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A $Sc(OTf)_3$-catalyzed cascade reaction of *o*-aminoacetophenone with methanamine: construction of dibenzo[*b*,*h*][1,6]naphthyridine derivatives†

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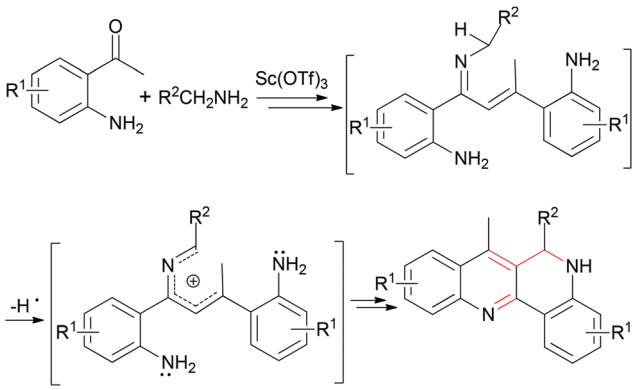
An unexpected $Sc(OTf)_3$-catalyzed and air-mediated cascade reaction of *o*-aminoacetophenones with methanamines was discovered as an efficient synthetic approach to a novel class of fluorescent fused-four-ring dibenzo[*b*,*h*][1,6]naphthyridine derivatives. Two possible mechanisms of the reaction were proposed. The photophysical properties of the dibenzo[*b*,*h*][1,6]naphthyridine **1a** were initially considered.

Introduction

A cascade reaction,[1] in which the reactive intermediate from one step directly undergoes further transformations, is very important in organic synthesis, because such sequential processes can not only rapidly build up complex molecules, but also efficiently enhance the chemo-, regio-, and diastereoselectivity for the overall transformation. It is one of the most practiced methods for the preparation of complex heterocyclic compounds from commercially available starting materials.[2]

The naphthyridine moiety is an important building block in various natural products. It has exhibited a broad range of biological activities, medical applications and also fluorescence activities. For example, 1,6-naphthyridine was reported to be a promising scaffold with drug-like properties;[3] 1,8-naphthyridine derivatives were found as a new class of chemotherapeutic agents[4] and also showed anti-aggressive and potent anti-inflammatory activities;[5] a naphthyridine carboxamide provided evidence for discordant resistance between mechanistically identical inhibitors of HIV-1 integrase.[6] Furthermore, fluorescent naphthyridine derivatives can be used as luminescence materials in molecular recognition[7] and fluorescence detection.[8] However, except for a few reports,[9] in which naphthyridine derivatives were synthesized through one-pot multicomponent processes, multi-step synthesis procedures were required in most cases.[3–8]



Scheme 1 An unexpected cascade reaction catalyzed by $Sc(OTf)_3$.

Rare earth metal Lewis acids have been widely utilized in the past few decades.[10] Our group has paid special attention to multicomponent condensation reactions (MCR) catalyzed by rare earth metal Lewis acids as well.[11] Herein, we report an $Sc(OTf)_3$-catalyzed unexpected cascade reaction of *o*-aminoacetophenones with methanamines (Scheme 1). In this reaction, two C=C bonds, one C–C bond and one C–N bond were formed with high selectivity to generate a novel series of fluorescent fused-four-ring naphthyridine derivatives. Besides, an air-mediated C–H activation occurred in the reaction, which was rarely reported before.[12]

Results and discussion

Recently, Wang and co-workers[13] reported efficient methods of synthesizing 2-phenylquinazolines (Scheme 2). However, the

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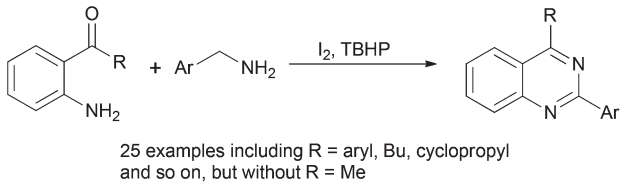
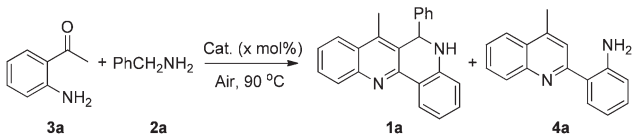
†Electronic supplementary information (ESI) available: Copies of NMR spectral data and crystallographic information in CIF format for compounds **1a**. CCDC 796953. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob02220c

‡These authors contributed equally to this work.



Scheme 2 The previous reported reactions of 2-aminobenzoketones with benzylic amines.

Table 1 The optimization of the cascade reaction[a]



Entry	Cat.	*x*	Solvent	Yield of **1a**[b] (%)	Yield of **4a**[c] (%)
1	None	—	Neat	0	0
2	$AlCl_3$	10	Neat	12	Trace
3	$FeCl_3$	10	Neat	4	Trace
4	AgOTf	10	Neat	7	30
5	$Bi(OTf)_3$	10	Neat	18	24
6	$Pd(OAc)_2$	10	Neat	Trace	Trace
7	$Yb(OTf)_3$	10	Neat	24	23
8	$Sc(OTf)_3$	10	Neat	72	28
9	$Sc(OTf)_3$	5	Neat	70	20
10	$Sc(OTf)_3$	2	Neat	56	17
11[d]	$Sc(OTf)_3$	5	Neat	43	15
12[e]	$Sc(OTf)_3$	5	Neat	33	22
13	$Sc(OTf)_3$	5	Toluene	75	16
14	$Sc(OTf)_3$	5	Dioxane	52	20
15	$Sc(OTf)_3$	5	DCE	28	30
16[f]	$Sc(OTf)_3$	5	Ethanol	14	18
17[g]	$Sc(OTf)_3$	5	**2a**	Trace	Trace
18[h]	$Sc(OTf)_3$	5	**3a**	68	25

[a] The reactions of *o*-aminoacetophenone **3a** (1.25 mmol) with benzylamine **2a** (0.5 mmol) with 2 mL solvent or no solvent were carried out for 12 h at 90 °C. [b] Isolated yields based on **2a**. [c] Isolated yields based on **3a**. [d] The reaction was performed at 65 °C. [e] The reaction was performed at 110 °C. [f] The reaction was performed at reflux. [g] Excess amount of benzylamine **2a** was used as the solvent. [h] Excess amount of *o*-aminoacetophenone **3a** was used as the solvent.

desired product 4-methyl-2-phenylquinazoline could not be obtained when R (Scheme 2) was the methyl group. A very recent report on similar work by Han and coworkers[14] also did not cover such a case. This inspired our research on why the methyl group was an exception.

Initially, *o*-aminoacetophenone (**3a**) and benzylamine (**2a**) were chosen as model substrates. In the absence of a catalyst, no product was detected (Table 1, entry 1). Then the reaction was performed in the presence of 10 mol% $Sc(OTf)_3$, an unknown compound with strong fluorescence was isolated as the main product. A crystal[15] with green fluorescence was obtained from the evaporation of the solution of the product in CH_2Cl_2–CH_3OH (1/2) through solvent diffusion. X-ray crystal structure analysis revealed that a naphthyridine derivative **1a** bearing a novel fused-four-ring structure was generated (Fig. 1).

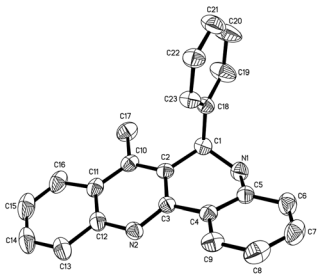


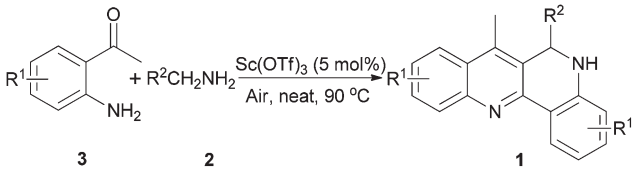
Fig. 1 The molecular structure of compound **1a**.

Further investigations into the reaction were performed. Besides the product **1a**, another compound **4a** was isolated as the main byproduct in most cases. Their yields are presented in Table 1. The reaction could be promoted by a variety of Lewis acids with different efficiencies (Table 1, entries 2–8). However, none of them was better than $Sc(OTf)_3$ which achieved the best result giving the desired product **1a** in 72% yield. Then the optimal loading of $Sc(OTf)_3$ was revealed to be 5 mol% (Table 1, entries 8–10). The best reaction temperature was 90 °C (Table 1, entries 9, 11–12). When toluene was employed as the solvent, the reaction could undergo slightly more smoothly giving **1a** in 75% yield (Table 1, entry 13). The use of other solvents, such as dioxane, 1,2-dichloroethane (DCE) or more starting materials **3a**, **2a** did not improve the yield (Table 1, entries 14–18). It is worth mentioning that when the reaction was conducted in ethanol, neither **1a** nor the byproduct **4a** was obtained in high yield, which may be caused by the ligand effect that ethanol competed with benzylamine to coordinate to $Sc(OTf)_3$. Considering the economical viability and environmental benefit, in most cases, the reaction was still performed under solvent-free conditions for further investigation.

The substrate scope of the cascade reaction of *o*-aminoacetophenones with methanamines was then explored under the optimal conditions. The isolated yields of the corresponding products **1a–p** are exhibited in Table 2. The reactions of all substituted benzylamines with *o*-aminoacetophenone gave the corresponding products in good yields (Table 2, entries 1–8). Heteroaromatic methanamines were suitable substrates for this reaction as well (Table 2, entries 9 and 10). Notably, aliphatic amines could also react with *o*-aminoacetophenone affording the corresponding products, though the yields were relatively low (Table 2, entries 11–13). Furthermore, substituted *o*-aminoacetophenones were explored. 1-(2-Amino-5-bromophenyl)ethanone could also react with methanamines giving the corresponding products in moderate yields (Table 2, entries 14–16). Unfortunately, *o*-aminoacetophenones bearing electron-donating substituents reacting with benzylamine gave messy mixtures (Table 2, entries 17 and 18).

The mechanism of the cascade reaction was further discussed. Initially, the main byproduct 2-(4-methylquinolin-2-yl)-aniline **4a** was suspected to be a key intermediate of the reac-

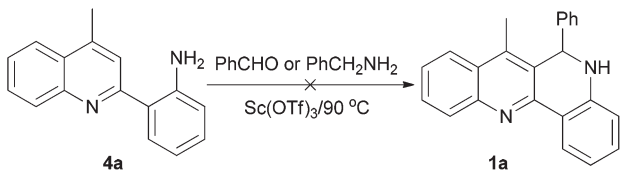
Table 2 The scope of the cascade reaction[a]



3 2 1

Entry	R^1	R^2	Product 1a–p	Yield of 1a–p[b] (%)
1	H	Ph	**1a**	70
2	H	4-$CH_3C_6H_4$	**1b**	78
3	H	4-*t*BuC_6H_4	**1c**	80
4	H	4-ClC_6H_4	**1d**	72
5	H	4-FC_6H_4	**1e**	76
6	H	3-FC_6H_4	**1f**	76
7	H	2-FC_6H_4	**1g**	80
8	H	3,4-F,F-C_6H_3	**1h**	82
9	H	Pyridin-2-yl	**1i**	61
10	H	5-Methyl-thiophen-2-yl	**1j**	81
11[c]	H	CH_3	**1k**	35
12	H	C_3H_7	**1l**	42
13[d]	H	$C_{15}H_{31}$	**1m**	55
14[d]	5-Br	Ph	**1n**	45
15[d]	5-Br	4-ClC_6H_4	**1o**	50
16[d]	5-Br	3,4-F,F-C_6H_3	**1p**	68
17[e]	4,5-OMe,OMe	Ph	—	—
18[e]	4,5-(OCH_2O)	Ph	—	—

[a] Reaction conditions: *o*-aminoacetophenones **3** (1.25 mmol), methanamines **2** (0.5 mmol). [b] Isolated yields based on **2**. [c] Aqueous solution of ethylamine was used. [d] Toluene was used as the solvent. [e] The starting materials were converted to a complex mixture.



4a 1a

Scheme 3 Compound **4a** reacted with benzylamine or benzaldehyde.

tion. Thus the reaction of compound **4a** with benzylamine was conducted in the presence of $Sc(OTf)_3$ at 90 °C. However, the desired product **1a** was not observed. In addition, the isolated **4a** could not react with benzaldehyde *via* cross-dehydrogenative coupling (CDC)[16] under the same conditions (Scheme 3).

On the basis of our results and previous related reports, a proposed mechanism is depicted in Scheme 4.[17] Firstly, imine or enamine **a** was formed through the condensation of **2** and **3**. Then, **a** reacted with *o*-aminoacetophenone **3** through the intermolecular aldol reaction, which led to intermediate **b** by dehydration. This reaction underwent smoothly in the presence of $Sc(OTf)_3$,[18] which could be a very efficient catalyst for aldol condensation. It is worth noting that trace product **1a** was detected when benzylamine was used as the solvent, and the product was afforded in 68% yield when *o*-aminoacetophenone was used as the solvent (Table 1, entries 17 and 18). It could be explained that an excess amount of benzylamine led to much less *o*-aminoacetophenone to react with imine **a**.

Then intermediate **b** was oxidized to **d** by oxygen in air *via* the radical reaction. To support this hypothesis, a typical radical scavenger tetramethylpiperidine *N*-oxide (TEMPO) was added to the reaction of *o*-aminoacetophenone with benzylamine under the optimal conditions, and no trace of the desired product **1a** could be obtained (Scheme 5a). Then, the template reaction was carried out under an oxygen and argon atmosphere, respectively. Trace product **1a** was found under argon atmosphere (Scheme 5b), which clearly revealed that the oxygen plays an important role in the reaction. In the case of pure oxygen, 4-methyl-2-phenylquinazoline **5a** was isolated as the main product (Scheme 5c), which should have been afforded *via* the transformation reported by the previous literature (Scheme 2), and only 22% yield of the desired product **1a** was obtained, revealing that there was a competition between aldol condensation (**a** to **b**) and oxidation (**a** to **i**). This method can be an alternative synthetic method of compound **5**.[19] However, when the reaction was carried out in air, oxidation (**b** to **d**) took place only after the aldol condensation (**a** to **b**) completed.

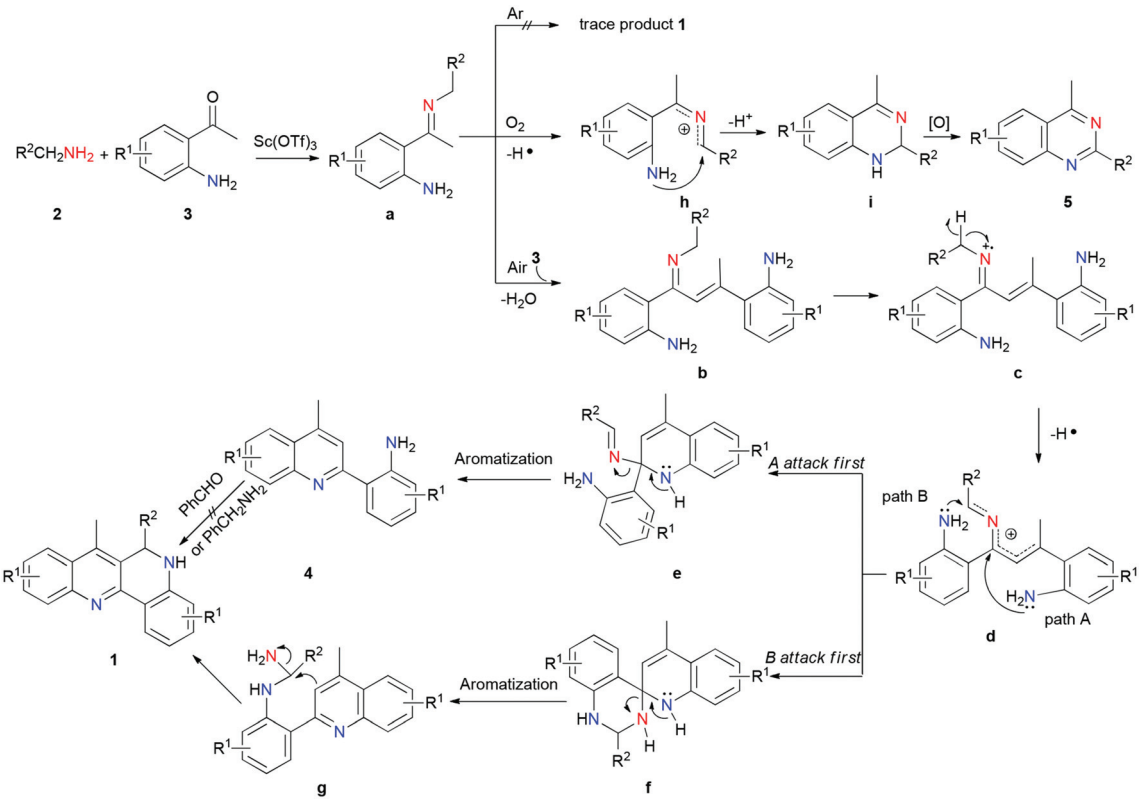
Once intermediate **d** was formed, paths **A** and **B** were in competition. The reaction went to path **A** to afford the main byproduct **4**. When the reaction went to path **B**, a supposed spiro intermediate **f** was generated, and the spiro was then broken down to generate intermediate **g**, which emitted NH_3 and gave the final product **1**.

However, there might be another mechanism (Scheme 6).[17] In the presence of $Sc(OTf)_3$, *o*-aminoacetophenone **3** reacted with aldehyde, which was formed from the corresponding methanamine *via* oxidation, to afford 2,3-dihydroquinolin-4(1*H*)-ones **7**.[20] **7** further reacted with **3** to give the product **1**.

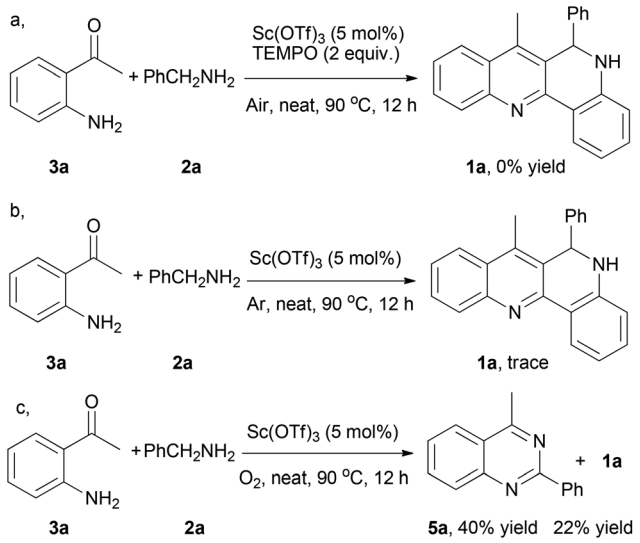
To verify this mechanism, two control experiments were conducted (Scheme 7). First, the benzaldehyde was detected by HPLC in a mixture of benzylamine and $Sc(OTf)_3$ after heating in air for 2 h. Then several aldehydes were chosen to react with *o*-aminoacetophenone **3a**. In the cases of benzaldehyde and 4-chlorobenzaldehyde, **1a** and **1d** were detected as trace products in complex mixtures, respectively. However, in the cases of 4-methylbenzaldehyde and butyraldehyde, the corresponding product **1b** or **1l** was not detected.

Though the second proposed mechanism (Scheme 6) was more concise, several problems existed. First, the reaction of methanamines with *o*-aminoacetophenones giving imines should undergo more smoothly than the transformation of methanamines to aldehydes. Second, only several aldehydes could react with *o*-aminoacetophenone giving the products in very low yields went against with the substrate scope study that almost all the methanamines were suitable substrates for the cascade reaction. On the other hand, the result that a trace of product **1a** was detected under an argon atmosphere was inconsistent with the first proposed mechanism (Scheme 4) as well. Thus, we speculated that both the pathways were possible processes to form the products.

Due to the intermolecular hydrogen bond (N_1–H–N_2, can be seen from supplementary crystallographic data†), the compound **1a** was stable and was not further oxidized in the



Scheme 4 The proposed mechanism of the cascade reaction (some easy steps and the role of $Sc(OTf)_3$ were omitted for clarity).



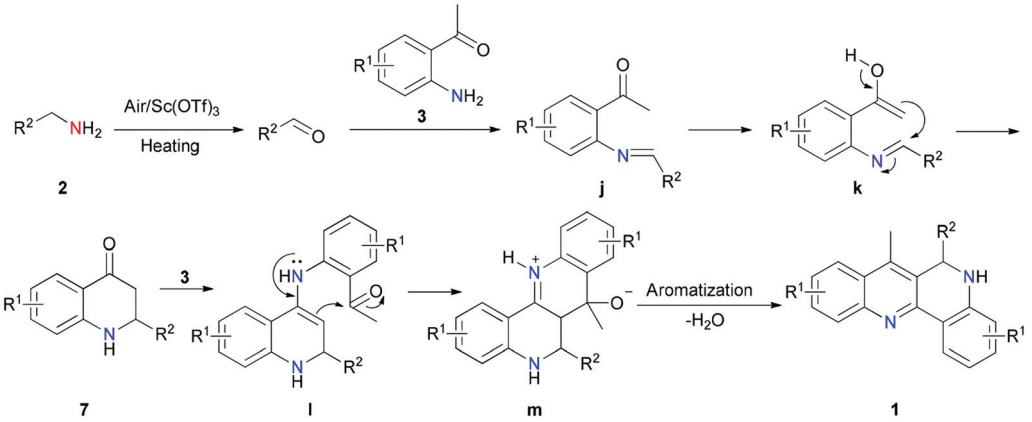
Scheme 5 Several control experiments.

cascade reaction. But in the presence of an excess amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), the isolated compound **1a** could be converted to the highly conjugated compound **6a** in quantitative yield (Scheme 8).

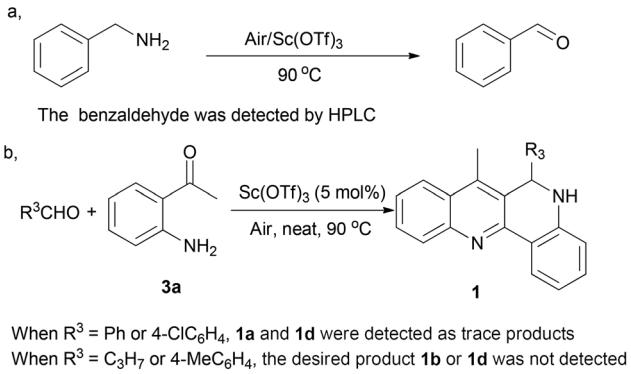
It was observed that the products, dibenzo[*b*,*h*][1,6]-naphthyridine derivatives **1**, showed strong fluorescence, thus we further investigated the photophysical properties of **1a** by ultraviolet spectra and fluorescence spectra in solvents with different polarities. The absorption spectra of **1a** was less dependent on the solvent polarity (Fig. 2), while the emission spectra shifted dramatically to longer wavelengths with the solvent polarity increased from hexane (fluorescence maximum λ_{em} = 428 nm) to methanol (λ_{em} = 525 nm) (Fig. 3b), and **1a** exhibited amazing fluorescence color variations in various solvents under illumination with 365 nm light: dark blue to yellow (Fig. 3a). The high sensitivity of the emission spectra of **1a** to solvent may be due to a charge shift away from the amino group in the excited state, towards the electron acceptor: the quinoline group. This led to a large dipole moment in the excited state, which interacted with the polar solvent molecules to reduce the energy of the excited state, resulting in emission at lower energies and longer wavelengths.

Conclusions

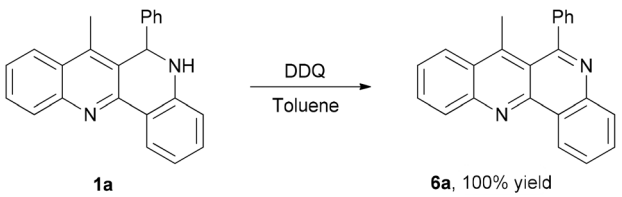
In conclusion, we have reported an unexpected and efficient synthesis of a novel class of fluorescent heterocyclic compounds with naphthyridine moieties, using the $Sc(OTf)_3$-catalyzed cascade reaction of *o*-aminoacetophenones with methanamines. Efforts were made to research the mechanism of the cascade reaction and two possible mechanisms were proposed. The fluorescence properties of the novel fused-four-ring heterocyclic compound **1a** were initially disclosed. The



Scheme 6 Another possible mechanism of the cascade reaction (some easy steps were omitted for clarity).



Scheme 7 Control experiments for the cascade reaction.



Scheme 8 Compound **1a** oxidized by DDQ.

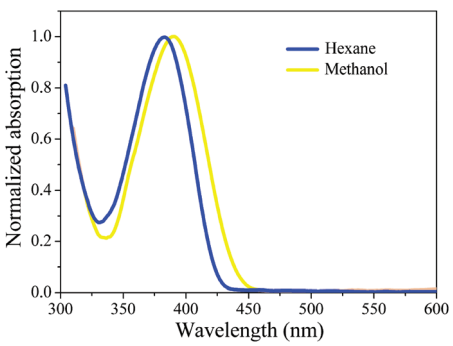


Fig. 2 Normalized absorption spectra of **1a** in hexane and methanol.

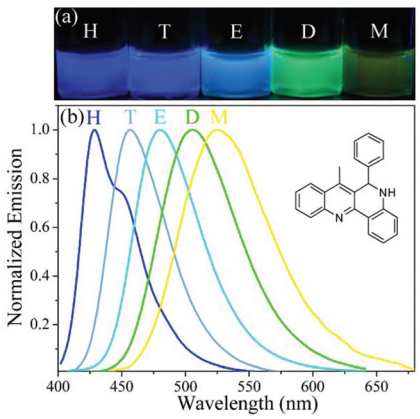


Fig. 3 Fluorescence photographs (a) and fluorescence emission spectra (excitation wavelength, λ_{ex} = 383 nm) (b) of **1a** in different solvents. H, hexane; T, toluene; E, ethyl acetate; D, dimethylformamide; M, methanol.

fluorescence emission spectra of **1a** exhibited a prominent solvatofluorochromism with the increase of solvent polarity, which may result in potential application in molecular recognition and fluorescence detection.

Experimental section

General information

^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively using tetramethylsilane as an internal reference. Chemical shifts (δ) and coupling constants (J) were expressed in parts per million and hertz, respectively. Melting points were uncorrected. Samples for IR were prepared as a thin film on a KBr plate. High resolution mass spectra (HRMS) were recorded on a Micromass GCT with the electron ionization (EI) resource. All reagents were obtained from commercial sources and used without further purification.

General procedure for synthesis of 1a–p

To a mixture of *o*-aminoacetophenones (1.25 mmol) and methanamines (0.5 mmol) was added $Sc(OTf)_3$ (5 mol%). After stirring at 90 °C under an air atmosphere for 12 h, the mixture was extracted with CH_2Cl_2 and H_2O. The organic layer was dried with Na_2SO_4, and then concentrated *in vacuo*. The products **1a–p** were obtained by column chromatography on silica gel with 5–10% ethyl acetate in petroleum ether as the eluent.

Acknowledgements

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