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Fluorogenic aldehydes bearing arylethynyl groups: turn-on aldol reaction sensors for evaluation of organocatalysis in DMSO

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ABSTRACT

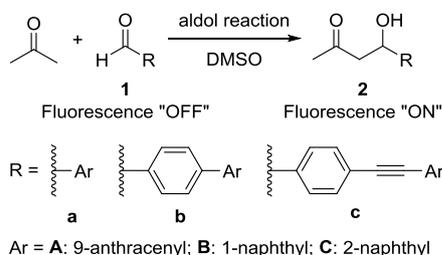
Fluorogenic aromatic aldehydes bearing arylethynyl groups were developed. They were used for monitoring the reaction progress of organocatalytic aldol reactions in DMSO through an increase in the fluorescence intensity based on the formation of the fluorescent aldol product. The ratios of the fluorescence intensities of the aldols to the aldehydes were more than 300. These results suggest that the fluorescence assay system using the aldehyde is useful for the rapid identification of superior aldol catalysts and reaction conditions.

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The methods for monitoring the reaction progress of chemical transformations through an increase in the fluorescence intensity are useful for screening of catalysts and reaction conditions, as well as the characterization of catalysis on a small scale.¹ Various fluorogenic substrates have been developed for monitoring the reaction progress of catalytic cleavage reactions, functional group transformations,^{2,3,4} and bond-forming including carbon–carbon bond-forming reactions.^{5,6,7,8,9} Practical utility of the substrates have been demonstrated.¹⁰ Herein, we report the synthesis and the use of fluorogenic aldehydes bearing arylethynyl groups that are suitable for monitoring the organocatalytic aldol reactions in DMSO that is frequently used as an organic solvent in such reactions.

As previously reported, aldol reaction progress can be monitored through an increase in fluorescence using a fluorogenic aldehyde.⁷ To be of practical use, the ratio of fluorescence intensity of the aldol product to that of the fluorogenic aldehyde should be high and the aldehyde should show no fluorescence or very weak fluorescence.⁷ In addition, the reactivity of aldehyde group in fluorogenic aldehyde should be appropriate for the use.¹¹ We have recently reported use of 9-anthraldehyde to monitor peptide-catalyzed aldol reactions in aqueous solutions.^{7c} However, the reactivity of 9-anthraldehyde was relatively low in both aqueous and DMSO conditions (*vide*

infra); this may be because the 9-anthracene moiety acts as a bulky group and hinders the reactions. To develop fluorescence monitoring systems with appropriate reactivity that retain desired fluorescence features of 9-anthraldehyde and its aldols, aldehydes smaller than 9-anthraldehyde such as naphthaldehydes and benzaldehyde derivatives conjugated to aryl groups were designed (Scheme 1). These aldehydes and their aldol products were synthesized or purchased and evaluated in fluorescence and organocatalytic reactivity in DMSO.



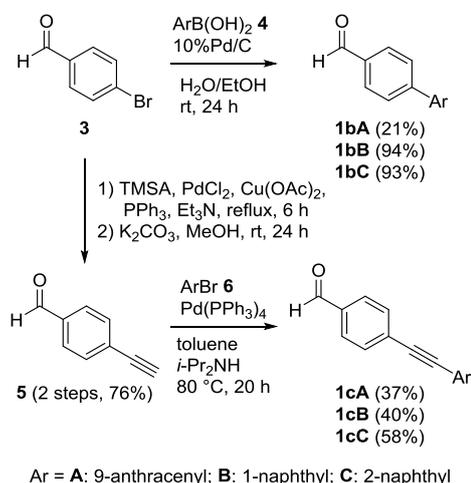
Scheme 1. Fluorogenic substrates for aldol reactions

The syntheses of 4-arylbenzaldehyde derivatives **1b** and 4-arylethynylbenzaldehyde derivatives **1c** are shown in Scheme 2.

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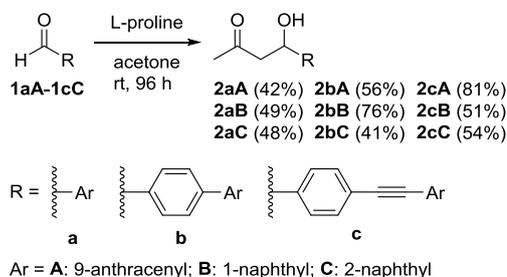
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The Pd/C-catalyzed phosphine-free Suzuki–Miyaura reactions¹² of 4-bromobenzaldehyde (**3**) and boronic acids **4** at room temperature afforded the 4-arylbenzaldehyde derivatives **1bA–1bC** in moderate to excellent (21–94%) yields (Scheme 2). 4-Ethynylbenzaldehyde (**5**) was synthesized from **3** and trimethylsilylacetylene (TMSA) in 76% yield over two steps.¹³ The Sonogashira coupling reactions¹⁴ of aldehyde **5** and aryl bromides **6** at 80 °C afforded the corresponding aldehydes **1cA–1cC** in moderate to good (37–58%) yields.



Scheme 2. Preparation of benzaldehyde derivatives **1**.

Aldols **2** were prepared by the organocatalytic L-proline-catalyzed aldol reactions¹⁵ between acetone and benzaldehyde derivatives **1** (Scheme 3). Nine derivatives **2aA–2cC** were prepared in moderate to good (41–81%) yields at room temperature without any special operation.



Scheme 3. Organocatalytic aldol reactions of benzaldehyde derivatives **1**.

First, aldehydes **1aA–1aC** were evaluated. 9-Anthraldehyde (**1aA**) emits very weak fluorescence in many solvents upon UV irradiation at the appropriate wavelengths;¹⁶ whereas, it is known that anthracen-9-ylmethanol emits strong blue fluorescence.¹⁷ Similarly, aldol **2aA** was highly fluorescent in DMSO.^{7c} The ratio of the fluorescence intensities of **2aA** to **1aA** was 322 in DMSO (Table 1, entry 1). To test the utility of **1aA** for monitoring the reaction progress of a typical organocatalytic aldol reaction, the reaction between acetone and aldehyde **1aA** was performed using L-proline as the catalyst, and the fluorescence intensity was recorded (Figure 1, see also the Supplementary Material for the details of the fluorescence spectra). Although aldol **2aA** was highly fluorescent, the increase in the fluorescence intensity observed during the reaction was low; the slope over 1 h was 0.09. The L-proline-catalyzed aldol reaction of aldehyde **1aA** with acetone to afford **2aA** was too

slow to obtain any reasonable data. The bulkiness of the 9-anthracenyl group probably caused the slow reaction. When less bulky naphthalene derivatives **1aB/2aB** and **1aC/2aC** were evaluated, no fluorescence was observed at 1 μM concentration in DMSO under the UV irradiation at 220 and 235 nm, respectively (Table 1, entries 2 and 3). Although naphthalene derivatives are known to be fluorescent,¹⁸ the results of the fluorescence measurements of **1aB/2aB** and **1aC/2aC** in DMSO indicate that naphthaldehydes are not good fluorogenic substrates for the analysis of the formation of the aldols at the initial stages of the reactions.

Next, arylbenzene derivatives **1b** and arylolethynylbenzene derivatives **1c** were evaluated. Aldehydes **1bA–1bC** and **1cA–1cC** emitted very weak fluorescence, whereas aldols **2bA–2bC** and **2cA–2cC** emitted strong fluorescence in DMSO under the irradiation at appropriate wavelengths (Table 1, entries 4–9). The ratios of the fluorescence intensities of **2b/1b** varied from 4.6 to 60 (Table 1, entries 4–6), whereas those of **2c/1c** were more than 100 (Table 1, entries 7–9). The best pair of aldol/aldehyde among those tested was **2cB/1cB** with a fluorescence intensity ratio of 368 (Table 1, entry 8).¹⁹ The UV light images of aldehyde **1cB** and aldol **2cB** clearly shows the OFF–ON property of the pair (Figure 2).

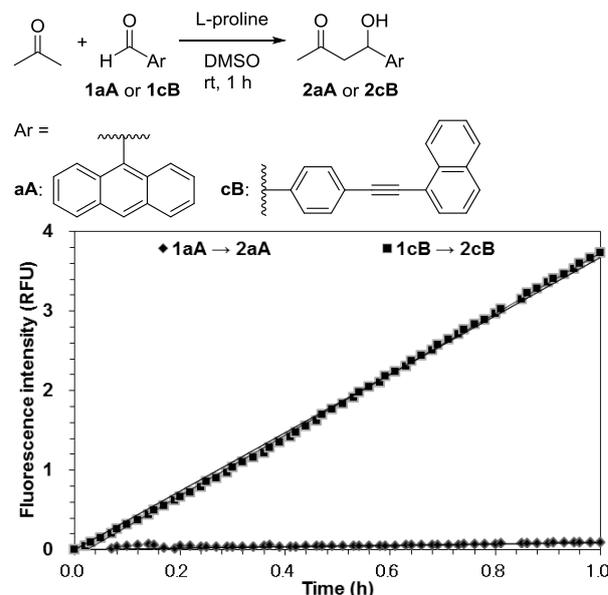


Fig. 1. Fluorescence monitoring of aldol reactions; reaction conditions: aldehyde (10 μM), L-proline (1 mM) in 20% acetone/75% DMSO/5% H₂O; reaction volume 3 mL; the reaction was performed in a quartz cuvette. For the reaction of **1aA** with acetone, the fluorescence intensity of **2aA** was monitored at $\lambda_{\text{ex}} = 265$ nm and $\lambda_{\text{em}} = 420$ nm; the slope over 1 h was 0.09. For the reaction of **1cB** with acetone, the fluorescence intensity of **2cB** was monitored at $\lambda_{\text{ex}} = 330$ nm and $\lambda_{\text{em}} = 351$ nm; the slope over 1 h was 3.68.

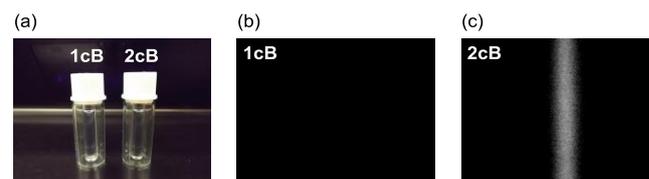


Fig. 2. Photographs of the solutions of 1-naphthylethynylbenzene derivatives in DMSO (0.1 mM): (a) aldehyde **1cB** and aldol **2cB** under visible light; (b) aldehyde **1cB** and (c) aldol **2cB** under UV light at $\lambda_{\text{ex}} = 254$ nm (UV lamp), $\lambda_{\text{em}} = 300$ –400 nm (UV camera with filters BLF-390B and UTVAF-50S-33U, Sigma Koki Co., Ltd., Japan).

Table 1. Fluorescent properties of aryl aldehyde derivatives **1** and the corresponding aldols **2**.

Entry	Wavelength (nm)		Fluorescence intensity				
	λ_{ex}	λ_{em}	Aldehyde 1	Aldol 2			
1	265	419	1aA	1.66×10^4	2aA	5.34×10^3	322
2	220	-	1aB	-	2aB	-	-
3	235	-	1aC	-	2aC	-	-
4	265	401	1bA	4.17×10^4	2bA	2.49×10^3	60
5	300	342	1bB	5.66×10^4	2bB	2.63×10^2	4.6
6	270	363	1bC	8.51×10^4	2bC	1.33×10^3	16
7	270	432	1cA	6.16×10^4	2cA	8.21×10^3	133
8	330	351	1cB	2.08×10^4	2cB	7.65×10^3	368
9	330	347	1cC	2.12×10^4	2cC	6.42×10^3	303

All the measurements were carried out in 1.0 μM DMSO solution.

Aldehyde **1cB** showed the lowest fluorescence among aldehydes **1bA–1bC** and **1cA–1cC**; therefore, the utility of aldehyde **1cB** in monitoring the reaction to afford aldol **2cB** was examined. The time course of the L-proline-catalyzed aldol reaction of acetone with aldehyde **1cB** showed a significant increase in the fluorescence intensity (Figure 1); the slope over 1 h was 3.68. This slope was 41-fold greater than that of the L-proline-catalyzed reaction of **1aA** with acetone to afford aldol **2aA**. These results indicate that aldehyde **1cB** is an excellent fluorogenic aldehyde for monitoring the reaction progress of aldol reactions in DMSO.

In summary, we developed fluorogenic aldehydes that can be used to monitor the reaction progress of L-proline-catalyzed aldol reactions in DMSO through an increase in the fluorescence intensity. This type of fluorescence assay system may be useful for the rapid identification of superior aldol catalysts. The studies on the full scope of the fluorescence monitoring systems for chemical transformations using fluorogenic substrates containing arylethynylbenzene moieties are currently under investigation and will be reported in due course.

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Supplementary Material

Supplementary data of fluorescence spectra and synthesis and characterization of compounds associated with this article can be found, in the online version, at doi:10.1016/XX.

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 19. The ratios of the fluorescence intensities of **2cB**/**1cB** in various solvents: 232-fold in CHCl₃ (at $\lambda_{\text{ex}} = 320$ nm and $\lambda_{\text{em}} = 347$ nm), 323-fold in AcOEt (at $\lambda_{\text{ex}} = 318$ nm and $\lambda_{\text{em}} = 343$ nm), 22-fold in 2-PrOH (at $\lambda_{\text{ex}} = 318$ nm and $\lambda_{\text{em}} = 343$ nm), 764-fold in CH₃CN (at $\lambda_{\text{ex}} = 318$ nm and $\lambda_{\text{em}} = 343$ nm), 31-fold in DMF (at $\lambda_{\text{ex}} = 324$ nm and $\lambda_{\text{em}} = 347$ nm), and 15-fold in Na phosphate buffer (pH 7, at $\lambda_{\text{ex}} = 238$ nm and $\lambda_{\text{em}} = 360$ nm). The fluorescence intensity of aldol **2cB** in different solvent analyzed in the above-indicated λ_{ex} and λ_{em} wavelengths relative to that in DMSO (**2cB** in DMSO at $\lambda_{\text{ex}} = 330$ nm and $\lambda_{\text{em}} = 351$ nm: 100) was following: CHCl₃: 97; AcOEt: 117; 2-PrOH: 121; CH₃CN: 119; DMF: 108; Na phosphate buffer (pH 7): 14.