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Sequential Pd(II)−Pd(0) Catalysis for the Rapid Synthesis of Coumarins

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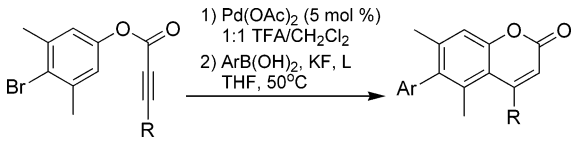

Electrophilic palladium-catalyzed cycloisomerization of brominated aryl propiolates produces brominated coumarins. The brominated coumarins can be diversified by reduction of the Pd(II) catalyst to Pd(0) followed by Suzuki, Sonogashira, Heck, or Hartwig−Buchwald coupling. Thus, a single loading of precatalyst can be used to conduct sequential reactions, allowing the synthesis of functionalized coumarins. Extension of this methodology toward the synthesis of coumarin libraries is discussed.

The ability to change a catalyst's function through modification of reaction conditions is a powerful strategy for generating complex structures using a single catalyst source.[1] For instance, Grubbs' ring-closing metathesis catalyst can be transformed into a hydrogenation catalyst, thus allowing the synthesis of saturated cyclic molecules.[2] Similarly, Evans has shown that Rh(I) catalysts can be used for tandem allylic alkylation/Pauson−Khand annulations.[3] Such systems take advantage of the diversity of reactions catalyzed by ruthenium and rhodium. Since palladium is arguably the most versatile transition metal for catalysis, it is not surprising that palladium features prominently in a number of tandem transformations.[4,5] These tandem palladium-catalyzed reactions often involve at least one step that is a palladium-catalyzed cross-coupling of aryl or vinyl halides; however, we are unaware of any reports involving

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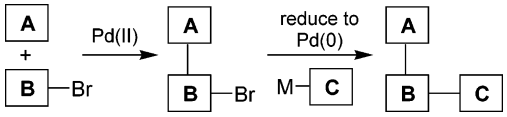
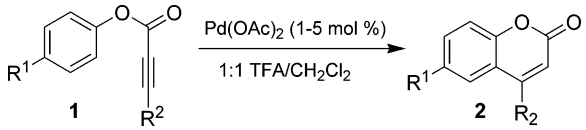


SCHEME 2



tandem Pd(II)- and Pd(0)-catalyzed reactions that exploit the compatibility of electrophilic palladium(II) catalysts with aryl or vinyl halides.[6] Such a method could be a powerful tool for combinatorial synthesis because a single precatalyst could be used to form two new C−C bonds (Scheme 1). Herein the application of sequential Pd(II)−Pd(0) catalysis toward the rapid synthesis of coumarins is described.

Fujiwara reported that electrophilic palladium catalysts effect the cycloisomerization of arylated alkynoates (**1**) to provide coumarins (**2**), and in one example, an aryl bromide was carried through the reaction (Scheme 2).[7] It seemed logical that the Pd(II) catalyst used for the Fujiwara cyclization could be reduced to Pd(0), which would allow the subsequent diversification of the coumarin core by use of cross-coupling reactions.

Initial investigation focused on examining the electrophilic cycloisomerization of brominated aryl alkynoates using the conditions of Fujiwara. For example, treatment of **1a** ($R^1 = CMe_3$, $R^2 = p\text{-}BrC_6H_4$) with 5 mol % $Pd(OAc)_2$ in trifluoroacetic acid for 1 h at room temperature provided the brominated coumarin **2a** in 87% yield (Chart 1). The analogous *m*-bromo (**2b**) and *o*-bromo (**2c**) coumarins were isolated in slightly lower yields. Bromine could also be incorporated on the coumarin arene (**2f** and **2g**); however, additional donor groups are needed to provide the requisite nucleophilicity for successful hydroarylation. The fact that bromoarenes are not reduced under the conditions of Pd(II)-catalyzed hydroarylation highlights the complementary functional group compatibility of Pd(II) and Pd(0).[8]

Next, the conditions necessary for Suzuki cross-coupling of the brominated coumarins were investigated. While a variety of conditions have been reported for cross-couplings of coumarins,[9] a slight modification of the general cross-coupling procedure developed by Buchwald

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(8) Bromoarenes are reduced under the conditions of an analogous Pd(0)-catalyzed hydroarylation: Trost, B. M.; Toste, F. D.; Greenman, K. *J. Am. Chem. Soc*. **2003**, *125*, 4518−4526.

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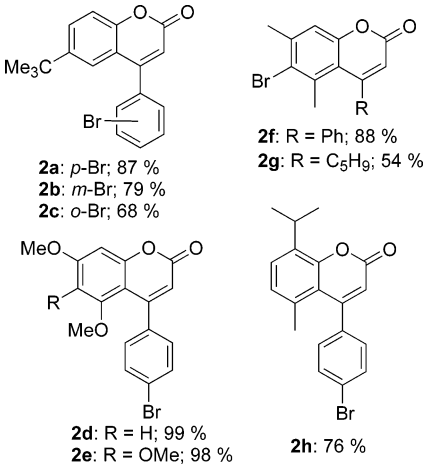
CHART 1



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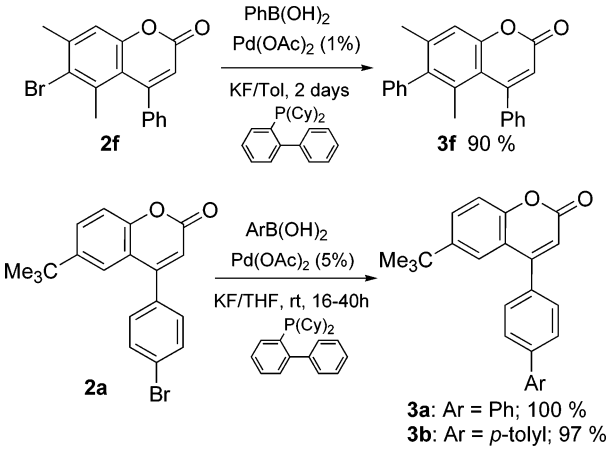

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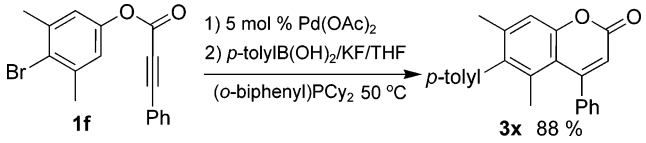

proved to be particularly effective (Scheme 3).[10] Since the procedures being developed are for application in combinatorial synthesis of coumarins on a small scale, yields were optimized rather than catalyst and ligand loadings.

Having established the viability of the individual reactions, the next goal was to perform the cyclization and Suzuki coupling sequentially using a single palladium precatalyst. The protocol developed involves performing the hydroarylation with 5 mol % $Pd(OAc)_2$ in CF_3CO_2H for 1−6 h at room temperature, followed by removal of the TFA. The flask is then charged with THF, 10 mol % (*o*-biphenyl)PCy_2, $ArB(OH)_2$, and 3 equiv of KF. It was gratifying to find that, under these conditions, product **3x** could be isolated in 88% yield from aryl ester **1f** (Scheme 4). This yield compares favorably with the 79% overall yield for the two-step sequence. Then, utilizing **1a** as a standard substrate, the cyclization/

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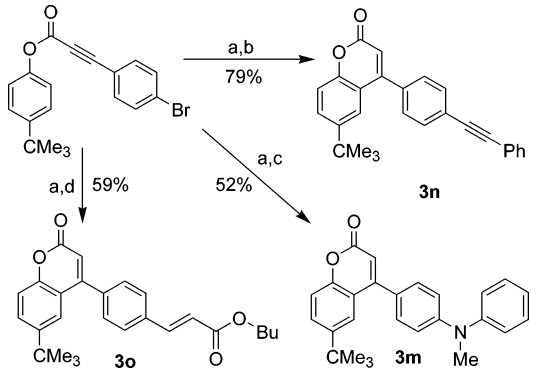
SCHEME 5[a]



[a] Conditions: (a) 5 mol % $Pd(OAc)_2$, 1:3 TFA/CH_2Cl_2; (b) PhCCH, piperidine, 10 mol % (*o*-biphenyl)P(*t*Bu)$_2$, 10 mol % CuI, CH_3CN, 50 °C; (c) *p*-$MeOC_6H_4NHMe$, NaO*t*Bu, 10 mol % (*o*-biphenyl)P(*t*Bu)$_2$, toluene, 50 °C

Suzuki coupling was investigated with a variety of aryl boronic acids (Chart 2). The sequential coupling reaction is rather general as is shown by the consistent yields with electron-rich and electron-poor boronic acids. Isolated yields for the product coumarins ranged from 62 to 80%. A variety of coumarins with multiple electron-donating substituents are obtained in somewhat higher yields (77−88%). The donor groups are important for facile, high-yielding Fujiwara hydroarylation. A limitation is encountered upon varying the position of bromination of the 4-phenyl ring. While *p*-bromo- and *m*-bromophenylpropiolate substrates that give rise to intermediates **2a** and **2b** afford 70 and 80% yield of the phenylated products **3a** and **3o**, respectively, the analogous *o*-bromophenylpropiolate substrate gives <10% of the expected coumarin. This low yield likely reflects a poor Suzuki coupling since the intermediate ortho-brominated coumarin **2c** is formed in 68% yield.

While the initial focus was on sequential hydroarylation−Suzuki couplings, the general concept laid out herein is likely to be applicable to many Pd(0)-catalyzed cross-couplings. Thus, the analogous hydroarylation/Sonogashira coupling occurs to give **3n** in 79% yield (Scheme 5). Additionally, sequential hydroarylation/Heck gives rise to olefinated coumarin **3o** in 59% yield and hydroarylation/Hartwig−Buchwald amination provides access to aminated coumarin **3m** in 52% yield. While this is a somewhat lower yield, it corresponds to a moderate average yield (72%) for two steps.

Finally, the methods developed herein were tested by synthesizing a small demonstration library of 16 biaryl coumarins. Four brominated aryl propiolates (A1−A4) as well as four aryl boronic acids (B1−B4, Chart 3) were selected for the initial library. The sequential coupling was run in parallel by the previously described procedure, modified only by utilization of parallel centrifugal solvent evaporation. The results are shown in Table 1. The purities of the crude products were generally good; however, the coupling of **A2** with electron-deficient aryl boronic acids **B3** and **B4** gave crude products in unacceptably low purity. Importantly, purification by mass-directed fractionation raised the purity levels of 13 of the 16 products to >95%. In the interest of optimizing the purity of product coumarins, only center cuts of HPLC

CHART 2

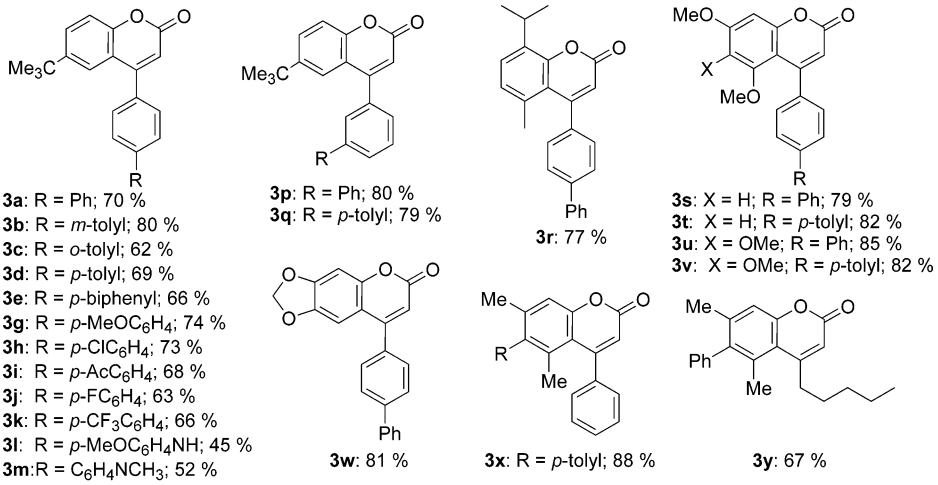


CHART 3

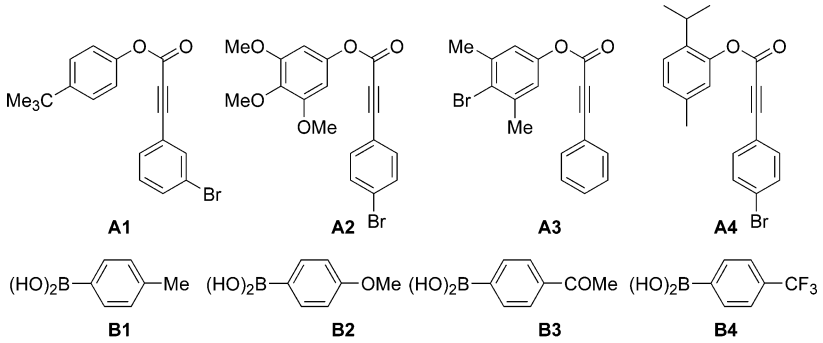


TABLE 1. Yields and Purities of Coumarins Synthesized in Parallel

product	crude purity[a]	% recovery[b]	% yield	purity after MDF[a,b]
A1B1	87	43	52	96
A1B2	90	52	66	95
A1B3	87	78	83	98
A1B4	86	27	33	98
A2B1	78	41	47	95
A2B2	85	57	65	89
A2B3	61	42	35	73
A2B4	44	19	22	98
A3B1	94	40	52	99
A3B2	91	50	62	100
A3B3	82	50	47	100
A3B4	88	45	53	100
A4B1	73	30	31	96
A4B2	70	35	40	97
A4B3	83	64	62	91
A4B4	70	31	36	97

[a] HPLC area % using UV detection from 245 to 355 nm. [b] Purified by mass-directed fractionation.

peaks were collected. Thus, the overall yields are somewhat lower than those observed for compounds prepared individually.

In conclusion, a simple procedure for the rapid synthesis of coumarins was developed on the basis of sequential Pd(II)- and Pd(0)-catalyzed reactions. These methods are currently being applied to the synthesis of larger coumarin libraries as well as developing other transformations on the basis of tandem Pd(II)−Pd(0) catalysis.

Experimental Section

General Procedure for the Sequential Hydroarylation/Suzuki Coupling. Aryl alkynoate **1** (0.14 mmol) and $Pd(OAc)_2$ (1.5 mg, 0.007 mmol) were dissolved in a 3:1 mixture of TFA/CH_2Cl_2 (0.5 mL). The resulting solution was stirred at room temperature for 1−6 h. The solvent was removed under vacuum, and arylboronic acid (0.21 mmol), KF (0.42 mmol), and 2-(dicyclohexylphosphino)biphenyl (0.014 mmol) were added under an inert atmosphere (N_2 or Ar). THF (1 mL) was added, and the reaction mixture was heated at 50 °C for 16 h. After removal of the solvent, the crude mixture was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent.

Preparation of 6-*tert*-Butyl-4-(4-(methyl(phenyl)-amino)phenyl)-2*H*-chromen-2-one (3m). 4-*tert*-Butylphenyl-3-(4-bromophenyl)propiolate (50 mg, 0.14 mmol) and $Pd(OAc)_2$ (1.5 mg, 0.007 mmol) were dissolved in a 3:1 mixture of TFA/CH_2Cl_2 (0.5 mL). The resulting solution was stirred at room temperature for 1 h. The solvent was removed under vacuum, and *p*-anisidine (21 mg, 0.17 mmol), sodium *tert*-butoxide (19 mg, 0.20 mmol), and 2-(di*tert*butylphosphino)biphenyl (10 mol %) were added under an Ar atmosphere. Next, 1 mL of

toluene was added and the reaction mixture was heated to 50 °C for 16 h. The product was purified by column chromatography on silica gel. ^{1}H NMR ($CDCl_3$): δ 7.68 (d, J = 2.3 Hz, 1H, ^{t}Bu*Ph*); 7.58 (dd, J = 2.3, 8.8 Hz, 1H, ^{t}Bu*Ph*); 7.41 (t, J = 7.6 Hz, 2H, *Ph*NPhC=CH); 7.36 (d, J = 8.8 Hz, 2H, *Ph*C=CH); 7.26 (dt, J = 2.6, 7.3 Hz, 2H, *Ph*NPhC=CH); 7.34 (d, J = 8.8 Hz, 1H, ^{t}Bu*Ph*); 7.19 (t, J = 7.3 Hz, 1H, *Ph*NPhC=CH); 6.98 (d, J = 8.8 Hz, 2H, *Ph*C=CH); 6.33 (s, 1H, CHCO); 3.42 (2, 3H, NCH_3), 1.30 (s, 9H, ^{t}Bu). ^{13}C{^{1}H} NMR: δ 161.5 (CO), Ph ring and C=C (155.8, 152.3, 150.2, 147.8, 146.9, 129.7, 129.6, 129.2, 125.0, 124.9, 124.6, 123.3, 118.3, 116.8, 115.6, 113.5), 40.2 (NCH_3), ^{t}Bu (34.6, 31.3). IR ν_{max} (NaCl)/cm^{-1}: 3058, 1717, 1705, 1610, 1591, 1614, 1495, 1369, 1354, 1193, 1130. HR-MS: $C_{26}H_{26}NO_2$ calcd, 384.1964 (M + 1); found, 384.1956.

Preparation of 6-*tert*-Butyl-4-(4-(2-phenylethynyl)-phenyl)-2*H*-chromen-2-one (3n). 4-*tert*-Butylphenyl-3-(4-bromophenyl)propiolate (50 mg, 0.14 mmol) and $Pd(OAc)_2$ (1.5 mg, 0.007 mmol) were dissolved in a 3:1 mixture of TFA/CH_2Cl_2 (0.5 mL). The resulting solution was stirred at room temperature for 1 h. The solvent was removed under vacuum, and CuI (0.9 mg, 0.005 mmol) and 2-(di*tert*butylphosphino)biphenyl (10 mol %) were added under an Ar atmosphere. Next, phenylacetylene (17 μL, 0.15 mmol), piperidine (27 μL, 0.23 mmol), and 1 mL of CH_3CN were added, and the reaction mixture was heated to 50 °C for 16 h. The product was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent. ^{1}H NMR ($CDCl_3$): δ 7.71 (d, J = 8.2 Hz, 2H, *Ph*C=CH); 7.62 (dd, J = 2.3, 8.8 Hz, 1H, ^{t}Bu*Ph*); 7.58 (dd, J = 2.0, 7.6 Hz, 2H, PhC≡C); 7.49 (d, J = 2.3 Hz, 1H, ^{t}Bu*Ph*); 7.48 (d, J = 8.2 Hz, 2H, *Ph*C=CH); 7.37−7.40 (m, 3H, PhC≡C); 7.36 (d, J = 8.8 Hz, 1H, ^{t}Bu*Ph*); 6.39 (s, 1H, CHCO); 1.28 (s, 9H, ^{t}Bu). ^{13}C{^{1}H} NMR: δ 160.9 (CO), Ph ring and C=C (155.2, 152.2, 147.3, 135.0, 132.0, 131.7, 129.7, 128.7, 128.5, 128.4, 124.9, 122.9, 122.7, 117.9, 116.9, 115.0), C≡C (91.3, 88.4), ^{t}Bu (34.6, 31.2). IR ν_{max} (NaCl)/cm^{-1}: 3055, 1720, 1614, 1570, 1510, 1371, 1186, 1018. HR-MS: $C_{27}H_{23}O_2$ calcd, 379.1698 (M + 1); found, 379.1701.

Preparation of (*E*)-Butyl-3-(4-(6-*tert*-butyl-2-oxo-2*H*-chromen-4-yl)phenyl)acrylate (3o). 4-*tert*-Butylphenyl-3-(4-bromophenyl)propiolate (50 mg, 0.14 mmol) and $Pd(OAc)_2$ (1.5 mg, 0.007 mmol) were dissolved in a 3:1 mixture of TFA/CH_2Cl_2 (0.5 mL). The resulting solution was stirred at room temperature for 1 h. The solvent was removed under vacuum, and Cs_2CO_3 (52 mg, 0.16 mmol) and tri(*o*-tolyl)phosphine (10 mol %) were added under an argon atmosphere. Next, butyl acrylate (29 μL, 0.20 mmol) and 1 mL of DMA were added, and the reaction was heated at 120 °C for 16 h. The product was purified by column chromatography on silica gel (ether/hexane = 1/2). ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 16.1 Hz, 1H, C*H*=CHCO$_2$,); 7.70 (d, J = 8.0 Hz, 2H, *Ph*CH=CH); 7.61 (dd, J = 2.3, 8.8 Hz, 1H, ^{t}Bu*Ph*); 7.51(d, J = 8.0 Hz, 2H, *Ph*CH=CH); 7.45 (d, J = 2.3 Hz, 1H, ^{t}Bu*Ph*); 7.36 (d, J = 8.8 Hz, 1H, ^{t}Bu*Ph*); 6.56 (d, J = 16.1 Hz, 1H, CH=C*H*CO$_2$); 6.37 (s, 1H, C*H*COPh); 4.24 (t, J = 6.6 Hz, 2H, OCH_2); 1.67−1.75 (m, 2H, OCH_2CH_2); 1.41−1.50 (m, 2H, CH_2CH_3); 1.27 (s, 9H, ^{t}Bu), 0.98 (t, J = 7.6 Hz, 3H, CH_2CH_3). ^{13}C{^{1}H} NMR: δ 166.7, 160.9, 155.0, 152.2, 147.3, 143.2, 136.9, 135.8, 129.7, 129.0, 128.4, 122.9, 119.8, 117.8, 116.9, 115.1, 64.6, 34.5, 31.2, 30.7, 19.2, 13.7. IR ν_{max} (NaCl)/cm^{-1}: 3055, 1720, 1637, 1614, 1568, 1371, 1312, 1205, 1178, 1128. HR-MS: *m/z* $C_{26}H_{29}O_4$ calcd, 405.2066 [M + H]; found, 405.2070.

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Supporting Information Available: Spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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