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

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ABSTRACT

Fluorogenic aromatic aldehydes bearing arylenyl 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 florescent 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.

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.\textsuperscript{1} Various fluorogenic substrates have been developed for monitoring the reaction progress of catalytic cleavage reactions, functional group transformations,\textsuperscript{2,3,4} and bond-forming including carbon–carbon bond-forming reactions.\textsuperscript{5,6,7,8} Practical utility of the substrates have been demonstrated.\textsuperscript{9} Herein, we report the synthesis and the use of fluorogenic aldehydes bearing arylenyl 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.\textsuperscript{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.\textsuperscript{7} In addition, the reactivity of aldehyde group in fluorogenic aldehyde should be appropriate for the use.\textsuperscript{11} We have recently reported use of 9-anthraldehyde to monitor peptide-catalyzed aldol reactions in aqueous solutions.\textsuperscript{5,6} However, the reactivity of 9-anthraldehyde was relatively low in both aqueous and DMSO conditions (\textit{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.

\begin{center}
\begin{tikzpicture}
\begin{scope}[every node/.style={minimum width=2cm,minimum height=1cm}]
\node (1) at (0,0) {OH};
\node (2) at (1.5,0) {OH};
\node (3) at (0,-1) {R};
\node (4) at (1.5,-1) {R};
\node (5) at (0,1) {\textsuperscript{1}H\textsuperscript{R} \textit{aldol reaction} \textsuperscript{DMSO}};
\node (6) at (1.5,1) {\textit{Fluorescence "ON"}};
\node (7) at (0,-2) {$R = \text{Ar}$};
\node (8) at (0,-3) {$a$};
\node (9) at (1.5,-3) {$b$};
\node (10) at (0,-4) {$c$};
\node (11) at (1.5,-4) {$\text{Ar} = 9\text{-}naphthyl$; $1\text{-}naphthyl$; $2\text{-}naphthyl$};
\end{scope}
\end{tikzpicture}
\end{center}

**Scheme 1.** Fluorogenic substrates for aldol reactions

The syntheses of 4-arylbenzaldehyde derivatives \textit{1b} and 4-arylenylbenzaldehyde derivatives \textit{1c} are shown in Scheme 2.

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The Pd/C-catalyzed phosphine-free Suzuki–Miyaura reactions 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. The Sonogashira coupling reactions of aldehyde 5 and aryl bromides 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 reactions 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–1cC were evaluated. 9-Anthraldehyde (1aA) emits very weak fluorescence in many solvents upon UV irradiation at the appropriate wavelengths; whereas, it is known that anthrach-9-ylmethanol emits strong blue fluorescence. The ratio of the fluorescence intensities of 2aA to 1aA was measured in DMSO. 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 slow to obtain any reasonable data. The bulkiness of the 9-anthracenyl group probably caused the slow reaction. When less bulky naphthalene derivatives 1bB/2aB and 1cC/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, the results of the fluorescence measurements of 1bB/2aB and 1cC/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 arylylbenzene derivatives 1e were evaluated. Aldehydes 1bA–1bC and 1eA–1eC emitted very weak fluorescence, whereas aldols 2bA–2bC and 2aA–2aC emitted strong fluorescence in DMSO under the irradiation at appropriate wavelengths (Table 1, entries 4–9). The ratios of the fluorescence intensities of 2bA/1bB varied from 4.6 to 60 (Table 1, entries 4–6), whereas those of 2cA/1cA were more than 100 (Table 1, entries 7–9). The best pair of aldol/aldehyde among those tested was 2bB/1cA with a fluorescence intensity ratio of 368 (Table 1, entry 8). The UV light images of aldehyde 1bA and aldol 2bB clearly shows the OFF–ON property of the pair (Figure 2).

The UV light images of aldehyde 1aA and aldol 2aA were clearly shows the OFF–ON property of the pair (Figure 2).
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 arylethenylbenzene 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.

References and notes


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