstituted products were afforded in good to excellent yields by using tricyclohexylphosphine as the ligand at 60 °C (Table 2). It was found that electron-withdrawing as well as electron-donating substituents attached on arylboronic acids are tolerated under these conditions. The success of this method opens a new access to unsymmetrically bis-arylated coumarins.

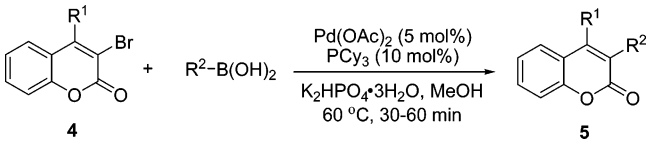
Symmetrically 3,4-diarylated coumarins can also be directly generated under suitable conditions. For example, by increasing the amount of arylboronic acid to 3.0 equiv compared to substrate, reaction of 3-bromo-4-trifloxycoumarin **2a** with 4-methoxyphenylboronic acid leads to the corresponding symmetrically 3,4-diarylated coumarin **5a** in 81% yield. This

(10) Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429.

(11) For recent reviews, see: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(12) For selected examples, see: (a) De Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; John Wiley & Sons: Weinheim, Germany, 2004. (b) Lesuisse, D.; Albert, E.; Bouchoux, F.; Cerede, E.; Lefrancois, J.; Levif, M.; Tessier, S.; Trica, B.; Teutscha. G. *Bioorg. Med. Chem. Lett.* **2001**, 1709. (c) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478. (d) Chan, D. C. M.; Fu, H.; Forsch, R. A.; Queener, S. F.; Rosowsky, A. *J. Med. Chem.* **2005**, *48*, 4420. (e) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146. (f) Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379. (g) Wu, X.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 346.

TABLE 2. Cross-Coupling Reaction of 4 with Arylboronic Acids[a]

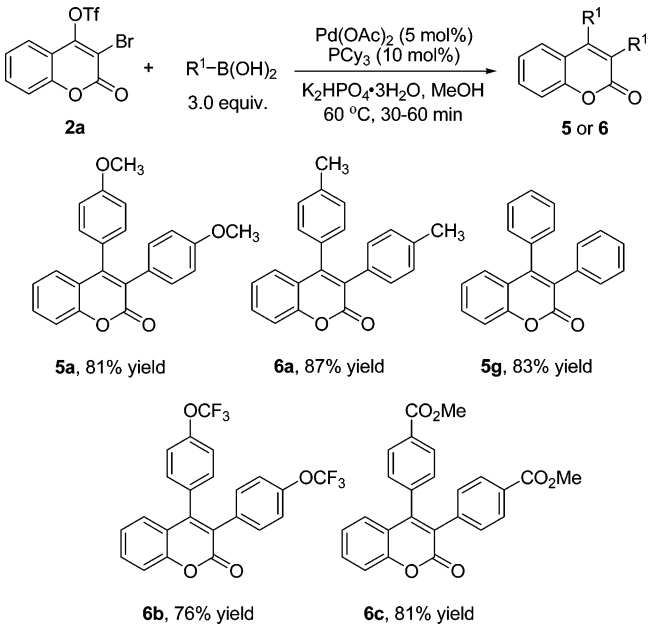


4 5

entry	substrate **4**	R^2	product **5**	yield (%)[b]
1	**4a**	4-$MeOC_6H_4$	**5a**	98
2	**4a**	4-$CF_3OC_6H_4$	**5b**	96
3	**4a**	4-MeC_6H_4	**5c**	92
4	**4a**	C_6H_5	**5d**	83
5	**4a**	4-$NO_2C_6H_4$	**5e**	46
6	**4a**	4-$MeO_2CC_6H_4$	**5f**	68
7	**4c**	C_6H_5	**5g**	94
8	**4c**	4-$MeOC_6H_4$	**5h**	96
9	**4e**	4-$MeOC_6H_4$	**5i**	81
10	**4f**	4-$MeOC_6H_4$	**5j**	83

[a] Reaction conditions: substrate (0.30 mmol), arylboronic acid (1.5 equiv), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), $K_2HPO_4 \cdot 3H_2O$ (3.0 equiv), methanol (2.0 mL), 60 °C, 0.5−1.0 h. [b] Isolated yield.

SCHEME 3. Synthesis of 3,4-Diarylcoumarin 5 or 6



protocol proved to be very useful for a range of arylboronic acids, affording the desired products in good yields (Scheme 3).

Toward the goal of a diversified library of coumarins, different consecutive transformations were expected to furnish coumarin derivatives of more molecular complexity. However, in some cases initial functionalization at C-3 of the coumarin nucleus is required. That means a C-3/C-4 reaction order. Such a reverse site-selectivity in favor of the less electron-deficient position may be expected if a newly introduced leaving group deactivates the usual preference for C-4 regioselectivity. Considering the inert reactivity of tosylate over bromide in Suzuki−Miyaura cross-coupling reactions,[13,14] we hypothesized that a tosyloxy group at the C-4 position of the coumarin core would decrease the reactivity of this more electron-deficient position, and that the site-selectivity may even be redirected to the C-3 position. Tosylate was also selected because 3-bromo-4-tosyloxycoumarin **3a** could be easily accessed as described previously, and has the additional benefit of being more stable than 3-bromo-4-trifloxycoumarin **2a**.

To explore the possibility of C-3/C-4 selectivity, we again choose arylboronic acid as the reaction partner (screening results are shown in Table 3). Treatment of 3-bromo-4-tosyloxycoumarin **3a** with 2-methoxyphenylboronic acid under modified conditions from Scheme 2 did afford the desired C-3 monocoupled product **7a** in 9% yield (Table 3, entry 4). Encouraged by this result, reaction conditions were systematically investigated. It was noted that Pd(0) catalysts and phosphine ligand-containing palladium complexes improved the yield of **7a** dramatically (Table 3, entries 1−6). In conjunction with $Pd(PPh_3)_4$, $NaHCO_3$ was the best base after screening (Table 3, entry 14). Sterically hindered electron-rich phosphine ligands were found to be somewhat beneficial to this transformation (Table 3, entries 15−24), and 62% yield of product **7a** was generated when P(2,6-dimethoxyphenyl)$_3$ was utilized as the ligand (Table 3, entry 22). The THF/H_2O cosolvent remained the one of choice. Meanwhile, it was found that water was crucial to the reaction with only a trace amount of product was detected in the absence of water. Increasing the amount of 2-methoxyphenylboronic acid (1.5 equiv) reduced **7a** yield (47%) as the excess boronic acid facilitated the generation of disubstituted product (result not shown in Table 3).

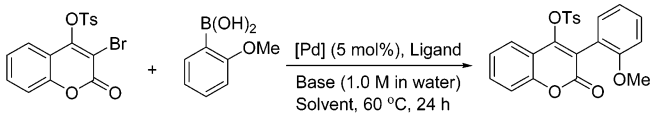
The optimized conditions showed that the coupling reaction proceeded essentially at the C-3 position. Thus, reverse site-selectivity was displayed by replacing the trifloxy group with a tosyloxy group at the C-4 position of the coumarin scaffold. Selectivity of C-3 to C-4 substitution would be helpful at this point. Modulation of site-selectivity based on this strategy is of great significance since more complexity can now be introduced. The generality of this new protocol was thus further investigated (Table 4). As shown, in most of cases, different substituted arylboronic acids furnished the corresponding 3-monoarylated products in moderate to good yields. Better results were observed when arylboronic acids bearing electron-donation groups were utilized. For instance, compound **3a** reacted with 4-methoxyphenylboronic acid, leading to the desired product **7e** in 75% yield (Table 4, entry 5), while 24% yield of product **7f** was afforded when 4-(methoxycarbonyl)-phenylboronic acid was employed in the reaction (Table 4, entry 6). These conditions also proved to be useful for fluoro-substituted coumarin derivative **3b** as well (entries 7 and 8).

As the remaining tosyloxy group at the C-4 position of compounds **7** is in principle coupling with another arylboronic acid, the 3-monoarylated coumarins could be further elaborated to unsymmetrically diarylated coumarin derivatives. To our delight, this protocol proceeded successfully under the conditions shown in Table 2, although a slightly longer reaction time was needed (Table 5). The reactions of various arylboronic acids with different 3-monoarylated coumarins occurred smoothly, leading to the corresponding 3,4-disubstituted coumarins in excellent yields. For example, 4-(trifluoromethoxy)phenylbo-

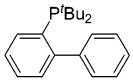
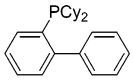
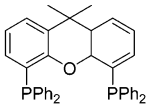
(13) For examples, see: (a) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058. (b) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

(14) For examples, see: (a) Santana, L.; Uriarte, E.; Gonzalez-Diaz, H.; Zagotto, G.; Soto-Otero, R.; Mendez-Alvarez, E. *J. Med. Chem.* **2006**, *49*, 1149. (b) Rivkin, A.; Adams, B. *Tetrahedron Lett.* **2006**, *47*, 2395. (c) Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Lett.* **2006**, *47*, 3755 and references cited therein. (d) Gellert, M.; O'Dea, M. H.; Itoh, T.; Tomizawa, J. I. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4474. (e) Pereira, N. A.; Pereira, B. M. R.; Celia do Nascimento, M.; Parente, J. P.; Mors, W. B. *Planta Med.* **1994**, *60*, 99. (f) Levine, C.; Hiasa, H.; Marians, K. J. *Biochim. Biophys. Acta* **1998**, 29.

TABLE 3. Conditions Screened for Monocoupling of 3-Bromo-4-tosyloxycoumarin 3a with 2-Methoxyphenylboronic Acid[a]

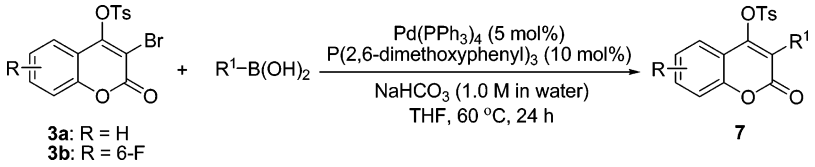


3a **7a**

Entry	[Pd] (5 mol%)	Ligand (10 mol%)	Base	Solvent	Yield (%)[b]
1	$Pd(PPh_3)_4$	-	CsF	THF	48
2	$Pd_2(dba)_3$	-	CsF	THF	27
3	$Pd(PPh_3)_2Cl_2$	-	CsF	THF	22
4	$Pd(PhCN)_2Cl_2$	-	CsF	THF	9
5	$Pd(OAc)_2$	-	CsF	THF	trace
6	$Pd(dppf)Cl_2$	-	CsF	THF	38
7	$Pd(PPh_3)_4$	-	Na_2CO_3	THF	38
8	$Pd(PPh_3)_4$	-	K_2CO_3	THF	43
9	$Pd(PPh_3)_4$	-	Cs_2CO_3	THF	46
10	$Pd(PPh_3)_4$	-	KF	THF	21
11	$Pd(PPh_3)_4$	-	NaOH	THF	NR
12	$Pd(PPh_3)_4$	-	K_2HPO_4	THF	trace
13	$Pd(PPh_3)_4$	-	K_3PO_4	THF	33
14	$Pd(PPh_3)_4$	-	$NaHCO_3$	THF	50
15	$Pd(PPh_3)_4$	PCy_3	$NaHCO_3$	THF	42
16	$Pd(PPh_3)_4$	PPh_3	$NaHCO_3$	THF	29
17	$Pd(PPh_3)_4$	dppp	$NaHCO_3$	THF	19
18	$Pd(PPh_3)_4$	dppf	$NaHCO_3$	THF	trace
19	$Pd(PPh_3)_4$		$NaHCO_3$	THF	trace
20	$Pd(PPh_3)_4$		$NaHCO_3$	THF	47
21	$Pd(PPh_3)_4$	$P(o\text{-}tol)_3$	$NaHCO_3$	THF	59
22	$Pd(PPh_3)_4$	$P(2,6\text{-dimethoxyphenyl})_3$	$NaHCO_3$	THF	62
23	$Pd(PPh_3)_4$		$NaHCO_3$	THF	27
24	$Pd(PPh_3)_4$	$P(2\text{-furyl})_3$	$NaHCO_3$	THF	27
25	$Pd(PPh_3)_4$	$P(2,6\text{-dimethoxyphenyl})_3$	$NaHCO_3$	MeCN	trace
26	$Pd(PPh_3)_4$	$P(2,6\text{-dimethoxyphenyl})_3$	$NaHCO_3$	toluene	20
27	$Pd(PPh_3)_4$	$P(2,6\text{-dimethoxyphenyl})_3$	$NaHCO_3$	DCE	49
28	$Pd(PPh_3)_4$	$P(2,6\text{-dimethoxyphenyl})_3$	$NaHCO_3$	dioxane	trace
29	$Pd(PPh_3)_4$	$P(2,6\text{-dimethoxyphenyl})_3$	$NaHCO_3$	PrOH	trace

[a] Reaction conditions: substrate (0.30 mmol), arylboronic acid (1.1 equiv), [Pd] catalyst (5 mol %), ligand (10 mol %), solvent (2.0 mL), base (4.0 equiv, 1.0 M in H_2O), 60 °C, 24 h. [b] Isolated yield.

TABLE 4. Monocoupling of 3-Bromo-4-tosyloxycoumarin 3 with Arylboronic Acid[a]



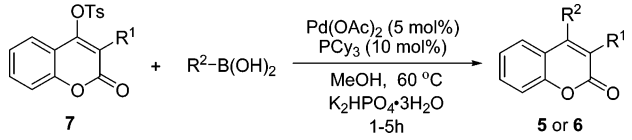
3a: R = H
3b: R = 6-F

7

entry	substrate	R^1	product	yield (%)[b]
1	**3a**	2-$MeOC_6H_4$	**7a**	62
2	**3a**	4-$CF_3OC_6H_4$	**7b**	70
3	**3a**	4-MeC_6H_4	**7c**	42
4	**3a**	C_6H_5	**7d**	54
5	**3a**	4-$MeOC_6H_4$	**7e**	75
6	**3a**	4-$MeO_2CC_6H_4$	**7f**	24
7	**3b**	4-$MeOC_6H_4$	**7g**	48
8	**3b**	2-$MeOC_6H_4$	**7h**	32

[a] Reaction conditions: substrate (0.30 mmol), arylboronic acid (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %), P(2,6-dimethoxyphenyl)$_3$ (10 mol %), THF (2.0 mL), $NaHCO_3$ (4.0 equiv, 1.0 M in H_2O), 60 °C, 24 h. [b] Isolated yield.

TABLE 5. Second Monocoupling of Compound 7 with Arylboronic Acids[a]



7 **5** or **6**

entry	substrate	R^2	product	yield (%)[b]
1	**7e**	4-$MeOC_6H_4$	**5a**	92
2	**7e**	4-$CF_3OC_6H_4$	**5k**	99
3	**7e**	4-MeC_6H_4	**5*l***	93
4	**7e**	C_6H_5	**5f**	94
5	**7e**	4-$MeO_2CC_6H_4$	**5j**	74
6	**7c**	4-MeC_6H_4	**6a**	92
7	**7c**	4-$MeOC_6H_4$	**5c**	93

[a] Reaction conditions: substrate (0.30 mmol), arylboronic acid (1.5 equiv), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), $K_2HPO_4 \cdot 3H_2O$ (3.0 equiv., methanol (2.0 mL), 60 °C, 1−5 h. [b] Isolated yield.

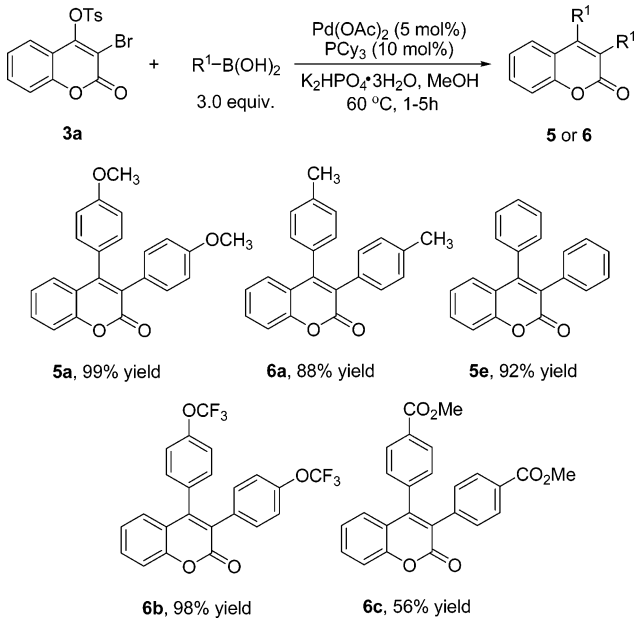
ronic acid coupled with compound **7e** gave the product **5g** in almost quantitative yield (Table 5, entry 2). Reaction of compound **7e** with 4-(methoxycarbonyl)phenylboronic acid also gave the corresponding product **5j** in 74% yield (Table 5, entry 5).

Similarly, symmetrically 3,4-diarylated coumarins **5** or **6** could be generated under the conditions shown in Scheme 3, from the reactions of 3-bromo-4-tosyloxycoumarin **3a** with arylboronic acid (3.0 equiv). Again, excellent yields were observed for this kind of transformation when arylboronic acids bearing electron-donation groups were used (Scheme 4). Inferior results was displayed in the presence of 4-(methoxycarbonyl)-phenylboronic acid (56% yield).

We also tried the one-pot synthesis of the 3,4-disubstituted coumarins from 3-bromo-4-trifloxycoumarin **2a** or 3-bromo-4-tosyloxycoumarin **3a** (Scheme 5). For example, reaction of 3-bromo-4-trifloxycoumarin **2a** with 4-methoxyphenylboronic acid and 4-(trifluoromethoxy)phenylboronic acid subsequently afforded the desire product **5b** in 16% yield (Scheme 5, eq 1). However, only a trace amount of product **5c** was detected when 3-bromo-4-tosyloxycoumarin **3a** was utilized as the substrate (Scheme 5, eq 2).

Armed with this encouraging strategy of tunable site-selective dicouplings, we briefly explored the synthetic application of this work for diversified coumarins. For example, Buchwald−

SCHEME 4. Synthesis of 3,4-Diarylcoumarin 5 or 6

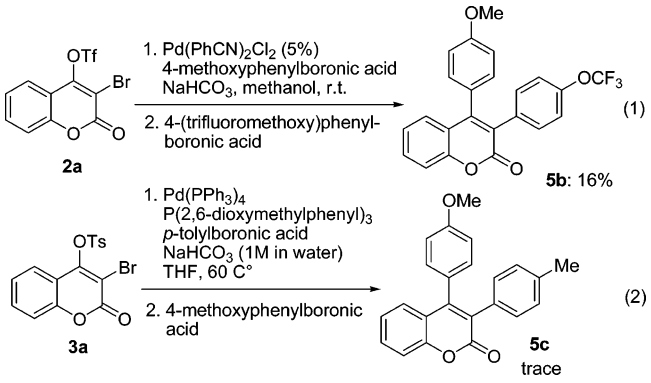


3a **5** or **6**

5a, 99% yield **6a**, 88% yield **5e**, 92% yield

6b, 98% yield **6c**, 56% yield

SCHEME 5. One-Pot Synthesis of Bis-Arylated Coumarins

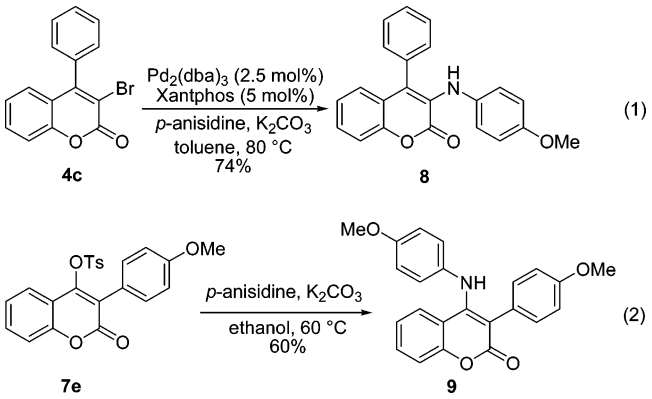


2a **5b**: 16%

3a **5c** trace

Hartwig amination of bromine derivative **4c** with *p*-anisidine in the presence of $Pd_2(dba)_3$ and Xantphos provided the corresponding 3-amino-4-aryl coumarin **8** in 74% yield (Scheme 6, eq 1). While the 3-aminocoumarin core is a ubiquitous subunit in many natural products with remarkable biological activities,[14] the 4-aminocoumarin scaffold is extensively incorporated in

SCHEME 6. Synthesis of 3-Amino-4-arylcoumarin or 3-Aryl-4-aminocoumarin



fluorescent brighteners.[15] 4-Amino-3-aryl coumarin **9** was generated by consecutive Suzuki−Miyaura reaction/nucleophilic substitution of 3-aryl-4-tosyloxy coumarin **7e** (Scheme 6, eq 2). These promising results displayed the potential of this strategy for numerous synthetic applications to diversified coumarins.

In summary, on the basis of different selectivities of 3-bromo-4-trifloxycoumarins and 3-bromo-4-tosyloxycoumarins in Suzuki−Miyaura cross-couplings, we have developed a tunable strategy that allows Pd-catalyzed dicoupling reactions to proceed in reversible sequences. This new protocol tremendously facilitates the concise synthesis of diversified 3,4-diarylated coumarins, especially unsymmetrically 3,4-diarylated ones. Since both monocoupled intermediates from 3-bromo-4-trifloxycoumarins and 3-bromo-4-tosyloxycoumarins can be further elaborated by many other transformations, this work now opens the door for numerous synthetic applications to diversified coumarins. Efforts toward this goal and screening for biological activity of these small molecules are being undertaken in our laboratory.

Experiment Section

General Procedure for the Pd-Catalyzed Monocoupling of 2a with Arylboronic Acids (Scheme 2). Under nitrogen atmosphere, a mixture of compound **2a** (0.30 mmol), arylboronic acid (1.1 equiv), $Pd(PhCN)_2Cl_2$ (5 mol %), and $NaHCO_3$ (3.0 equiv) in methanol (2.0 mL) was stirred at room temperature for a period of time. After completion of the reaction as indicated by TLC, the reaction mixture was purified directly by flash column chromatography on silica gel to afford the corresponding product **4**. Selected examples: 3-Bromo-4-(4-methoxyphenyl)-2*H*-chromen-2-one (**4a**): 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.91 (s, 3H), 7.07 (d, J = 8.8 Hz, 2H), 7.15−7.27 (m, 4H), 7.39 (d, J = 8.0 Hz, 1H), 7.54−7.58 (m, 1H). ^{13}C NMR (100 MHz) δ (ppm) 160.3, 157.4, 154.5, 152.4, 131.9, 129.8, 127.7, 127.3, 124.6, 120.5, 116.8, 114.2, 112.8, 55.4. MS m/z 331 (M^+). Anal. Calcd for $C_{16}H_{11}BrO_3$: C, 58.03; H, 3.35. Found: C, 58.05; H, 3.15. 3-Bromo-4-(4-(trifluoromethoxy)phenyl)-2*H*-chromen-2-one (**4d**): 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.03 (d, J = 7.8 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.34−7.43 (m, 5H), 7.58 (t, J = 7.8 Hz, 1H). ^{19}F NMR (376 MHz) δ (ppm) −57.6. ^{13}C NMR (100 MHz) δ (ppm) 157.2, 153.4, 152.5, 149.9, 133.7, 132.4, 130.1, 127.4, 125.0, 124.4, 121.8, 121.4, 120.1, 119.2, 117.1, 116.7, 113.2. MS m/z 385 (M^+). Anal. Calcd for $C_{16}H_8BrF_3O_3$: C, 49.90; H, 2.09. Found: C, 50.05; H, 2.10.

General Procedure for the Pd-Catalyzed Cross-Coupling of Compound 4 with Arylboronic Acids (Table 2). $K_2HPO_4{\cdot}3H_2O$ (0.90 mmol, 3.0 equiv) was added to a mixture of compound **4** (0.30 mmol), arylboronic acid (1.5 equiv), $Pd(OAc)_2$ (5 mol %), and PCy_3 (10 mol %) in methanol (2.0 mL). The reaction mixture was stirred at 60 °C for a period of time. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel to afford the corresponding product **5**. Selected examples: 4-(4-Methoxyphenyl)-3-(4-(trifluoromethoxy)phenyl)-2*H*-chromen-2-one (**5b**): 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.80 (s, 3H), 6.83 (d, J = 8.7 Hz, 2H), 7.00−7.05 (m, 4H), 7.14−7.22 (m, 3H), 7.29 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz) δ (ppm) 161.2, 159.8, 153.4, 152.2, 148.5, 132.9, 132.4, 131.8, 130.9, 128.0, 126.2, 125.5, 124.3, 121.7, 120.6, 120.2, 119.2, 116.9, 116.6, 114.0, 55.3. MS m/z 413 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{15}F_3O_4$: C, 66.99; H, 3.67. Found: C, 66.72; H, 3.52. 4-(4-Methoxyphenyl)-3-phenyl-2*H*-chromen-2-one (**5d**):[16d] 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.78 (s, 3H), 6.81 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.2 Hz, 2H), 7.11−7.21 (m, 6H), 7.28 (dd, J = 8.3, 1.4 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.50 (t, J = 8.3 Hz, 1H). ^{13}C NMR (100 MHz) δ (ppm) 161.5, 159.5, 153.3, 151.5, 134.2, 131.5, 130.9, 130.7, 127.9 (5), 127.9 (1), 127.6, 127.0, 126.6, 124.2, 120.8, 116.9, 113.8, 55.3.

General Procedure for the Pd-Catalyzed Cross-Coupling of 2a with Arylboronic Acids (Scheme 3). A mixture of compound **2a** (0.30 mmol), arylboronic acid (3.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), and $K_2HPO_4{\cdot}3H_2O$ (3.0 equiv) in methanol (2.0 mL) was stirred at 60 °C for a period of time. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel to afford the corresponding product. Selected examples: 3,4-Diphenyl-2*H*-chromen-2-one (**5g**):[16c] 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.11−7.22 (m, 9H), 7.20−7.32 (m, 3H), 7.42 (d, J = 8.3 Hz, 1H), 7.51−7.55 (m, 1H). ^{13}C NMR (100 MHz) δ (ppm) 161.3, 153.2, 151.6, 134.5, 133.9, 131.4, 130.5, 129.4, 128.3 (3), 128.2 (5), 127.8, 127.7, 127.6, 127.0, 124.1, 120.5, 116.8. 3,4-Di(4-(methoxycarbonyl)phenyl)-2*H*-chromen-2-one (**6c**): 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.85 (s, 3H), 3.89 (s, 3H), 7.11−7.21 (m, 6H), 7.42 (d, J = 7.8 Hz, 1H), 7.53−7.58 (m, 1H), 7.83 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H). 13C NMR (100 MHz) δ (ppm) 166.6, 166.3, 160.6, 153.4, 151.3, 138.8, 138.4, 132.2, 130.7, 130.5, 129.8, 129.6, 129.5, 129.2, 127.6, 126.4, 124.6, 119.8, 117.1,52.4, 52.2. MS m/z 415 ($M^+ + 1$). Anal. Calcd for $C_{25}H_{18}O_6$: C, 72.46; H, 4.38. Found: C, 72.51; H, 4.00.

General Procedure for the Pd-Catalyzed Monocoupling of Compound 3 with Arylboronic Acids (Table 4). $NaHCO_3$ (4.0 equiv, 1.0 M in H_2O) was added to a mixture of compound **3** (0.30 mmol), arylboronic acid (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %), and P(2,6-dimethoxyphenyl)$_3$ (10 mol %) in THF (2.0 mL) at 60 °C. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperatureand extracted with EtOAc (3 × 2 mL). The organic phase was concentrated under reduced pressure. Purification by flash column chromatography on silica gel afforded the corresponding product **7**. Selected examples: 2-Oxo-3-(4-(trifluoromethoxy)phenyl)-2*H*-chromen-4-yl 4-methylbenzenesulfonate (**7b**): 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.40 (s, 3H), 6.99 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H),

(15) (a) Chavan, A. P. *J. Chem. Res.* **2006**, *3*, 179. (b) Rana, B. J.; Desai, K. R. *J. Inst. Chem.* (*India*) **1996**, *68*, 85. (c) Zhao, D.; Li, Z.; Xiu, J. *Chin. J. Chem. Eng.* **2000**, *8*, 366. (d) Sivakumar, K.; Xie, F.; Cash, B. M.; Long, S.; Barnhill, H. N.; Wang, Q. *Org. Lett.* **2004**, *6*, 4603.

(16) (a) Chatterjea, J. N.; Prasad Gupta, S. N.; Prasad, N. *Chem. Ber.* **1966**, *99*, 2699. (b) Rossi, R.; Bellina, F.; Carpita, A.; Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095. (c) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9423. (d) Reed, M. A.; Chang, M. T.; Snieckus, V. *Org. Lett.* **2004**, *6*, 2297. (e) Sabitha, G.; Reddy, G. J; Rao, A. V. S. *Synth. Commun.* **1988**, *18*, 639.

7.27−7.33 (m, 4H), 7.39−7.43 (m, 2H), 7.64 (t, J = 7.8 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz) δ (ppm) 161.2, 154.2, 152.5, 149.2, 146.1, 133.0, 132.6, 132.2, 129.7, 128.4, 128.0, 127.7, 125.5, 124.8, 121.6, 120.0, 119.6, 119.1, 117.1, 116.5, 21.5. MS m/z 477 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{15}F_3O_6S$: C, 57.98; H, 3.17. Found: C, 57.88; H, 2.93. 2-Oxo-3-*p*-tolyl-2*H*-chromen-4-yl 4-methylbenzenesulfonate (**7c**): 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.32 (s, 3H), 2.40 (s, 3H), 6.95 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 7.3 Hz, 2H), 7.27−7.40 (m, 4H), 7.60 (t, J = 7.8 Hz, 1H), 7.98 (d, J = 8.2 Hz, 1H). ^{13}C NMR (100 MHz) δ (ppm) 161.6, 153.6, 152.3, 145.3, 138.6, 133.0, 132.5, 130.4, 129.5, 128.6, 127.8, 126.9, 125.3, 124.7, 121.1, 117.4, 116.4, 21.7, 21.4. MS m/z 407 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{18}O_5S$: C, 67.97; H, 4.46. Found: C, 67.66; H, 4.43.

General Procedure for the Pd-Catalyzed Cross-Coupling of Compound 7 with Arylboronic Acids (Table 5). A mixture of compound **7** (0.30 mmol), arylboronic acid (1.5 equiv), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), and $K_2HPO_4 \cdot 3H_2O$ (3.0 equiv) in methanol (2.0 mL) was stirred at 60 °C for a period of time. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel to afford the corresponding product. Selected examples: 3-(4-Methoxyphenyl)-4-phenyl-2*H*-chromen-2-one (**5f**):[16e] 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.72, (s, 3H), 6.70 (d, J = 9.2 Hz, 2H), 7.05−7.21 (m, 6H), 7.30−7.33 (m, 3H), 7.40 (d, J = 8.2 Hz, 1H), 7.49−7.51 (m, 1H). ^{13}C NMR (100 MHz) δ (ppm) 161.5, 158.9, 153.1, 151.0, 134.7, 131.9, 131.2, 129.4, 128.4, 128.3, 127.7, 126.6, 126.0, 124.1, 120.6, 116.7, 113.3, 55.1. 3-(4-Methoxyphenyl)-4-(4-(trifluoromethoxy)phenyl)-2*H*-chromen-2-one **(5g):** 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.74 (s, 3H), 6.71 (d, J = 8.2, 2H), 7.01 (d, J = 9.2, 2H), 7.14−7.22 (m, 6H), 7.41 (d, J = 8.7, 1H), 7.51−7.55 (m, 1H). ^{13}C NMR (100 MHz): δ (ppm) 161.3, 159.2, 153.2, 149.6, 149.1, 133.4, 131.9, 131.6, 131.2, 127.4, 127.2, 125.7, 124.4, 121.7, 120.9, 120.3, 119.2, 117.0, 116.6, 113.5, 55.2. MS: m/z 413 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{15}F_3O_4$: C, 66.99; H, 3.67. Found: C, 66.98; H, 3.64.

General Procedure for the Pd-Catalyzed Cross-Coupling of Compound 3a with Arylboronic Acids (Scheme 4). A mixture of compound **3a** (0.30 mmol), arylboronic acid (3.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), and $K_2HPO_4 \cdot 3H_2O$ (3.0 equiv) in methanol (2.0 mL) was stirred at 60 °C for a period of time. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel to afford the corresponding product. Selected examples: 3,4-Bis(4-methoxyphenyl)-2*H*-chromen-2-one (**5a**): 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.74 (s, 3H), 3.80 (s, 3H), 6.72 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 7.03−7.07 (m, 4H), 7.17 (t, J = 7.6 Hz, 1H), 7.27 (dd, J = 8.2, 1.4 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz) δ (ppm) 161.6, 159.4, 158.8, 153.1, 150.9, 131.9, 131.1, 130.9, 127.7, 126.8, 126.5, 126.3, 124.0, 120.9, 116.7, 113.8, 113.3, 55.2, 55.2. MS m/z 359 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 76.83; H, 5.01. 3,4-Di-4-tolyl-2*H*-chromen-2-one **(6a):** 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.26, (s, 3H), 2.36, (s, 3H), 6.99−7.03 (m, 6H), 7.11−7.19 (m, 3H), 7.22 (dd, J = 7.8, 1.4, 1H), 7.40 (d, J = 8.2, 1H), 7.48−7.52 (m, 1H). ^{13}C NMR (100 MHz): δ (ppm) 161.5, 153.1, 151.3, 138.1, 137.3, 131.6, 131.2, 131.0, 130.4, 129.3, 129.0, 128.5, 127.8, 126.9, 124.0, 120.8, 116.7, 21.2 (9), 21.2 (5). MS: m/z 327 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.37; H, 5.70.

Pd-Catalyzed Buchwald−Hartwig Amination of Compound 4c with *p*-Anisidine (Scheme 6, eq 1). 3-(4-Methoxyphenylamino)-4-phenyl-2*H*-chromen-2-one (8): A mixture of compound **4c** (0.15 mmol), *p*-anisidine (1.2 equiv), $Pd_2(dba)_3$ (2.5 mol %), Xantphos (5 mol %), and K_2CO_3 (2.0 equiv) in toluene (1.0 mL) was stirred at 80 °C for 12 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel to afford the corresponding product in 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.68 (s, 3H), 6.19 (s, 1H), 6.49 (d, J = 8.7 Hz, 2H), 6.59 (d, J = 9.2 Hz, 2H), 7.11−7.25 (m, 7H), 7.31−7.39 (m, 2H). ^{13}C NMR (100 MHz) δ (ppm) 160.4, 155.7, 149.4, 134.3, 133.4, 129.6, 128.6, 128.2, 128.0, 127.8, 127.4, 125.1, 124.5, 123.4, 121.9, 116.5, 113.7, 55.6. MS m/z 344 ($M^+ + 1$). Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.57; H, 4.97; N, 3.91.

Nucleophilic Substitution of Compound 7e with *p*-Anisidine (Scheme 6, eq 2). 3-(4-Methoxyphenyl)-4-(4-methoxyphenylamino)-2*H*-chromen-2-one (9): A mixture of compound **7e** (0.15 mmol), *p*-anisidine (1.2 equiv), and K_2CO_3 (2.0 equiv) in ethanol (1.0 mL) was stirred at 60 °C for 3 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature and purified directly by flash column chromatography on silica gel to afford the corresponding product in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.78 (s, 3H), 3.81 (s, 3H), 6.17 (s, 1H), 6.78 (d, J = 8.7 Hz, 2H), 6.90−7.00 (m, 5H), 7.25−7.43 (m, 5H). ^{13}C NMR (100 MHz) δ (ppm) 162.2, 159.7, 157.1, 153.6, 149.5, 135.3, 131.7, 131.2, 126.3, 124.4, 123.0, 117.4, 115.4, 115.0, 114.8, 109.9, 55.6, 55.4. MS m/z 374 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 73.64; H, 5.35; N, 3.86.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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