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Discovery of a Full-Color-Tunable Fluorescent Core Framework through Direct C–H (Hetero)arylation of N-Heterocycles

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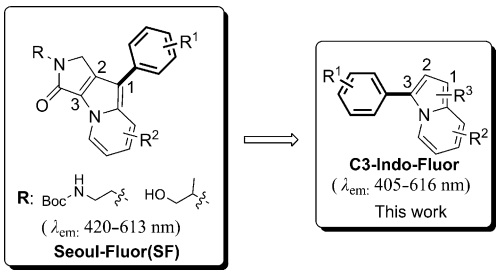
The importance of fluorescent molecules has been well documented in various fields of research.[1] The rational discovery of new fluorescent molecular frameworks has recently been the subject of growing interest.[2] The π-conjugated heteroaryl–(hetero)aryl motifs have been frequently chosen as the fluorescent core objects. Conventional routes to these structural units usually involve multistep condensation reactions, and/or traditional transition-metal-catalyzed Ar–X/Ar–M coupling reactions. These tiresome multistep syntheses and prefunctionalizations may limit the rapid assessment of molecular diversity to a certain extent. In particular, some important types of heteroaryl organometallic compounds and heteroaryl halides or pseudohalides are not easily accessible and may even be inadequately stable to participate in the coupling process, which has been recognized as one of the potential bottlenecks for the discovery of small organic fluorescent core skeletons. Thus, transition-metal-catalyzed direct C–H (hetero)arylation of N-heteroarenes would be one of the most ideal strategies to solve these problems. The tools can greatly streamline multistep chemical processes with a relatively high level of functional-group compatibility, and thus allow prompt and modular synthesis to combinatorial libraries of core skeletons.

Despite significant progress in developing small molecule-based fluorophores, it is still challenging to design novel color-tunable fluorescence libraries that span the whole visible (especially red) region, particularly with large Stokes shifts. Indolizine derivatives are an important type of N-fused heterocycles broadly found in biologically important natural products, synthetic pharmaceuticals, and molecular materials.[3] Recently, Park and co-workers developed a full-color-tunable fluorescent core skeleton named Seoul-Fluor, 1,2-dihydropyrrolo[3,4-β]indolizin-3-one, through an intramolecular 1,3-dipolar cycloaddition of an olefin with an azomethine ylide. The emission wavelength tenability covering the full color range (420–613 nm) was achieved by fine tuning of the phenyl moiety at the C1 position of the pyrrole



Scheme 1. Full-color-tunable fluorescent core skeletons based on indolizines.

ring and the R^2 group of the pyridine ring (Scheme 1).[4] During our investigation of the cross-coupling of indolizine-2-carboxylate **1** with chlorobenzene **2a**, we found that the aryl-substituted indolizine at the C3 position of the pyrrole ring (**3a**) exhibited significant photonic luminescence in the solid state (see reaction (1), below). Following our interest in C–H functionalization of N-heteroarenes to construct fluorescent core skeletons,[5] herein we explain how this concise strategy helped us to achieve the goal of full-color tunability of emission wavelength of the indolizine core, named C3-Indo-Fluor, by modifying the aromatic group at the C3 position of the pyrrole ring in combination with the R^2 substituent of the pyridine ring.

In spite of an increasing number of reports, the use of transition-metal-catalyzed C–H (hetero)arylation of N-heteroarenes to discover full-color-tunable fluorescent core frameworks still remains less explored. Given that (hetero)-aryl chlorides are both more readily available and less expensive than the corresponding iodides and bromides, the application of aryl chlorides as a coupling partner would provide us abundant opportunities in the combinatorial synthesis of a diversity-oriented fluorescence library. However, in the past several years, (hetero)aryl iodides and bromides represent the most widely used coupling partners because aryl chlorides are much less reactive.[6] Our investigation started with the coupling of methyl indolizine-2-carboxylate **1** with chlorobenzene **2a** as a model reaction to optimize the reaction conditions (reaction (1); also see the Supporting Information, Table S1). After screening several parameters (e.g., base, solvent, ligand, time, and temperature, etc.),

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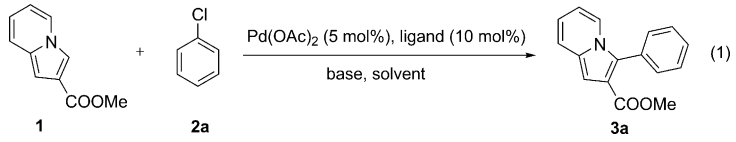
we found that the best result was obtained in the presence of a catalyst system comprising three equivalents of Cs_2CO_3, $Pd(OAc)_2$ (5 mol%) and $P(Cy)_3{\cdot}HBF_4$ (Cy = cyclohexyl) (10 mol%) in toluene at 130°C for 24 h, affording **3a** in 95% yield.

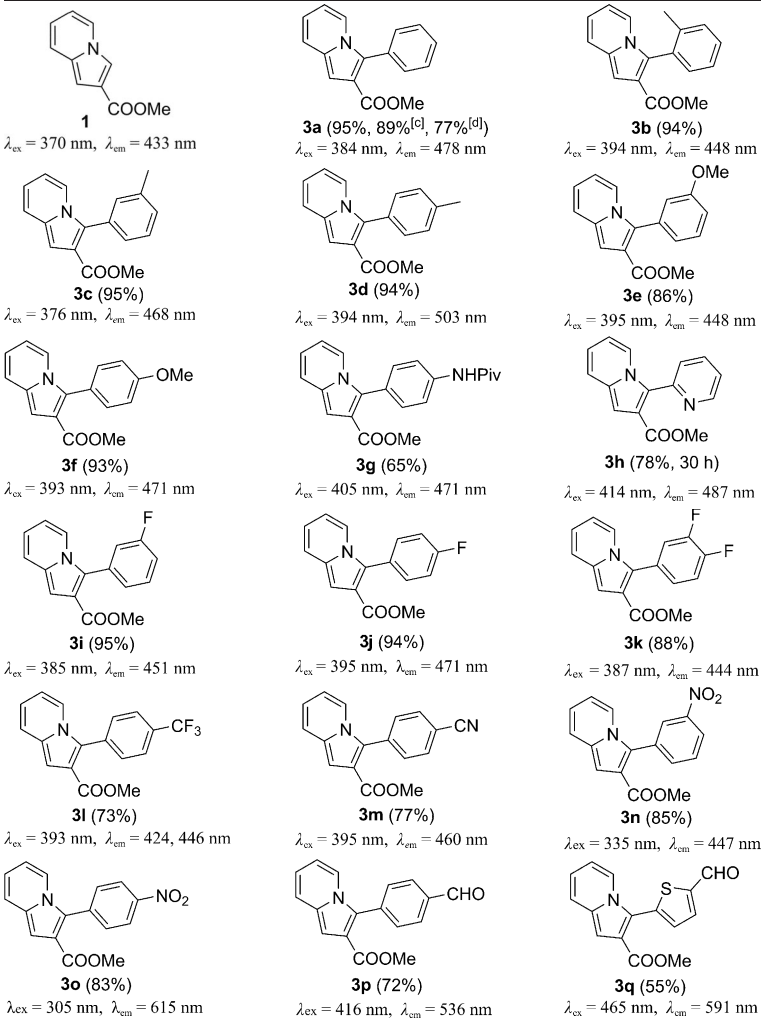


To gain insight into the relationship of structure–photophysical property, we tried to assemble a combinatorial library of 3-aryl-substituted indolizines. Fortunately, our catalytic system was compatible with both a variety of indolizines and (hetero)aryl chlorides, providing a great opportunity for us to conveniently introduce structurally diverse aryl substituents at the C3 position of the pyrrole ring.

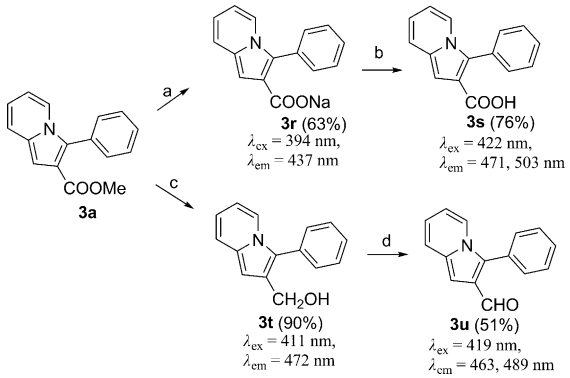
Owing to the easy and high-yielding synthesis,[7] methyl indolizine-2-carboxylate **1** was first chosen to investigate the effect of the R^1 group on the phenyl moiety on the fluorescence properties. We were pleased to find that our catalyst system was suitable for a wide range of (hetero)aryl chlorides. As shown in Table 1, whether the aryl chlorides were electron-rich, electron-poor, or sterically hindered, all of them afforded good yields. It is important to stress that the reaction conditions were compatible with the presence of crucial functional groups such as ester, amide, cyano, aldehyde, and nitro groups, which may be subjected to further synthetic transformations. For example, methyl 3-phenylindolizine-2-carboxylate (**3a**) was easily transformed into the corresponding aldehyde, hydroxyl, carboxylic acid, and sodium carboxylate derivatives (**3r**, **3s**, **3t**, and **3u**), therefore improving water solubility of the core skeleton (Scheme 2). The catalytic products **3p** and **3q** bearing the aldehyde group underwent the condensation with malononitrile to yield the corresponding dicyanovinyl derivatives **3v** and **3w**, respectively (Scheme 3).[8]

The design and synthesis of small organic molecules exhibiting highly efficient solid-state luminescence is of great importance for the development of optoelectronic devices such as OLEDs and solid-state organic lasers.[9] However, it is a challenging project, because the molecular aggregation of chromophores typically results in the quenching of luminescence in the solid state. Table 1 outlines the largest absorption maxima and solid state emission wavelengths of the new fluorescent compounds. With the R^3 as a carboxylate group, it is unprecedented to achieve a full-visible-color emission wavelength in the solid state in the range from blue to red (λ_{em}: 444–615 nm) by a simple change of substituents at one variation point of the single fluorophore core skeleton (Figure 1a). The emission wavelengths were proven to be heavily dependent on the substitutents at the C3 position. Both the electronic character and the substituent position of the R^1 group on the phenyl ring are important in determining the photophysical properties of C3-Indo-Fluor. A positional switch of the R^1 substituent from *ortho* to *meta* and *para* resulted in a bathochromic shift of the emission wavelength when R^1 is methyl, methoxy, fluoro, and nitro. For example, the substituent change of the nitro group from the *meta* to the *para*-position on the phenyl moiety gave rise

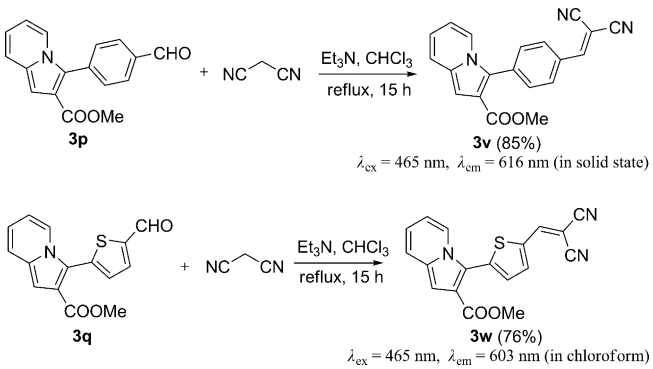
Table 1. Catalytic C-arylation of **1** with various chlorobenzenes and the corresponding photophysical data of catalytic product in the solid state.[a,b]



[a] Reactions were carried out using $Pd(OAc)_2$ (5 mol%), $P(Cy)_3{\cdot}HBF_4$ (Cy = cyclohexyl) (10 mol%), Cs_2CO_3 (3 equiv), methyl indolizine-2-carboxylate **1** (0.5 mmol) and chlorobenzene (1 mmol) in a 0.5 M toluene for 24 h at 130°C. [b] Isolated product yield. [c] 2 mol% Catalyst loading. [d] 1 mol% Catalyst loading.



Scheme 2. Modification of **3a**. Reaction conditions: a) 10% NaOH solution, 50°C; b) conc. HCl; c) DIBAL-H, CH_2Cl_2, −78°C, 0.5 h; d) MnO_2, CH_2Cl_2, 50°C, 4 h.



Scheme 3. Modification of **3p** and **3q**.

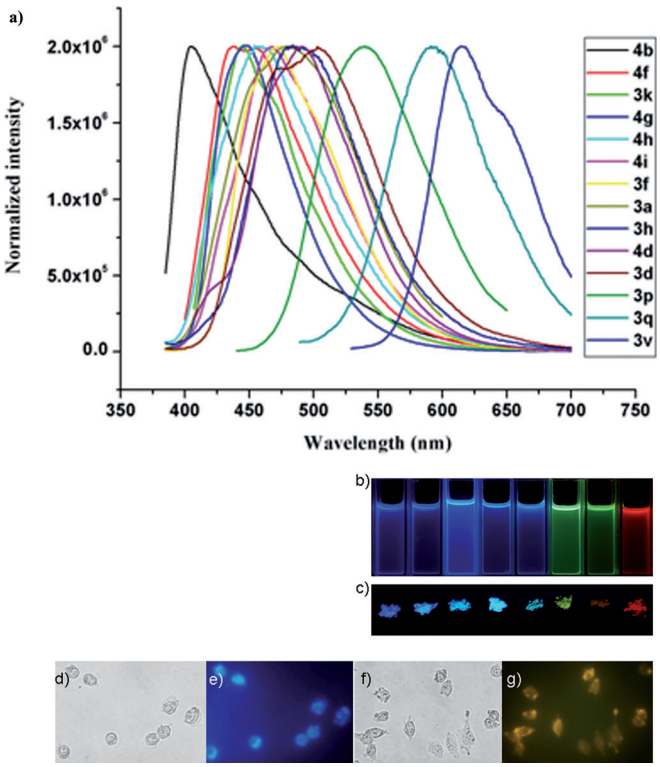


Figure 1. a) Emission spectra of selected indolizines in the solid state. Excitation and emission slit widths were 1.0 nm and 1.0 nm, respectively. b) Fluorescence images of indolizines in DMF or $CHCl_3$, irradiated at 365 nm. From left to right: **1**, **3k**, **3m**, **3a**, **3d**, **3p**, **3q**, and **3w** (**1**, **3k**, **3a**, and **3d** in DMF; **3m**, **3p**, **3q**, and **3w** in $CHCl_3$). c) Fluorescence images of indolizines (powder, λ_{ex} = 365 nm). From left to right: **1**, **3k**, **3m**, **3a**, **3f**, **3p**, **3q**, and **3v**. d) Bright-field transmission image of A375 cells incubated with **3p** (20 μM). e) Fluorescence image of A375 cells incubated with **3p** (20 μM). f) Bright-field transmission image of A375 cells incubated with **3w** (20 μM). g) Fluorescence image of A375 cells incubated with **3w** (20 μM).

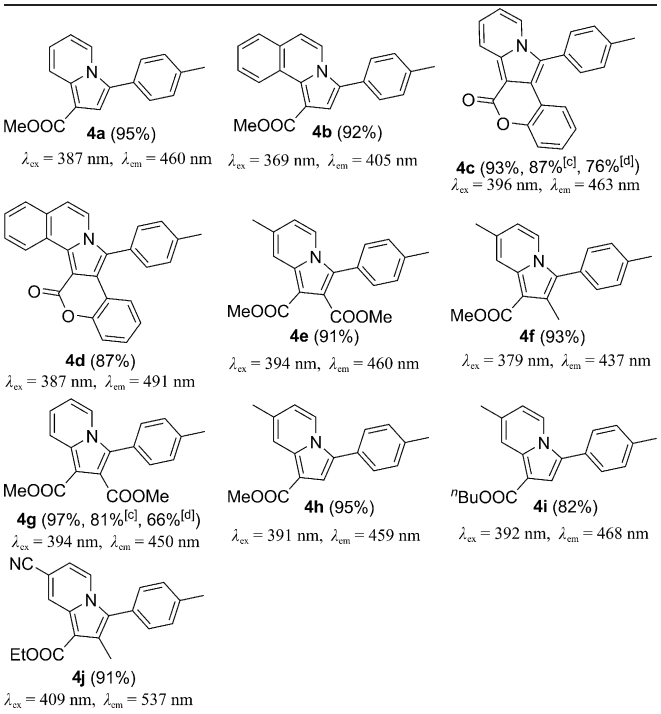
to a 168 nm bathochromic shift (Table 1, **3n** and **3o**). Notably, most of fluorophores exhibited a large Stokes shift in the solid state, which is an important factor to suppress the interference arising from background fluorescence. The condensation product **3v** starting from **3p** showed the longest emission wavelength (λ_{em} = 616 nm) in the solid state (Figure 1c). Whereas the fluorophore **3w** was hardly fluorescent in the solid state, a significant red fluorescence emission was observed with an emission wavelength of 603 nm in chloroform solution (Figure 1b).

Subsequently, we applied the current protocol to the coupling of a wide range of indolizines with 4-chlorotoluene to synthesize 3-*para*-tolyl-substituted indolizines in excellent yields (Table 2). With **4a**–**4j** in hand, a preliminary survey of photophysical properties was performed; the photophysical data of which is summarized in Table 2. The largest absorption maxima of these products appeared in the range of 369 to 409 nm, and the corresponding solid state emission wavelengths covered the range of 405–537 nm. Interestingly, when the indolizine **4a** was fused by a phenyl ring to form the benzoindolizine **4b**, in spite of a larger π-conjugated system, its emission color (λ_{em}) was greatly hypsochromically shifted from 460 to 405 nm rather than the bathochromic shift. The introduction of an electron-withdrawing group (EWG) such as the cyano group at the C7 position of the pyridine ring triggered a notable bathochromic shift, and displayed a large Stokes shift (128 nm; **4j**).

Molecular fluorescent-imaging techniques are helpful to understand biological processes at the molecular level, and are particularly useful for the early detection of diseases. Thus, the development of new fluorescent bioimaging probes still remains an attractive and promising goal. To further explore the practical application of new fluorescent molecules, the human malignant melanoma A375 cells were incubated with **3p** and **3w** in a physiological saline solution containing 1% DMSO for 1 h at 37°C after being cultured in DMEM Dulbecco's mimimum essential medium (containing 10% fetal bovine serum (FBS), 100 IU mL^{-1} penicillin, and 100 mg mL^{-1} streptomycin). As shown in Figure 1d–1g, **3p** and **3w** successfully marked A375 cells, and preferentially accumulated in the cytoplasm, suggesting that this class of membrane-permeable fluorophores (C3-Indo-Fluor) could be potentially useful reagents for biological imaging.

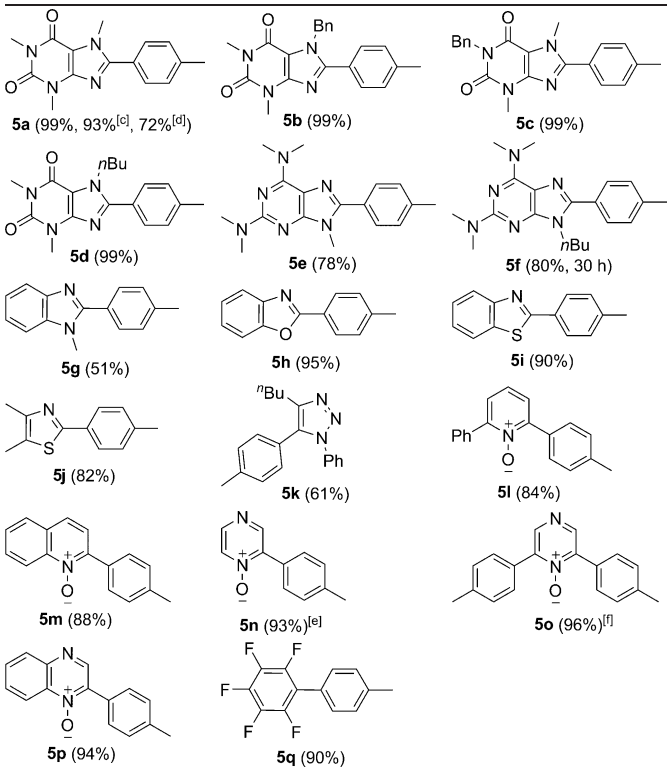
Finally, it was gratifying to find that the current catalytic system was amenable to the arylation of a variety of electron-rich heteroarenes as well as electron-deficient (hetero)-

Table 2. Catalytic C-arylation of various indolizines with 4-chlorotoluene and the corresponding photophysical data of catalytic product in the solid state.[a,b]



[a] Reactions were carried out using $Pd(OAc)_2$ (5 mol%), $P(Cy)_3{\cdot}HBF_4$ (Cy = cyclohexyl) (10 mol%), Cs_2CO_3 (3 equiv), indolizine (0.5 mmol) and 4-chlorotoluene (1 mmol) in a 0.5 M toluene for 24 h at 130 °C. [b] Isolated product yield. [c] 2 mol% Catalyst loading. [d] 1 mol% Catalyst loading.

Table 3. Catalytic C-arylation of (hetero)arenes with 4-chlorotoluene.[a,b]



[a] Reactions were carried out using $Pd(OAc)_2$ (5 mol%), $P(Cy)_3{\cdot}HBF_4$ (Cy = cyclohexyl) (10 mol%), Cs_2CO_3 (3 equiv), (hetero)arene (0.5 mmol) and 4-chlorotoluene (1 mmol) in a 0.5 M toluene for 24 h at 130 °C. [b] Isolated product yield. [c] 2 mol% Catalyst loading. [d] 1 mol% Catalyst loading. [e] Two equivalents of (hetero)arene were added. [f] Four equivalents of 4-chlorotoluene were added.

arenes (e.g., xanthines (caffeine, theophyline and theobromine), purines, imidazoles, thiazoles, oxazoles, 1,2,3-triazoles, and N-heteroarene N-oxides, etc.) in moderate to excellent yields (Table 3, **5a**–**5p**). In addition, perfluoroaromatics could also couple with aryl chloride in excellent yield (Table 3, **5q**). The (hetero)aryl-aryl motifs are prevalent substructures of many natural products, pharmaceuticals, fluorescent materials, and other advanced materials. For instance, 8-aryl or heteroaryl-substituted xanthines are highly potent and selective antagonists for human A_{2B} adenosine receptors and luminescent frameworks.[5,10,11] In our previous report, the compound **5a** features significant fluorescent emission and has proven to be a potentially useful bioimaging fluorescence probe.[5] Further investigations are underway to set up full-color-tunable fluorescence libraries through the direct C–H functionalization of these N-heterocycles. Although not yet investigated in detail, the C–H (hetero)arylation of N-heteroarenes with aryl chlorides could occur in good to excellent yields with a low palladium(II) loading of 1–2 mol% (Table 1, **3a**; Table 2, **4c** and **4g**; and Table 3, **5a**).

In conclusion, we have established a method for the direct C–H arylation of a wide range of heteroarenes as well as perfluoroaromatics with a broad spectrum of (hetero)aryl chlorides. Taking indolizines as a representative example, we have highlighted that the metal-catalytic direct C–H arylation of N-heterocycles can serve as a highly efficient and easily tunable synthetic tool for the discovery of a structurally diverse library of organic fluorophores. It is notable that a full coverage of solid state emission wavelengths in the visible (especially red) region (405–616 nm) with large Stokes shifts in C3-Indo-Fluor may be straightforwardly and succinctly achieved by the direct arylation of indolizines at the C3 position of the pyrrole ring. The fluorophores have successfully marked A375 cells, exhibiting their future potential as useful bioimaging fluorescence probes. Further screening of other types of fluorescent core frameworks and their application in biological imaging are currently in progress.

Acknowledgements

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Keywords: C–H arylation · fluorescent probes · full-color-tunable emission · indolizines · N-heteroarenes · palladium

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