ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 9613–9615

www.rsc.org/chemcomm

COMMUNICATION

Regioselective palladium-catalyzed direct cross-coupling of coumarins with simple arenes†

Minsik Min and Sungwoo Hong*

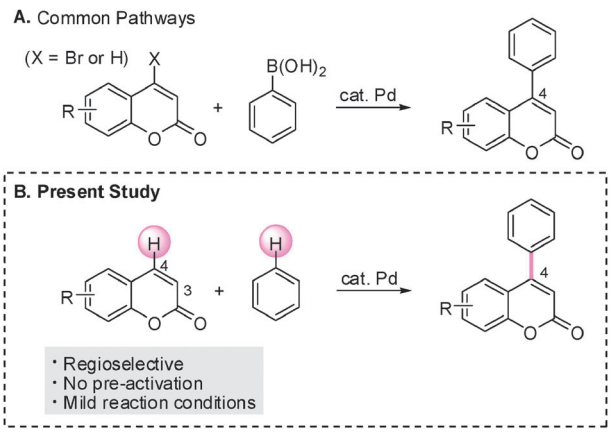
Received 25th June 2012, Accepted 9th August 2012
DOI: 10.1039/c2cc34551j

An efficient method for the C4-regiocontrolled C–H functionalization of coumarins to enable facile oxidative cross-couplings with simple arene components is disclosed.

Transition metal-catalyzed direct functionalization of C–H bonds has emerged as a straightforward and environmentally friendly synthetic tool.[1] In recent years, notable progress has been made toward enhancing the efficiency of the twofold direct C–H bond activation of (hetero)arenes.[2] The regioselective dehydrogenative arylation of indoles and pyrroles with simple arenes has been pioneered by several groups.[3] However, the oxidative double C–H bond functionalization approach is often limited by a modest substrate scope and the difficulties associated with controlling the site-selective C–H bond activation.[4]

Coumarins constitute a major class of naturally occurring compounds and privileged medicinal scaffolds that exhibit a broad range of biological activities.[5] Coumarins are also one of the most important classes of fluorophores, and they have been extensively investigated as powerful tools in complex biological systems.[6] The general methods for installing aryl groups and olefins have been developed based on transition metal-catalyzed cross-coupling reactions of 3- or 4-bromocoumarins with coupling substrates, such as organometallic reagents and alkenes.[7,8] Recently, an efficient synthetic route to 4-arylcoumarins (neoflavones) *via* palladium-catalyzed oxidative Heck coupling of coumarins and arylboronic acids was disclosed (Scheme 1A).[9]

In spite of the important contributions, a direct catalytic method for constructing these scaffolds *via* twofold oxidative C–H bond activation has not yet been reported. Driven by the need for a more efficient synthetic route to the coumarin derivatives, we were particularly interested in exploring a direct coupling approach that would avoid pre-functionalizing both the coumarin unit and the coupling partners prior to the coupling reaction (Scheme 1B). We envisioned that the initial electrophilic palladation of coumarin could proceed given the innate nucleophilic, albeit weak, characteristics of the coumarin core. The ability to selectively functionalize a single C–H bond



Scheme 1 Regioselective direct 4-arylation of coumarins.

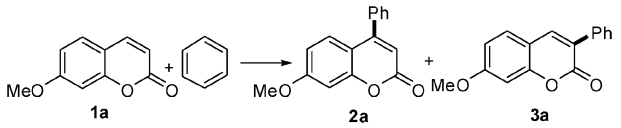
in the coumarin scaffold in the presence of electronically or sterically similar C–H bonds is crucial for realizing the utility of this approach.[10] Herein, we present the first example of the regiocontrolled C–H functionalization of coumarins to enable the catalytic cross-coupling of unactivated arenes with coumarins at the C4 position.

The nature of the substituents on the coumarin core has profound effects on the fluorescence, and the addition of electron-donating groups such as OMe and NEt_2 at position 7 on the coumarin core triggers a bathochromic shift with stronger charge transfer character.[7d,11] Therefore, we initially focused on the cross-coupling of 7-methoxycoumarin (**1a**) and benzene as test substrates to optimize the reaction conditions, as summarized in Table 1. Negligible activity was observed when 7-methoxycoumarin reacted with benzene under neat conditions (Table 1, entry 1). Low yields of the coupling products were obtained, except under conditions employing pivalic acid as the solvent. Recent reports have described palladium–pivalic acid combinations that exhibit good reactivity in C–H activation reactions by lowering the energy of C–H bond cleavage and by acting as partial proton shuttles during catalysis.[12] The use of $Cu(OAc)_2$ (entry 5) or the addition of 3-nitropyridine (entry 7) provided lower product yields with preference for the 4-aryl coumarin product **2a**.[3d] No coupling product was observed without the presence of an oxidant, and the oxidant's properties were critical to the coupling efficiency. The use of AgOPiv in conjunction with CsOPiv dramatically improved the catalytic efficiency, and the reactions were reasonably selective for the

Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 305-701, Korea.
E-mail: hongorg@kaist.ac.kr; Fax: +82 42-350-2810;
Tel: +82 42-350-2811

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc34551j

Table 1 Optimization of the dehydrogenative coupling conditions[a]



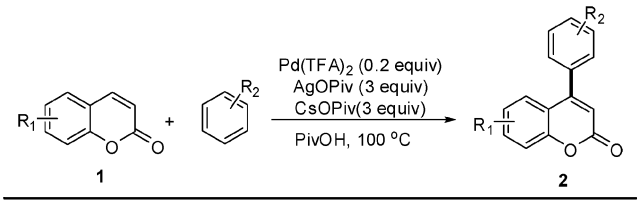
Entry	Catalyst	Oxidant	Additive	Solvent	Yield[b] (%) (**2**/**3**)[c]
1	$Pd(OAc)_2$	AgOAc	Cs_2CO_3	Benzene	Trace
2	$Pd(OAc)_2$	AgOAc	Cs_2CO_3	AcOH	14 (86 : 14)
3	$Pd(OAc)_2$	AgOPiv	—	PivOH	17 (88 : 12)
4	$Pd(OAc)_2$	—	CsOPiv	PivOH	Trace
5	$Pd(OAc)_2$	$Cu(OAc)_2$	CsOPiv	PivOH	7 (87 : 13)
6	$Pd(OAc)_2$	AgOAc	Cs_2CO_3	PivOH	53 (84 : 16)
7[d]	$Pd(OAc)_2$	AgOAc	Cs_2CO_3	PivOH	35 (87 : 13)
8	$Pd(OPiv)_2$	AgOAc	CsOPiv	PivOH	89 (86 : 14)
9	$Pd(OPiv)_2$	Ag_2CO_3	CsOPiv	PivOH	84 (88 : 11)
10	**$Pd(OPiv)_2$**	**AgOPiv**	**CsOPiv**	**PivOH**	**91 (91 : 9)**

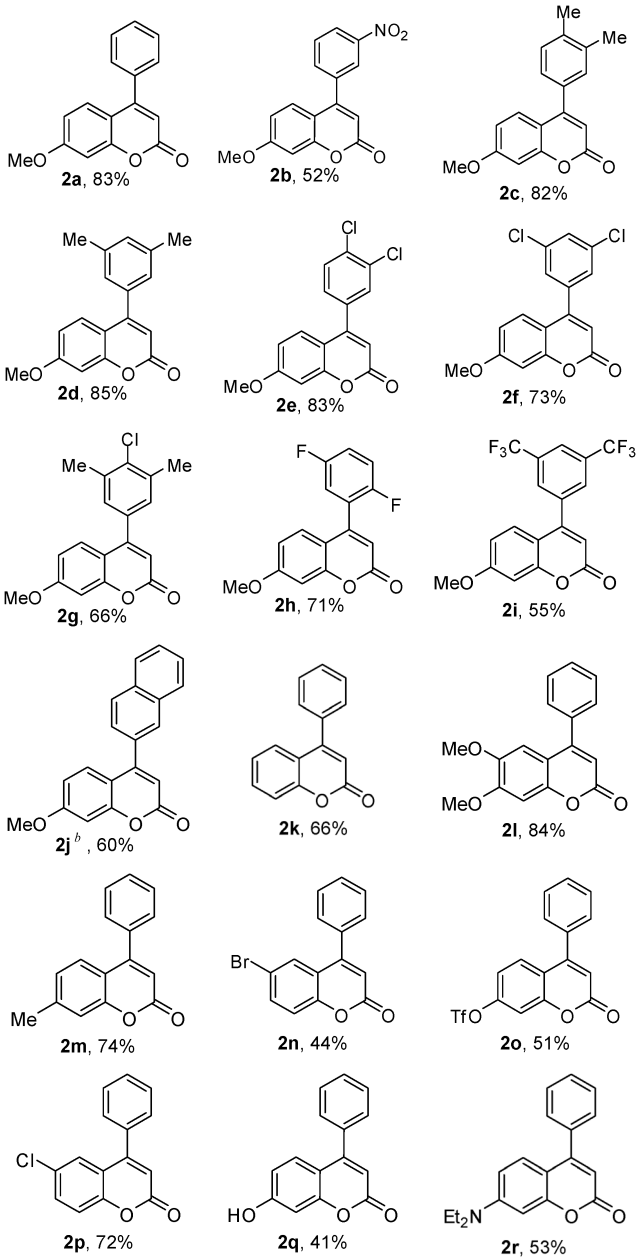
[a] Reactions were conducted with coumarin, benzene (30 equiv.), Pd (0.2 equiv.), oxidant (3 equiv.), and additive (3 equiv.) in PivOH at 100 °C under N_2 for 6–12 h. [b] Yields are reported after isolation and purification by flash silica gel chromatography. [c] Ratio was determined by ^{1}H NMR spectroscopy. [d] 0.2 equiv. of 3-nitropyridine was added.

4-arylcoumarin **2a**. An excess of benzene (30 equiv.) was needed to ensure complete conversion of 7-methoxycoumarin. Among the Pd species screened, $Pd(OPiv)_2$ (0.2 equiv.) was most effective in promoting coupling in the presence of AgOPiv (3 equiv.), and CsOPiv (3 equiv.) in pivalic acid at 100 °C (entry 10). The reaction conditions promoted the efficient C4 arylation of the coumarin with the best isolated yield and good selectivity (**2a**/**3a**, 91 : 9 in a 91% combined yield). This approach allows for the direct installation of aryl groups at the C-4 position, providing efficient access to the 4-arylcoumarin derivatives.

With the optimized conditions in hand, we next investigated the substrate scope of both the coumarin and the arene substrate, as summarized in Table 2. To our delight, we observed that the C4-functionalization process was amenable to a variety of arene types, including benzene substrates bearing methyl, fluoro, chloro, trifluoromethyl or nitro groups, with good C4 regioselectivity.[13] The coupling reaction of the coumarin with di- or tri-substituted benzenes was also efficient, and occurred at the more sterically accessible C–H bond of the benzene to provide only one regiomeric product.[14] In the case of the nitro group, the C–H bond acidity parameter seems to play an important role in selectivity of nitrobenzene, and a 52% yield of one regiomeric product **2k** was obtained.[15] In addition, a relatively broad range of functional groups (*e.g.*, alkyl, bromo, chloro, methoxy, dimethoxy, hydroxy, triflate, and diethylamino groups) on the coumarin core were compatible with the dehydrogenative coupling conditions and provided moderate to good yields. Substitution with an electron-donating OMe group at the 7-position enhanced the reaction efficiency (**2a** *vs.* **2k**). An amino group at the 7-position gave only moderate yield of desired product **2r**, most likely because the partially protonated amino group reduced the electron-donating properties under the reaction conditions. Expanding the scope from the phenyl to the naphthyl system was also possible, leading to the formation of **2j**. Notably, a coumarin bearing bromo or triflate substituents resulted in the isolation of the synthetically versatile **2n** and **2o** with intact bromo or triflate moieties under the reaction conditions, providing an opportunity for further formation of the C–C or C–heteroatom bonds.

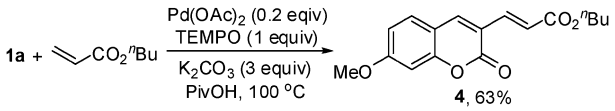
Table 2 Direct C4-arylation of the coumarins with various arenes[a]





[a] Reactions were conducted with coumarin, benzene (30 equiv.), $Pd(OPiv)_2$ (0.2 equiv.), AgOPiv (3 equiv.), and CsOPiv (3 equiv.) in PivOH at 100 °C under N_2 for 6–12 h. Yields are reported after isolation and purification by flash silica gel chromatography. [b] Naphthalene (10 equiv.) was used.

We also preliminarily investigated the possibility of whether this catalytic system could be effective towards the alkenylation of coumarins and observed that coumarin **1a** reacted with alkene (3 equiv.) under slightly altered reaction conditions (eqn (1)).[16]



(1)

In summary, we developed an efficient method for the oxidative cross-coupling of the coumarins and unactivated arenes *via* a palladium-catalyzed twofold C–H functionalization. This approach offers an unprecedented direct route to the C4-selective arylation of coumarins with simple arene partners under mild conditions. The substrate scope was broad, permitting the construction of a variety of 4-arylcoumarins (neoflavones), which are prominent structural motifs in many biologically active compounds. Detailed mechanistic studies and synthetic applications are now underway.

This research was supported by National Research Foundation of Korea (NRF) through general research grants (NRF-2010-0022179, 2011-0016436, 2011-0020322). M. Min is the recipient of a Global PhD Fellowship (NRF-2011-0007511).

Notes and references

1 For selected reviews on C–H activation, see: (*a*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*b*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*c*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*d*) L.-M. Xu, B.-J. Li, Z. Yang and Z.-J. Shi, *Chem. Soc. Rev.*, 2010, **39**, 712; (*e*) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (*f*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*g*) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (*h*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (*i*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*j*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*k*) L.-C. Campeau and K. Fagnou, *Chem. Soc. Rev.*, 2007, **36**, 1058.

2 For selected reviews, see; (*a*) S.-H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev.*, 2011, **40**, 5068; (*b*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792.

3 For selected reports, see: (*a*) B.-J. Li, S.-L. Tian, Z. Fang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2008, **47**, 1115; (*b*) H. Cho, S. J. Hwang and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 9254; (*c*) D. R. Stuart and K. Fagnou, *Science*, 2007, **316**, 1172; (*d*) D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072.

4 For selected reports, see: (*a*) M. Kitahara, N. Umeda, K. Hirano, T. Satoh and M. Miura, *J. Am. Chem. Soc.*, 2011, **133**, 2160; (*b*) C.-Y. He, S. Fan and X. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 12850; (*c*) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc.*, 2010, **132**, 1822; (*d*) K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2009, **131**, 9651; (*e*) D. Kim and S. Hong, *Org. Lett.*, 2011, **13**, 4466; (*f*) Y. Moon and S. Hong, *Chem. Commun.*, 2012, **48**, 7191.

5 (*a*) J. R. S. Hoult and M. Paya, *Gen. Pharmacol.*, 1996, **27**, 713; (*b*) I. Kostova, *Curr. Med. Chem.: Anti-Cancer Agents*, 2005, **5**, 29; (*c*) L. M. Kabeya, A. A. deMarchi, A. Kanashiro, N. P. Lopes, C. da Silva, M. T. Pupo and Y. M. Lucisano-Valima, *Bioorg. Med. Chem.*, 2007, **15**, 1516.

6 (*a*) R. S. Koefod and K. R. Mann, *Inorg. Chem.*, 1989, **28**, 2285; (*b*) P. T. Thuong, T. M. Hung, T. M. Ngoc, D. T. Ha, B. S. Min, S. J. Kwack, T. S. Kang, J. S. Choi and K. Bae, *Phytother. Res.*, 2010, **24**, 101; (*c*) R. Dayam, R. Gundla, L. O. Al-Mawsawi and N. Neamati, *Med. Res. Rev.*, 2008, **28**, 118.

7 (*a*) T. Janecki and R. Bodalski, *Synthesis*, 1989, 506; (*b*) T. Minami, Y. Matsumoto, S. Nakamura, S. Koyanagi and M. Yamaguchi, *J. Org. Chem.*, 1992, **57**, 167; (*c*) M.-S. Schiedel, C. A. Briehn and P. Bäuerle, *Angew. Chem., Int. Ed.*, 2001, **40**, 4677; (*d*) G.-J. Kim, K. Lee, H. Kwon and H.-J. Kim, *Org. Lett.*, 2011, **13**, 2799; (*e*) J. Gordo, J. Avó, A. J. Parola, J. C. Lima, A. Pereira and P. S. Branco, *Org. Lett.*, 2011, **13**, 5112.

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

9 (*a*) M. Khoobi, M. Alipour, S. Zarei, F. Jafarpour and A. Shafiee, *Chem. Commun.*, 2012, **48**, 2985; (*b*) Y. Li, Z. Qi, H. Wang, X. Fu and C. Duan, *J. Org. Chem.*, 2012, **77**, 2053.

10 (*a*) F. Chen, Z. Feng, C.-Y. He, H.-Y. Wang, Y.-L. Guo and X. Zhang, *Org. Lett.*, 2012, **14**, 1176; (*b*) Y.-Y. Yu, M. J. Niphakis and G. I. Georg, *Org. Lett.*, 2011, **13**, 5932; (*c*) L. Bi and G. I. Georg, *Org. Lett.*, 2011, **13**, 5413; (*e*) D. Cheng and T. Gallagher, *Org. Lett.*, 2009, **11**, 2639; (*d*) H. Geo, M. J. Niphakis and G. I. Georg, *J. Am. Chem. Soc.*, 2008, **130**, 3708.

11 G. Signore, R. Nifosi, L. Albertazzi, B. Storti and R. Bizzarri, *J. Am. Chem. Soc.*, 2010, **132**, 1276.

12 (*a*) M. Lafrance and K. Fagnou, *J. Am. Chem. Soc.*, 2006, **128**, 16496; (*b*) M. Lafrance, D. Lapointe and K. Fagnou, *Tetrahedron*, 2008, **64**, 6015; (*c*) S. Potavathri, K. C. Pereira, S. I. Gorelsky, A. Pike, A. P. LeBris and B. DeBoef, *J. Am. Chem. Soc.*, 2010, **132**, 14676.

13 In all cases, an appreciable amount of the C3 products (3–8%) was formed.

14 Ratio was determined by ^{1}H NMR spectroscopy.

15 The reaction with toluene produced a 2 : 1 mixture of the inseparable *meta*/*para* isomers in a 77% combined yield.

16 Unoptimized conditions.