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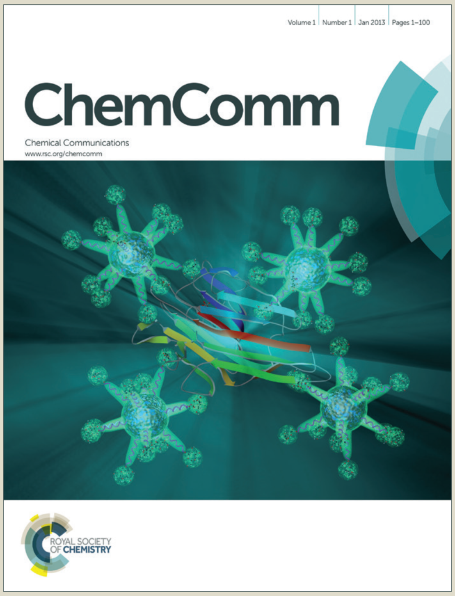

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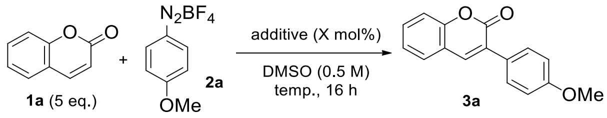
Metal-free C(3)-H arylation of coumarins promoted by catalytic amounts of 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin

Masahiro Kojima,[a] Kounosuke Oisaki*[a] and Motomu Kanai*[a,b]

The metal-free C-H arylation of coumarins was achieved in the presence of catalytic amounts of 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin. This mild and environmentally friendly Meerwein arylation provided facile access to a broad variety of 3-arylcoumarins in synthetically useful yields.

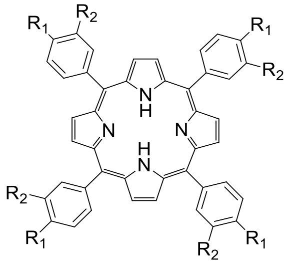
Coumarins represent a highly desirable structural motif in medicinal chemistry, chemical biology, and materials chemistry.[1-3] For example, 3-arylcoumarins have recently been reported to act as monoamine oxidase B (MAO-B) inhibitors,[1] which has important implications for the design of new drugs against Parkinson's and Alzheimer's disease. Coumarin derivatives also play a crucial role in chemical biology, as their fluorescent properties under physiological conditions can be controlled.[2] Coumarin-based dyes on the other hand are employed in artificial light-harvesting materials and act as dopants in organic light-emitting diodes.[3] Therefore, a new synthetic method allowing for effective diversification of the coumarin motif would potentially contribute to various fields of chemical science. The direct catalytic C-H bond functionalization of coumarins presents a facile, mild, atom efficient, and environmentally friendly option to extend existing coumarin libraries. And indeed, palladium-catalyzed C(3)-H and C(4)-H arylations have been reported to afford a variety of 3- and 4-arylcoumarins, respectively.[4] However, this synthetic approach is severely constrained by high temperatures, the need of stoichiometric amounts of metal oxidants, and its limited functional group tolerance. Another classical method for the direct C(3)-H arylation of coumarins is the Meerwein arylation,[5] but especially the copper-mediated Meerwein arylation of coumarins suffers from low to moderate yields.[6] Herein, we would like to report a porphyrin-mediated Meerwein C(3)-H arylation of coumarins in the absence of any metals.

Table 1 Optimization of the reaction conditions



Entry	Additive (X mol%)	Temperature (°C)	Yield (%)[a]
1	**4a** (5)	rt	0
2	**4b** (5)	rt	0
3	**4c** (5)	rt	17
4	**4d** (5)	rt	0
5	**4e** (5)	rt	24
6	**4f** (5)	rt	20
7[b]	**4e** (5)	rt	26
8	**4e** (10)	rt	31
9	**4e** (20)	rt	29
10	**4e** (10)	40	68 (63)[c]
11	none	40	0
12[d]	Eosin Y (1)	rt	8
13	Ascorbic acid (10)	rt	0
14	KI (10)	rt	15
15	Benzoyl peroxide (2)	rt	0
16	PhNEt$_2$ (10)	rt	0

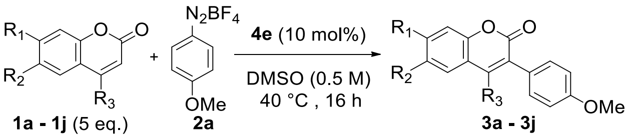
[a] Yields were determined by ^{1}H NMR. [b] In the dark. [c] Isolated yield.
[d] Exposed to visible light irradiation.

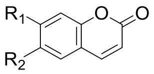
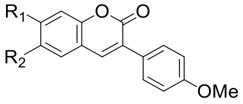
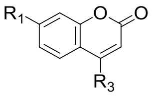
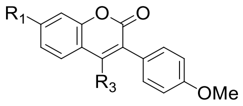


4a: R$_1$ = R$_2$ = H
4b: R$_1$ = OMe, R$_2$ = H
4c: R$_1$ = NH$_2$, R$_2$ = H
4d: R$_1$ = NMe$_2$, R$_2$ = H
4e: R$_1$ = NEt$_2$, R$_2$ = H
4f: R$_1$ = NH$_2$, R$_2$ = OMe

In 2012, König disclosed an Eosin Y-mediated Meerwein arylation under exposure to photoirradiation (visible light),[7a] and the observed mild reaction conditions, as well as the absence of potentially environmentally harmful metal catalysts, renders this metal-free reaction protocols particularly attractive. König's seminal work was soon followed by several reports on metal-free Meerwein arylations of (hetero)arenes,[7a] alkenes,[7f] alkynes,[7b,7c] and isonitriles.[7h] On the other hand, several catalytic and/or stoichiometric transition metal-free promoters, such as organic dyes,[7] TEMPONa,[8] iodide,[9] ascorbic acid,[10] benzoyl peroxide,[11] bases,[12] or methanol[13] were identified to mediate Meerwein-type arylations. However, to the best of our knowledge, none of these metal-free arylation methods has so far been applied to the C-H arylation of coumarins.[14]

Table 2 Scope of coumarin derivatives



Entry	Coumarin (2)	Product (3): Yield
		
1	**1a**: R_1 = H, R_2 = H	**3a**: 63%
2	**1b**: R_1 = H, R_2 = Me	**3b**: 61%
3	**1c**: R_1 = OMe, R_2 = H	**3c**: 73%
4	**1d**: R_1 = OEt, R_2 = H	**3d**: 78%
5	**1e**: R_1 = OH, R_2 = H	**3e**: 66%
6	**1f**: R_1 = NEt$_2$, R_2 = H	**3f**: 70%
7	**1g:** R_1 = H, R_2 = NO$_2$	**3g**: 36%
8[a]	**1h:** R_1 = H, R_2 = NHPiv	**3h**: 60%
		
9	**1i**: R_1 = NEt$_2$, R_3 = Me	**3i**: 63%
10	**1j**: R_1 = H, R_3 = OH	**3j**: 71%

[a] 2.5 equiv. of **1h** were used.

Our initial hypothesis was based on the idea that organic electron mediators that are chemically more stable than Eosin Y should enable the metal-free C-H arylation of coumarins. A good example for such stable mediators is porphyrins, which have an established track record as robust electron mediators in artificial photosynthetic systems.[15] The beneficial electron-donating ability of metal-free porphyrins in combination with the advantageous electron-accepting ability of their radical cations, formed by one-electron oxidation, should render these compounds ideal catalyst candidates for synthetic transformations involving redox processes.[16]

Initially, we investigated catalytic amounts of 5,10,15,20-tetrakisphenylporphyrins **4a-f**, in order to assess their potential to promote the C(3)-H arylation of coumarins with 4-methoxybenzenediazonium tetrafluoroborate (**2a**; entries 1-6; Table 1). Using 5,10,15,20-tetrakis(4-aminophenyl)porphyrin (**4c**) afforded the targeted coumarin **3a** in 17% yield (entry 3; Table 1). Although **4d** did not promote the reaction presumably due to its very low solubility,[17] the highest yield for **3a** was obtained from **4e** (24%, entry 5; Table 1), whereby the presence or absence of light did not affect the yield significantly, suggesting a thermal reaction pathway (entry 7; Table 1). Optimal reaction conditions were established for 10 mol% of **4e** (entries 5, 8, 9; Table 1) and 40 °C, which furnished **3a** in 63% yield (entry 10; Table 1). The reaction did not proceed in the absence of **4e** (entry 11; Table 1), and previously-reported promoters provided **3a** in lower yield (0-15%, entries 12-15; Table 1). These observations suggest that **4e** is the most effective organic promoter for the Meerwein-type C-H arylation of coumarins,[18,19] whereby the *N,N*-diethylaniline moiety alone is unable to afford **3a** (entry 16; Table 1), implying that the presence of the porphyrin skeleton is indispensable.

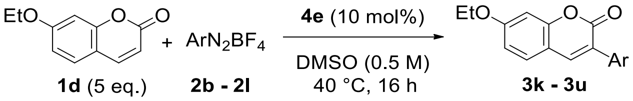
Subsequently, the optimized reaction conditions were used to evaluate the scope with respect to the coumarin derivatives (Table 2). Coumarins with electron-donating groups (*e.g.* Me, OMe, OEt, OH, or NEt$_2$) afforded **3b-f** in good yield (61-78%, entries 2-6; Table 2). Electron-deficient 6-nitrocoumarin (**1g**), as well as amide substituted coumarin **1h** furnished the corresponding target compounds in 36 and 60% yield, respectively (entries 7, 8; Table 2), and it should be noted that the functional groups of **1g** and **1h** were not compatible with oxidative Heck-type C(3)-H arylation conditions.[4] C(4)-substituted coumarins **1i** and **1j** are also good substrates (63-71%, entries 9, 10; Table 2), despite their intrinsically high steric demand.

The scope of this reaction with respect to the aryldiazonium tetrafluoroborates is summarized in Table 3. Unsubstituted phenyldiazonium tetrafluoroborate **2b**, as well as diazonium tetrafluoroborate **2c** with an electron-donating methyl substituent, afforded the corresponding coupling products in good yield (70-72%, entry 1, 2; Table 3). Diazonium tetrafluoroborates with electron-withdrawing halogen, ester, trifluoromethyl, or nitro substituents afforded comparable yields (45-71%, entries 4-9; Table 3). Especially the high tolerance towards bromo- and iodo-substituents should be highlighted here, as they were not tolerant in Heck-type reactions and they may be beneficial for further derivatizations. Marginally lower yields were obtained from aryl diazonium tetrafluoroborates with substituents at *ortho*- or *meta*-position (53-59%, entries 10, 11; Table 3). These results corroborate the high versatility of the present C-C bond formation reactions, especially compared to the previously reported Heck-[4] or Meerwein-type C-H arylations of coumarins.[5]

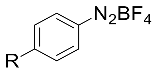
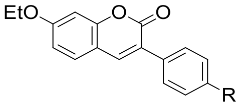
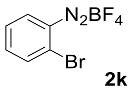
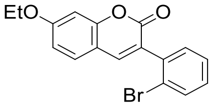
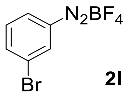
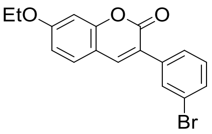
Preliminary mechanistic investigations for this porphyrin-mediated transformation supported the presence of the aryl diazonium-derived aryl radical intermediates and the coumarin-derived benzyl radical intermediates.[20] Based on these observations, a working hypothesis for the reaction mechanism is postulated in Scheme 1. One electron reduction of aryl diazonium tetrafluoroborate with **4e** affords aryl radical **5** (Ar$^{\bullet}$) and nitrogen gas. Addition of the aryl radical to coumarin (**1a**) furnishes a benzyl radical intermediate **6**, which is oxidized either by **4e** radical cation or by another aryl diazonium tetrafluoroborate. The moderate yield produced for nitro-substituted substrates (36%, entry 7; Table 2 and 45%, entry 9; Table 3) could be rationalized by considering that the electron-withdrawing functionality retards oxidation of **6** by **4e**$^{\bullet+}$. Regeneration of **4e** or the alternative radical chain process promotes the reactions until aryl diazonium tetrafluoroborates are consumed.

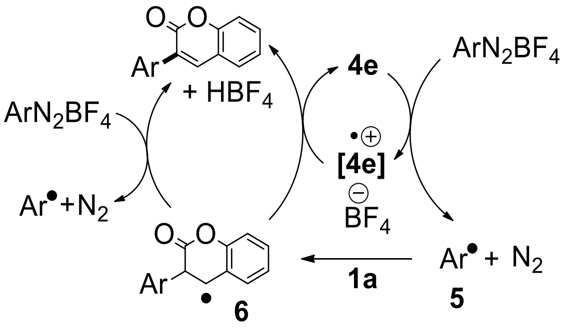
In conclusion, we established a metal-free Meerwein-type C(3)-H arylation of coumarins by using catalytic amounts of 5,10,15,20-tetrakis(4-diethylaminophenyl)porphyrin (**4e**). This method is characterized by a high functional group tolerance and mild reaction conditions, while providing versatile access to a wide variety of 3-arylcoumarins in synthetically useful yields, thus rendering this method superior to previously reported Meerwein-type arylations. Further studies on the exact reaction mechanism as well as on applications involving other types of Meerwein arylations are currently in progress in our laboratory and will be reported in due course.

Table 3 Scope of aryl diazonium tetrafluoroborates



1d (5 eq.) **2b - 2l** **3k - 3u**

Entry	Aryl diazonium tetrafluoroborate (**1**)	Product (**3**): Yield
		
1	**2b**: R = H	**3k**: 70%
2	**2c**: R = Me	**3l**: 72%
3	**2d**: R = F	**3m**: 67%
4	**2e**: R = Cl	**3n**: 65%
5	**2f**: R = Br	**3o**: 71%
6	**2g**: R = I	**3p**: 56%
7	**2h:** R = CO_2Et	**3q**: 60%
8	**2i:** R = CF_3	**3r**: 67%
9	**2j:** R = NO_2	**3s**: 45%
10	 **2k**	 **3t**: 53%
11	 **2l**	 **3u**: 59%



Scheme 1 Plausible reaction mechanisms

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Notes and references

[a]Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. [b]JST-ERATO Kanai Life Science Catalysis Project, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: oisaki@mol.f.u-tokyo.ac.jp; kanai@mol.f.u-tokyo.ac.jp

† Electronic Supplementary Information (ESI) available: Experimental details including procedures, syntheses, and the characterization of new products, as well as preliminary mechanistic studies. See DOI: 10.1039/c000000x/

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17 Solubility of **4e** is more than 10 times greater than that of **4d** according to the solubility evaluation (SI, section 3c). It is also reported that **4d** is not soluble in common organic solvents. For details, see: N. Datta-Gupta, T. J. Bardos, *J. Heterocyclic Chem.*, 1966, **3**, 495.

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19 An ICP analysis showed unambiguously that the amount of metal contamination (Ti, Fe, Cu, Pd) in **4e** was below the detection limit: Ti < 2.6 ppb, Fe < 3.5 ppb, Cu < 1.2 ppb, Pd < 4.5 ppb.

20 An aryl radical-trap experiment (SI, section 3a) and a radical clock experiment (SI, section 3b) suggested the involvement of aryl and benzyl radical intermediates, respectively.