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# Substituent-dependent reactivity in aldehyde transformations: 4-(phenylethynyl)benzaldehydes versus simple benzaldehydes

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ABSTRACT

Effects of substituents on transformations of 4-(phenylethynyl)benzaldehydes and related benzaldehydes were analyzed in aldol and thiazolidine formation reactions. The aldol reaction of 4-cyanobenzaldehyde was 54-fold faster than that of 4-methoxybenzaldehyde. In contrast, the aldol reaction of 4-(4-cyanophenylethynyl)benzaldehyde was only 1.4-fold faster than that of 4-(4-methoxyphenylethynyl)benzaldehyde. Electronic features of substituents are significantly less influential in a diphenylacetylene system than in a simple benzene system.



## 1. Introduction

Electron-withdrawing and electron-donating functional groups often determine the reactivity of molecules.[1,2] Understanding the nature of the substituent effect is important to the design and synthesis of functionalized molecules. Although it is often considered that π-systems efficiently transmit the substituent effect through resonance,[1,2] with the exceptions of effects on simple benzene derivatives, there is not much information regarding to what extent electronic features of substituents alter the reactivity of molecules. Here we report effects of substituents in nucleophilic addition reactions on aldehyde groups attached to diphenylacetylene derivatives.

Diphenylacetylene derivatives and related compounds containing a π-conjugated C–C triple bond are important as synthons, probes, and other functional molecules.[3,4] In reported crystal structures of diphenylacetylene derivatives, two phenyl groups connected to the ethynylene group are located in a single plane (i.e., the coplanar conformation).[5] This indicates that the phenyl groups are conjugated.[3,5] Previously reported fluorescence data of diarylacetylene derivatives also suggest that the two aryl groups of the diarylacetylene moiety are π-conjugated.[3,4a–c] These reported results suggest that electronic features of substituents attached to one end of a diarylacetylene π-system are likely to significantly influence the reactivity of groups attached at the other end of the π-system. On the other hand, the degree of the substituent effect may vary depending on factors other than π-conjugation. In this study, to provide information useful for the design, synthesis, and use of diphenylacetylene derivatives, reactivities on 4-(phenylethynyl) benzaldehyde with various substituents and on simple benzaldehyde with the same substituents were analyzed in aldol and thiazolidine formation reactions and changes in the reactivities were compared.

## 2. Results and discussion

### 2.1. Substituent effect in aldol reactions

First, effect of substituents was analyzed in aldol reactions. Aldol reactions are important C–C bond forming reactions. One of potential uses of the substituted 4-(phenylethynyl)benzaldehydes is as fluorogenic probes to monitor the progress of aldol reactions.[4d] Effects of substituents have previously been observed in enamine-based aldol reactions of benzaldehydes.[2c]

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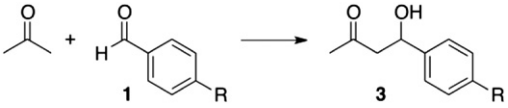
Aldol reactions of acetone with a series of substituted benzaldehydes (**1**) and of substituted 4-(phenylethynyl)benzaldehydes (**2**) were performed using proline as the catalyst[4d,6] in DMSO-$d_6$. Formation of aldol products (**3** and **4**) was monitored by $^1$H NMR. To provide information useful for the design and synthesis of diphenylacetylene derivatives, reaction conditions that were similar to those used actual syntheses were used. To quickly analyze the reactivity differences between the simple benzaldehyde series and the 4-(phenylethynyl)benzaldehyde series under these conditions, initial reaction rates and the ratios of the rates were determined and compared.

For both the simple benzaldehydes (Table 1) and the 4-(phenylethynyl)benzaldehydes (Table 2), reactions of aldehydes bearing the electron-withdrawing cyano substituent were faster than those of aldehydes bearing the electron-donating methoxy group (entries 2 vs entries 4). The degree of contribution of the substituents on 4-(phenylethynyl)benzaldehyde to reaction velocities was very different from that of the substituents on the simple benzaldehyde (Fig. 1). For the aldol reaction of benzaldehydes **1**, initial rates ranged 0.3–15 mM/h (Table 1). Formation of **3b** from **1b** was 54-fold faster than the formation of **3d** from **1d** (Fig. 1 and Table 1 entries 2 and 4). In contrast, for 4-(phenylethynyl)benzaldehydes **2**, the range of initial rates was 2.6–3.6 mM/h (Table 2). Formation of **4b** from **2b** was only 1.4-fold faster than the formation of **4d** from **2d** (Fig. 1 and Table 2 entries 2 and 4). Effect of substituents was significantly reduced through the (phenylethynyl)phenyl moiety compared to effects through the single phenyl group.

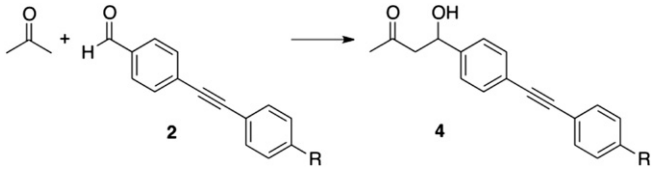
**Table 1**
Comparison of initial rates of aldol reactions of acetone with benzaldehyde derivatives[a]



| Entry | R | 1 | 3 | $V_1$ (mM/h)[b] | $V_1/V_{1a}$[c] |
|---|---|---|---|---|---|
| 1 | H | **1a** | **3a** | 1.7 | 1.0 |
| 2 | CN | **1b** | **3b** | 15 | 8.6 |
| 3 | Me | **1c** | **3c** | 1.2 | 0.7 |
| 4 | OMe | **1d** | **3d** | $2.8\times10^{-1}$ | 0.2 |
| 5 | Ethynyl | **1e** | **3e** | 2.1 | 1.2 |
| 6 | $CF_3$ | **1f** | **3f** | 6.6 | 3.8 |

[a] Reaction conditions: [acetone] 666 mM, [**1**] 44.4 mM, and [L-proline] 6.7 mM in DMSO-$d_6$ at 21 °C.
[b] Initial rate of the formation of **3**.
[c] Relative initial rate determined by comparing with the initial rate of the reaction of **1a** to afford **3a**.

**Table 2**
Comparison of initial rates of aldol reactions of acetone with 4-(phenylethynyl) benzaldehyde derivatives[a]



| Entry | R | 2 | 4 | $V_2$ (mM/h)[b] | $V_2/V_{2a}$[c] | $V_2/V_{1a}$[d] |
|---|---|---|---|---|---|---|
| 1 | H | **2a** | **4a** | 2.7 | 1.0 | 1.6 |
| 2 | CN | **2b** | **4b** | 3.6 | 1.3 | 2.1 |
| 3 | Me | **2c** | **4c** | 3.2 | 1.2 | 1.8 |
| 4 | OMe | **2d** | **4d** | 2.6 | 1.0 | 1.5 |
| 5 | $CF_3$ | **2f** | **4f** | 2.8 | 1.0 | 1.6 |

[a] Reaction conditions: [acetone] 666 mM, [**2**] 44.4 mM, and [L-proline] 6.7 mM in DMSO-$d_6$ at 21 °C.
[b] Initial rate of the formation of **4**.
[c] Relative initial rate determined by comparing with the initial rate of the reaction of **2a** to afford **4a**.
[d] Relative initial rate determined by comparing with the initial rate of the reaction of **1a** to afford **3a** (Table 1).

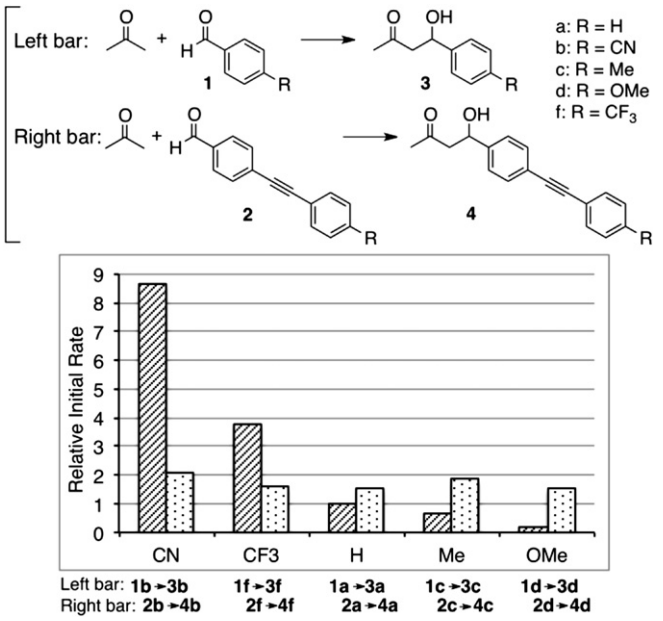
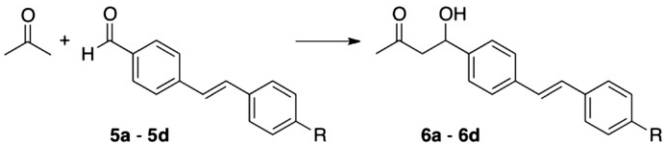



**Fig. 1.** Relative initial rates ($V_1/V_{1a}$ and $V_2/V_{1a}$) of proline-catalyzed aldol reactions of **2** determined by comparing with the initial rate of the reaction of **1a**.

To estimate the contribution of the C–C triple bond within the (phenylethynyl)benzaldehyde derivatives in transmitting electronic features of substituents, the aldol reactions of styrylbenzaldehydes **5**, which had a C–C double bond instead of the C–C triple bond of **2**, were analyzed (Scheme 1). Reactions of **5** were performed under the same conditions used for the aldol reactions shown in Tables 1 and 2. Initial rates of the formation of **6a** and **6b** were 2.0 and 2.2 mM/h, respectively. The rate of the formation of **6b** was only 1.1-fold of that of the formation of **6a** and was slower than that of the formation of **4b** (Note that formation of **4b** was 1.3-fold faster than the formation of **4a**). These results indicated that the C–C triple bond between two phenyl groups better transmitted the electronic features of substituents than did the C–C double bond. Both **2** and **5** have π-conjugated systems; the phenylethynylphenyl moiety of **2** and the *trans*-stilbene moiety of **5** are coplanar in the most stable conformation.[3,5,7] The C–C triple bond is shorter than the C–C double bond. In addition, the C–C triple bond provides stronger π-conjugation than the C–C double bond by bridging two benzene rings in linear structure. These features may underline the reactivity differences between **2** and **5** (i.e., influence of substituents on reactivities: **1**>>**2**>**5**).

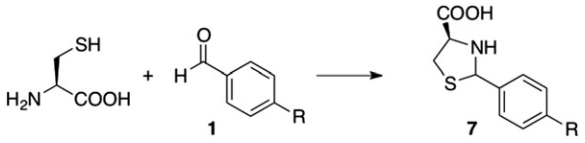



**Scheme 1.** Aldol reactions of styrylbenzaldehydes.

## 2.2. Substituent effect in thiazolidine formation reactions

Next, effect of substituents was analyzed in the thiazolidine formation[8] reactions. Aldehydes were mixed with cysteine and the formation of thiazolidine was monitored by $^1$H NMR. Initial rates were determined and compared (Tables 3 and 4). Initial rates

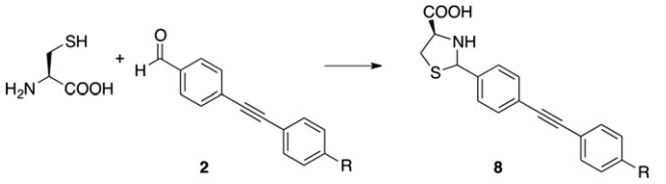
**Table 3**
Comparison of initial rates of reactions between cysteine and benzaldehyde derivatives[a]




| Entry | R | 1 | 7 | $V_1$ (mM/h)[b] | $V_1/V_{1a}$[c] |
|---|---|---|---|---|---|
| 1 | H | **1a** | **7a** | 1.5 | 1.0 |
| 2 | CN | **1b** | **7b** | 11 | 7.3 |
| 3 | Me | **1c** | **7c** | $9.2\times10^{-1}$ | 0.6 |
| 4 | OMe | **1d** | **7d** | $6.5\times10^{-1}$ | 0.4 |
| 5 | Ethynyl | **1e** | **7e** | 2.4 | 1.5 |

[a] Reaction conditions: [cysteine] 4.7 mM, [**1**] 4.0 mM, in 5%(v/v) $D_2O$/DMSO-$d_6$ at 22 °C.
[b] Initial rate of the formation of **7**.
[c] Relative initial rate determined by comparing with the initial rate of the reaction of **1a** to afford **7a**.

**Table 4**
Comparison of initial rates of reactions between cysteine and 4-(phenylethynyl) benzaldehyde derivatives[a]




| Entry | R | 2 | 8 | $V_2$ (mM/h)[b] | $V_2/V_{2a}$[c] | $V_2/V_{1a}$[d] |
|---|---|---|---|---|---|---|
| 1 | H | **2a** | **8a** | 2.3 | 1.0 | 1.5 |
| 2 | CN | **2b** | **8b** | 3.0 | 1.3 | 1.9 |
| 3 | Me | **2c** | **8c** | 1.7 | 0.7 | 1.1 |
| 4 | OMe | **2d** | **8d** | 1.9 | 0.8 | 1.3 |

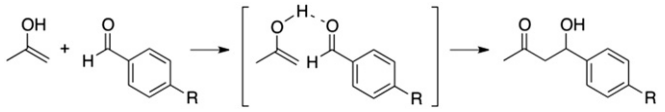
[a] Reaction conditions: [cysteine] 4.7 mM, [**2**] 4.0 mM in 5%(v/v) $D_2O$/DMSO-$d_6$ at 22 °C.
[b] Initial rate of the formation of **8**.
[c] Relative initial rate determined by comparing with the initial rate of the reaction of **2a** to afford **8a**.
[d] Relative initial rate determined by comparing with the initial rate of the reaction of **1a** to afford **7a** (Table 3).

ranged 0.65–11 mM/h for aldehydes **1** (Table 3) and 1.7–3.0 mM/h for aldehydes **2** (Table 4). For the thiazolidine formation, like the aldol reaction described above, effects of electron-withdrawing and electron-donating substituents were significantly reduced through the (phenylethynyl)phenyl group compared to the phenyl group.

## 2.3. Theoretical analysis of substituent effect in aldol reactions

To understand how the electronic features of substituents influence the reactivity of the aldehydes, stable conformations of reactant aldehydes and transition states of an aldol reaction of the aldehydes were determined theoretically.[9] All computations were performed using Gaussian 09 program package.[10] Theoretically, the most stable conformation of aldehydes **2a**, **2b**, and **2d** was the coplanar conformation in which the two benzene rings and the aldehyde group were on a single plane. This result is consistent with the previous reports that the most stable conformation of diphenylacetylene is the coplanar conformation.[3,5] The result of the stable conformation also supports that there is π-conjugation from the substituent to the aldehyde group over the entire 4-(phenylethynyl)benzaldehyde derivative.

For theoretical analysis of aldol reactions of aldehydes **1** and **2** with acetone, a reaction of an enol to yield the aldol product via a six-membered transition state was used (Scheme 2). Theoretical analysis of the aldol reactions involving an enol is simpler than that of the corresponding proline-catalyzed[11] aldol reactions. To obtain information about the substituent effect, the simple enol route was employed for the theoretical analysis. The transition states were determined using the density functional theory (DFT) method at the B3LYP/6-31G(d) level.[10] Energy differences (ΔΔ*G*) between the Gibbs free energies of the transition states are shown in Tables 5 and 6.




**Scheme 2.** Aldol reaction used for computation.

**Table 5**
Energy differences of transition states of the aldol reaction of benzaldehyde derivatives and calculated and observed relative rates[a]

| Entry | 1 | Computed ΔΔ*G* (kcal/mol)[b] | Computed $k_1/k_{1a}$[c] | Observed $V_1/V_{1a}$[d] |
|---|---|---|---|---|
| 1 | **1a** | 0.00 | 1.00 | 1.0 |
| 2 | **1b** | −1.22 | 7.77 | 8.6 |
| 3 | **1d** | 0.84 | 0.24 | 0.2 |

[a] Energies of transition states of the aldol reaction shown in Scheme 2 were theoretically determined using the DFT method at the B3LYP/6-31G(d) level.
[b] Calculated based on the transition state energy of the aldol reaction of **1a** at 25 °C.
[c] Calculated from the ΔΔ*G*.
[d] Experimentally obtained data; taken from Table 1.

**Table 6**
Energy differences of transition states of the aldol reaction of 4-(phenylethynyl) benzaldehyde derivatives and calculated and observed relative rates[a]

| Entry | 2 | Computed ΔΔ*G* (kcal/mol)[b] | Computed $k_2/k_{2a}$[c] | Observed $V_2/V_{2a}$[d] |
|---|---|---|---|---|
| 1 | **2a** | 0.00 | 1.00 | 1.0 |
| 2 | **2b** | −0.18 | 1.35 | 1.3 |
| 3 | **2d** | 0.07 | 0.88 | 1.0 |

[a] Energies of transition states of the aldol reaction shown in Scheme 2 were theoretically determined using the DFT method at the B3LYP/6-31G(d) level.
[b] Calculated based on the transition state energy of the aldol reaction of **2a** at 25 °C.
[c] Calculated from the ΔΔ*G*.
[d] Experimentally obtained data; taken from Table 2.

The computed energy difference between transition states generated from **1a** and **1b** was 1.22 kcal/mol (Table 5, entry 2); the aldol reaction of **1b** was calculated to be theoretically 7.77-fold faster than the reaction of **1a** at 25 °C. For transition states of **2a** and **2b**, the computed energy difference was only 0.18 kcal/mol (Table 6 entry 2), indicating that reaction of **2b** was theoretically 1.35-fold faster than the reaction of **2a** at 25 °C. Similarly, based on the computed energy difference between the transition states generated from **1a** and **1d** and from **2a** and **2d**, the reaction rate of **1d** was calculated to be 0.24-fold of the reaction rate of **1a** and the reaction rate of **2d** was calculated to be 0.88-fold of the reaction rate of **2a** (Tables 5 and 6). Although the reaction used in the theoretical analysis was not that used in actual experimental evaluation of the reactivities of the aldehydes, the theoretically calculated relative rates of the aldol reactions were highly similar to those of the experimentally observed relative rates.

The computed stable conformation of **2** is the coplanar, but single bonds can rotate. Energy differences between the stable conformation and other conformations, such as perpendicular conformation, were relatively small.[3,5] Computational results for

the aldol reaction showed that the energy differences between substituents were relatively small in the reaction of aldehyde **2** compared to those in the reaction of aldehyde **1**. These results indicate that reactivity of molecules is more affected by dynamics of molecular movement than by the most stable conformation. During formation of the transition state, it is not necessary that aldehydes **2** retain π-conjugation over the entire diphenylacetylene π-system.

### 2.4. Extent of changes in the reactivity by substituents

Extent of changes in relative rates of aldol reactions by the attachment of substituents in aldehyde **2** were compared with those in aldehyde **1** (Table 7). The experimentally observed acceleration of the rate by the cyano group in the reaction of aldehyde **2** was 7-fold less than that in the reaction of aldehyde **1**. Computational analysis also indicated that the acceleration by the cyano group in the reaction of aldehyde **2** was 6-fold less than that in the reaction of aldehyde **1**. Slowdown of the rate by the methoxy group in the reaction of aldehyde **2** was 5-fold and 4-fold less than in the reaction of aldehyde **1** in the actual reaction and in the computational analysis, respectively.

**Table 7**
Changes in the reactivity in aldol reactions[a]

| | Reaction of aldehyde **1**[a] | Reaction of aldehyde **2**[a] | Changes in acceleration or slowdown[b] |
|---|---|---|---|
| $V_{R=CN}/V_{R=H}$ observed | 8.6 | 1.3 | 7 |
| [computed] | [7.77] | [1.35] | 6 |
| $V_{R=CF3}/V_{R=H}$ observed | 3.8 | 1.0 | 4 |
| $V_{R=OMe}/V_{R=H}$ observed | 0.2 | 1.0 | 1/5 |
| [computed] | [0.24] | [0.88] | 1/4 |

[a] Values taken from Tables 1, 2, 5 and 6. Observed values: $V_1/V_{1a}$ and $V_2/V_{2a}$. Computed values: $k_1/k_{1a}$ and $k_2/k_{2a}$.
[b] Determined as $(V_1/V_{1a})/(V_2/V_{2a})$ and $(k_1/k_{1a})/(k_2/k_{2a})$, respectively.

In the thiazolidine formation reaction, the acceleration by the cyano group in the reaction of aldehyde **2** was 6-fold less than that in the reaction of aldehyde **1**, and the slowdown by the methoxy group in the reaction of aldehyde **2** was 2-fold less than that in the reaction of aldehyde **1** (Table 8).

**Table 8**
Changes in the reactivity in thiazolidine formation reactions[a]

| | Reaction of aldehyde **1**[a] | Reaction of aldehyde **2**[a] | Changes in acceleration or slowdown[b] |
|---|---|---|---|
| $V_{R=CN}/V_{R=H}$ observed | 7.3 | 1.3 | 6 |
| $V_{R=OMe}/V_{R=H}$ observed | 0.4 | 0.8 | 1/2 |

[a] Values taken from Tables 3 and 4. $V_1/V_{1a}$ and $V_2/V_{2a}$.
[b] Determined as $(V_1/V_{1a})/(V_2/V_{2a})$.

Both the acceleration and the slowdown by the introduction of substituents in the reactions of 4-(phenylethynyl)benzaldehyde **2** were reduced from those in the reactions of benzaldehyde **1**. For most cases, the reduction in the acceleration and in the slowdown ranged between 4-fold and 7-fold. As described above, the reaction rate of the aldol reaction of 4-cyanobenzaldehyde (**1b**) was 54-fold faster than that of 4-methoxybenzaldehyde (**1d**) and the aldol reaction of 4-(4-cyanophenylethynyl)benzaldehyde (**2b**) was only 1.4-fold faster than that of 4-(4-methoxyphenylethynyl)benzaldehyde (**2d**). The approximately 40-fold-difference in the influence of the substituents between aldehyde **1** and aldehyde **2** can be attributed to the combination of the changes in the acceleration and the slowdown.

## 3. Conclusion

We investigated the nature of the substituent effect on 4-(phenylethynyl)benzaldehydes. Electronic features of the substituent at one end of the π-system of the diphenylacetylene did not significantly influence the reactivity of the group at the other end of the π-system. Changes in rates by the substituent effect on transformations of 4-(phenylethynyl)benzaldehydes were approximately 4-fold to 7-fold less than those of simple benzaldehydes in each of acceleration and slowdown directions. The range of the rates of reactions of 4-(phenylethynyl)benzaldehydes with various substituents was approximately 1/40 of that of the rates of reactions of benzaldehydes with the same substituents. Although actual substituent effect may be dependent on many factors (such as reaction type, catalyst, catalytic mechanism, and solvent), experimental and theoretical results obtained here indicate that electronic features of substituents are significantly less influential in a diphenylacetylene system than in a simple benzene system. These results suggest that for the development of functional diarylacetylene derivatives, design of functions of the molecules can be the main focus without much consideration of the reactivity differences depending on substituent.

## 4. Experimental section

### 4.1. General

For thin layer chromatography (TLC), compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (3.7 mL), sulfuric acid (5 mL), and acetic acid (1.5 mL) in ethanol (135 mL) followed by heating. Flash column chromatography was performed using silica gel 60 (230–400 mesh). For $^1$H NMR, proton chemical shifts were given in parts per million in $\delta$ relative to tetramethylsilane in $CDCl_3$ or to residual proton signals of deuterated solvent in $CDCl_3$ ($\delta$ 7.27 ppm) or DMSO-$d_6$ ($\delta$ 2.50 ppm). For $^1$H and $^{13}$C NMR, carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ ($\delta$ 77.0 ppm) or DMSO-$d_6$ ($\delta$ 39.5 ppm). High-resolution mass spectra were recorded on an ESI ion trap mass spectrometer.

### 4.2. Determination of initial rates

*4.2.1. Determination of initial rates of aldol reactions (for Tables 1 and 2).* Reaction was initiated by adding 190 μL of 16 mM L-proline solution in DMSO-$d_6$ to a mixture of 60 μL of 5 M acetone solution in DMSO-$d_6$ and 200 μL of 100 mM aldehyde solution in DMSO-$d_6$ at 21 °C; final concentrations: [acetone] 666 mM, [aldehyde] 44.4 mM, and [proline] 6.7 mM in DMSO-$d_6$. Formation of the aldol product was monitored by $^1$H NMR (Table S1, Fig. S1). For each aldehyde, reactions were performed twice or more and identical or very similar results were obtained. Data of one reaction for each aldehyde were used for the rate determination. Initial rate was determined as the slope of a linear least-squares fitting of the time-product plots. In the absence of proline, no formation of the aldol product was detected.

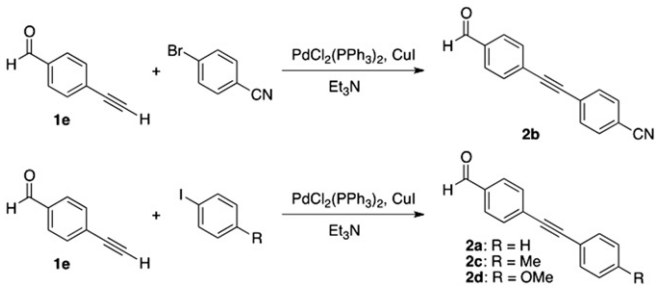
*4.2.2. Determination of initial rates of reactions of aldehydes with cysteine (for Tables 3 and 4).* Reaction was initiated by adding 200 μL of 10 mM aldehyde solution in DMSO-$d_6$ to 300 μL of

7.86 mM L-cysteine solution in 8.6%(v/v) $D_2O$/DMSO-$d_6$ at 22 °C; final concentrations: [aldehyde] 4 mM and [cysteine] 4.7 mM in 5%(v/v) $D_2O$/DMSO-$d_6$. Formation of the thiazolidine was monitored by $^1$H NMR (Table S2). Initial rate was determined as the slope of a linear least-squares fitting of the time-product plots.

### 4.3. Synthesis and characterization of standards of aldehydes

*4.3.1. 4-(Phenylethynyl)benzaldehydes **2**.* Aldehydes **2a**–**d** and **2f** were synthesized by Sonogashira coupling reactions.[4e]

*4.3.2. 4-((4-Formylphenyl)ethynyl)benzonitrile (**2b**).*[4e] A mixture of $PdCl_2(PPh_3)_2$ (10.0 mg, 0.014 mmol), $Et_3N$ (4.2 mL, 30 mmol), 4-ethynylbenzaldehyde[4f,g] (**1e**) (182 mg, 1.40 mmol), and 4-bromobenzonitrile (260 mg, 1.43 mmol) was stirred at room temperature for 5 min; CuI (5.0 mg, 0.026 mmol) was added and the mixture was stirred at 70 °C for 3 h under an argon atmosphere. After being cooled to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with brine (2×30 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography ($CH_2Cl_2$/hexane=5:1) to afford **2b** (197 mg, 61%) as a pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.04 (s, 1H), 7.90 (d, $J$=8.3 Hz, 2H), 7.71–7.63 (m, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 191.2, 136.0, 132.34, 132.27, 132.2, 129.6, 128.4, 127.4, 118.3, 112.3, 92.5, 91.2. HRMS: calcd for $C_{16}H_{10}NO$ ($MH^+$) 232.0757, found 232.0762.




### 4.4. General procedure for the synthesis of 2a, 2c, 2d, and 2f

A mixture of $PdCl_2(PPh_3)_2$ (11 mg, 0.016 mmol, 0.01 equiv), $Et_3N$ (4.7 mL, 34 mmol), 4-ethynylbenzaldehyde (**1e**)[4f,g] (201 mg, 1.55 mmol, 1.0 equiv), and iodobenzene derivative (1.63 mmol) was stirred at room temperature for 5 min; CuI (6 mg, 0.03 mmol, 0.02 equiv) was added and the mixture was stirred at 35–40 °C for 17–24 h under an argon atmosphere.[4e] After being cooled to room temperature, the mixture was diluted with EtOAc and washed with brine. The organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography to afford **2**.

*4.4.1. 4-(Phenylethynyl)benzaldehyde (**2a**).*[4i,12] Reaction was performed on a 44%-scale (i.e., using 0.68 mmol of **1e**) of the general procedure. Flash column chromatography ($CH_2Cl_2$/hexane=5:1), 106 mg, 76%, pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.02 (s, 1H), 7.87 (d, $J$=8.1 Hz, 2H), 7.68 (d, $J$=8.1 Hz, 2H), 7.58–7.56 (m, 2H), 7.40–7.37 (m, 3H). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.03 (s, 1H), 7.95 (d, $J$=8.0 Hz, 2H), 7.77 (d, $J$=8.0 Hz, 2H), 7.62–7.60 (m, 2H), 7.47–7.45 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 191.4, 135.4, 132.4, 132.1, 131.8, 129.6, 129.0, 128.5, 122.5, 93.5, 88.6. HRMS: calcd for $C_{15}H_{11}O$ ($MH^+$) 207.0804, found 207.0808.

*4.4.2. 4-(4-Methylphenylethynyl)benzaldehyde (**2c**).*[13] Flash column chromatography ($CH_2Cl_2$/hexane=5:1), 298 mg, 87%, pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.02 (s, 1H), 7.86 (d, $J$=8.2 Hz, 2H), 7.67 (d, $J$=8.2 Hz, 2H), 7.46 (d, $J$=8.1 Hz, 2H), 7.19 (d, $J$=8.1 Hz, 2H), 2.39 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 191.4, 139.3, 135.2, 132.0, 131.7, 129.8, 129.5, 129.2, 119.4, 93.8, 88.0, 21.6. HRMS: calcd for $C_{16}H_{13}O$ ($MH^+$) 221.0961, found 221.0964.

*4.4.3. 4-(4-Methoxyphenylethynyl)benzaldehyde (**2d**).* Flash column chromatography ($CH_2Cl_2$/hexane=5:1), 276 mg, 75%, pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.01 (s, 1H), 7.86 (d, $J$=8.3 Hz, 2H), 7.65 (d, $J$=8.3 Hz, 2H), 7.51 (d, $J$=8.8 Hz, 2H), 6.91 (d, $J$=8.8 Hz, 2H), 3.85 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 191.4, 160.2, 135.1, 133.4, 131.9, 130.0, 129.6, 114.5, 114.2, 93.8, 87.5, 55.3. HRMS: calcd for $C_{16}H_{13}O_2$ ($MH^+$) 237.0910, found 237.0913.

*4.4.4. 4-(4-Trifluoromethylphenylethynyl)benzaldehyde (**2f**).* Reaction was performed on a 66%-scale (i.e., using 1.02 mmol of **1e**) of the general procedure. Flash column chromatography ($CH_2Cl_2$/hexane=2:1), 219 mg, 78%, pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 10.05 (s, 1H), 7.90 (d, $J$=8.1 Hz, 2H), 7.71 (d, $J$=8.1 Hz, 2H), 7.68 (d, $J$=8.7 Hz, 2H), 7.65 (d, $J$=8.7 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 191.2, 135.8, 132.2, 132.0, 130.5 (q, $J_{C,F}$=32.8 Hz), 129.6, 128.7, 126.3, 125.3 (q, $J_{C,F}$=3.7 Hz), 123.8 (q, $J_{C,F}$=272 Hz), 91.6, 90.6. HRMS: calcd for $C_{16}H_{10}OF_3$ ($MH^+$) 275.0678, found 275.0686.

*4.4.5. 4-Styrylbenzaldehyde (**5a**).*[14] Aldehyde **5a** was synthesized by the method previously reported.[14]

*4.4.6. 4-(4-Formylstyryl)benzonitrile (**5b**).*[15] Aldehyde **5b** was synthesized according to a reported method.[14] A mixture of 4-bromobenzaldehyde (370 mg, 2.0 mmol), 4-cyanostyrene (310 mg, 2.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and $K_3PO_4$ (596 mg, 2.8 mmol) in *N*,*N*-dimethylacetamide (3 mL) was stirred at 140 °C for 14 h under nitrogen atmosphere. After being cooled to room temperature, the mixture was poured into water and extracted with $CH_2Cl_2$. Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc=4:1) to afford **5b** (275 mg, 59%) as a pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 9.93 (s, 1H), 7.81 (d, $J$=8.0 Hz, 2H), 7.61–7.52 (m, 6H), 7.16 (s, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 191.4, 142.0, 148.8, 135.8, 132.4, 130.8, 130.1, 129.9, 127.2, 127.1, 118.7, 111.3. HRMS: calcd for $C_{16}H_{12}NO$ ($MH^+$) 234.0913, found 234.0919.

### 4.5. Synthesis and characterization of standards of aldols

*4.5.1. Synthesis and characterization of standards of aldols.* Aldols **3**, **4**, and **6** were synthesized by pyrrolidine-catalyzed aldol reactions.[4d,16]

*4.5.1.1. 4-Hydroxy-4-(4-phenylethynylphenyl)butan-2-one (**4a**).* To a solution of aldehyde **2a** (33 mg, 0.16 mmol, 1.0 equiv) in acetone (0.49 mL, 6.67 mmol, 42 equiv), a solution of pyrrolidine in water (100 mM, 0.48 mL, 0.048 mmol, 0.3 equiv) was added at room temperature (23 °C) and the mixture was stirred. After 30 min, the mixture was diluted with water and extracted with $CH_2Cl_2$. Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography ($CH_2Cl_2$/EtOAc=10:1) to afford **4a** (22 mg, 52%) as a pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.55–7.52 (m, 4H), 7.37–7.34 (m, 5H), 5.19–5.15 (m, 1H), 3.42 (d, $J$=3.1 Hz, 1H), 2.91–2.80 (m, 2H), 2.21 (s, 3H). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.56–7.39 (m, 9H), 5.50 (d, $J$=4.8 Hz, 1H), 5.04–5.02 (m, 1H), 2.78–2.66 (m, 2H), 2.12 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 209.0, 142.9, 131.8, 131.6, 128.4, 128.3, 125.6, 123.2, 122.6, 89.5, 89.1, 69.5, 51.8, 30.8. HRMS: calcd for $C_{18}H_{16}O_2Na$ ($MNa^+$) 287.1043, found 287.1051.

### 4.6. General procedure for the synthesis of aldols 4b–d

To a mixture of aldehyde **2** (0.1–0.4 mmol, 1.0 equiv), acetone (40 equiv), and water (136 equiv or 2.45 mL/(aldehyde 1.0 mmol)) was added pyrrolidine (0.3 equiv) at room temperature (23 °C) and the mixture was stirred. After 2 h, the mixture was diluted with water and extracted with $CH_2Cl_2$. Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography ($CH_2Cl_2$/EtOAc=10:1) to afford aldol **4**. Reaction conditions were not optimized.

*4.6.1. 4-Hydroxy-4-(4-(4-cyanophenylethynyl)phenyl)butan-2-one (**4b**).* Reaction was performed using aldehyde **2b** (85 mg, 0.37 mmol) to afford **4b** (28 mg, 26%) as a pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.64–7.59 (m, 4H), 7.53 (d, $J$=8.1 Hz, 2H), 7.38 (d, $J$=8.1 Hz, 2H), 5.20–5.16 (m, 1H), 3.45 (d, $J$=3.1 Hz, 1H), 2.87–2.84 (m, 2H), 2.21 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 208.8, 143.9, 132.1, 132.06, 132.05, 128.2, 125.8, 121.5, 118.5, 111.5, 93.6, 87.8, 69.5, 51.7, 30.8. HRMS: calcd for $C_{19}H_{16}NO_2$ ($MH^+$) 290.1176, found 290.1182.

*4.6.2. 4-Hydroxy-4-(4-(4-methylphenylethynyl)phenyl)butan-2-one (**4c**).* Reaction was performed using aldehyde **2c** (30 mg, 0.14 mmol) to afford **4c** (5.0 mg, 13%) as a pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.51 (d, $J$=8.2 Hz, 2H), 7.43 (d, $J$=8.2 Hz, 2H), 7.35 (d, $J$=8.0 Hz, 2H), 7.17 (d, $J$=8.0 Hz, 2H), 5.20–5.16 (m, 1H), 3.34 (d, $J$=3.1 Hz, 1H), 2.92–2.80 (m, 2H), 2.38 (s, 3H), 2.21 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 209.0, 142.6, 138.4, 131.7, 131.5, 129.1, 125.6, 122.8, 120.1, 89.7, 88.5, 69.6, 51.8, 30.8, 21.5. HRMS: calcd for $C_{19}H_{18}O_2Na$ ($MNa^+$) 301.1199, found 301.1215.

*4.6.3. 4-Hydroxy-4-(4-(4-methoxyphenylethynyl)phenyl)butan-2-one (**4d**).* Reaction was performed using aldehyde **2d** (28 mg, 0.12 mmol) to afford **4d** (19 mg, 54%) as a pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.50 (d, $J$=8.1 Hz, 2H), 7.47 (d, $J$=8.8 Hz, 2H), 7.33 (d, $J$=8.1 Hz, 2H), 6.88 (d, $J$=8.8 Hz, 2H), 5.18–5.14 (m, 1H), 3.83 (s, 3H), 3.38 (d, $J$=3.2 Hz, 1H), 2.91–2.79 (m, 2H), 2.21 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 209.0, 159.7, 142.5, 133.1, 131.6, 125.6, 122.9, 115.3, 114.0, 89.5, 87.8, 69.6, 55.3, 51.8, 30.8. HRMS: calcd for $C_{19}H_{19}O_3$ ($MH^+$) 295.1329, found 295.1356.

*4.6.4. 4-Hydroxy-4-(4-(4-trifluoromethylphenylethynyl)phenyl)butan-2-one (**4f**).* The method for the synthesis of **4a** was employed using aldehyde **2f** (30 mg, 0.11 mmol) to afford **4f** (22 mg, 60%) as a pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.64 (d, $J$=8.8 Hz, 2H), 7.61 (d, $J$=8.8 Hz, 2H), 7.54 (d, $J$=8.3 Hz, 2H), 7.37 (d, $J$=8.3 Hz, 2H), 5.20–5.17 (m, 1H), 3.43 (s, 1H), 2.92–2.85 (m, 2H), 2.22 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 208.9, 143.5, 131.9, 131.8, 129.9 (q, $J_{C,F}$=32.6 Hz), 127.1, 125.7, 125.3 (q, $J_{C,F}$=3.8 Hz), 121.8, 124.0 (q, $J_{C,F}$=272 Hz), 91.5, 88.0, 69.5, 51.7, 30.8. HRMS: calcd for $C_{19}H_{15}O_2F_3Na$ ($MNa^+$) 355.0916, found 355.0923.

*4.6.5. (E)-4-Hydroxy-4-(4-styrylphenyl)butan-2-one (**6a**).* To a mixture of aldehyde **5a** (104.1 mg, 0.5 mmol, 1.0 equiv), acetone (1.0 mL, 14 mmol), and water (1.0 mL) was added pyrrolidine (12.5 μL, 0.15 mmol, 0.3 equiv) at room temperature (23 °C) and the mixture was stirred. After 30 min, the mixture was diluted with water and extracted with EtOAc. Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc=7:3) to afford **6a** (80 mg, 60%) as a colorless amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.46–7.42 (m, 4H), 7.34–7.27 (m, 4H), 7.21–7.17 (m, 1H), 7.03 (s, 2H), 5.09 (dd, $J$=8.8 Hz, 3.5 Hz, 1H), 3.20 (br s, 1H), 2.86–2.73 (m, 2H), 2.14 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 209.0, 142.1, 137.2, 136.8, 128.8, 128.7, 128.1, 127.6, 126.6, 126.5, 126.0, 69.6, 51.8, 30.8. HRMS: calcd for $C_{18}H_{18}O_2Na$ ($MNa^+$) 289.1199, found 289.1205.

*4.6.6. (E)-4-(4-(1-Hydroxy-3-oxobutyl)styryl)benzonitrile (**6b**).* To a mixture of aldehyde **5b** (85.0 mg, 0.36 mmol, 1.0 equiv), acetone (1.5 mL, 20 mmol), and water (1.5 mL) was added pyrrolidine (9.1 μL, 0.11 mmol, 0.3 equiv) at room temperature (23 °C) and the mixture was stirred. After 1 h, the mixture was diluted with water and extracted with EtOAc. Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash column chromatography (hexane/EtOAc=7:3) to afford **6b** (25 mg, 24%) as a pale yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.65–7.51 (m, 6H), 7.45–7.31 (m, 2H), 7.23–7.06 (m, 2H), 5.18 (dd, $J$=8.0, 3.5 Hz, 1H), 3.34 (br s, 1H), 2.93–2.82 (m, 2H), 2.22 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 208.9, 143.2, 141.7, 135.7, 132.4, 131.9, 127.0, 126.8, 126.7, 126.1, 119.0, 110.6, 69.5, 51.7, 30.8. HRMS: calcd for $C_{19}H_{18}NO_2$ ($MH^+$) 292.1332, found 292.1366.

### 4.7. Synthesis and characterization of standards of thiazolidines

*4.7.1. General procedure for the synthesis of standards of thiazolidines **7** and **8**.* A solution of L-cysteine (51 mg, 0.42 mmol) in water (0.4 mL) was added to a solution of aldehyde (0.35 mmol) in THF (3.5 mL) at room temperature and the mixture was stirred under an argon atmosphere. After 2–5 h, solvent was evaporated under reduced pressure and water (1–2 mL) was added. Generated solid was filtered and washed with water and $CH_2Cl_2$ to afford the corresponding thiazolidine.

*4.7.1.1. 2-Phenylthiazolidine-4-carboxylic acid (**7a**).*[8a,17] Reaction was performed on a 1.5-fold-scale of the general procedure. Colorless amorphous solid, 67 mg, 62%, dr 56:44. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.52 (d, $J$=7.4 Hz, 2H×0.44), 7.44 (d, $J$=7.4 Hz, 2H×0.56), 7.39–7.26 (m, 3H), 5.67 (s, 1H×0.56), 5.50 (s, 1H×0.44), 4.24 (dd, $J$=7.0, 4.6 Hz, 1H×0.56), 3.92–3.88 (m, 1H×0.44), 3.40–3.05 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.9, 172.2, 141.2, 138.9, 128.4, 128.3, 128.2, 127.6, 127.2, 126.9, 71.7, 71.0, 65.4, 64.9, 38.4, 37.9. HRMS: calcd for $C_{10}H_{12}NO_2S$ ($MH^+$) 210.0583, found 210.0596.

*4.7.1.2. 2-(4-Cyanophenyl)thiazolidine-4-carboxylic acid (**7b**).*[8a,17] Colorless amorphous solid, 56 mg, 70%, dr 61:39. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.83 (d, $J$=8.0 Hz, 2H×0.39), 7.78 (d, $J$=8.0 Hz, 2H×0.61), 7.72 (d, $J$=8.0 Hz, 2H×0.39), 7.60 (d, $J$=8.0 Hz, 2H×0.61), 5.80 (s, 1H×0.61), 5.59 (s, 1H×0.39), 4.14-4.11 (m, 1H×0.61), 3.95 (dd, $J$=8.8, 6.8 Hz, 1H×0.39), 3.38–3.06 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.6, 171.9, 147.9, 145.1, 132.3, 132.2, 128.7, 127.6, 118.7, 118.6, 110.7, 110.0, 70.5, 69.7, 65.7, 64.9, 38.1. HRMS: calcd for $C_{11}H_{11}N_2O_2S$ ($MH^+$) 235.0536, found 235.0547.

*4.7.1.3. 2-(4-Methylphenyl)thiazolidine-4-carboxylic acid (**7c**).*[8a] Reaction was performed on a 1.2-fold-scale of the general procedure. Colorless amorphous solid, 50 mg, 52%, dr 54:46. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.39 (d, $J$=8.0 Hz, 2H×0.46), 7.32 (d, $J$=8.0 Hz, 2H×0.54), 7.17 (d, $J$=8.0 Hz, 2H×0.46), 7.13 (d, $J$=8.0 Hz, 2H×0.54), 5.62 (s, 1H×0.54), 5.46 (s, 1H×0.46), 4.24 (dd, $J$=7.2, 4.4 Hz, 1H×0.54), 3.90–3.85 (m, 1H×0.46), 3.39–3.34 (m, 1H×0.46), 3.28 (dd, $J$=10.0, 7.2 Hz, 1H×0.54), 3.14 (dd, $J$=10.0, 4.4 Hz, 1H×0.54), 3.08–3.04 (m, 1H×0.46), 2.29 (s, 3H×0.46), 2.28 (s, 3H×0.54). $^{13}$C (100 MHz, DMSO-$d_6$): $\delta$ 173.0, 172.2, 138.0, 137.6, 136.8, 135.8, 129.0, 128.7, 127.1, 126.9, 71.7, 71.0, 65.3, 64.8, 38.4, 37.9, 20.7, 20.6. HRMS: calcd for $C_{11}H_{14}NO_2S$ ($MH^+$) 224.0740, found 224.0750.

*4.7.1.4. 2-(4-Methoxyphenyl)thiazolidine-4-carboxylic acid (**7d**).*[8a] Colorless amorphous solid, 14 mg, 15%, dr 1:1. $^1$H NMR

(400 MHz, DMSO-$d_6$): $\delta$ 7.43 (d, $J$=8.6 Hz, 2H×0.5), 7.36 (d, $J$=8.6 Hz, 2H×0.5), 6.92 (d, $J$=8.6 Hz, 2H×0.5), 6.88 (d, $J$=8.6 Hz, 2H×0.5), 5.59 (s, 1H×0.5), 5.45 (s, 1H×0.5), 4.25 (dd, $J$=7.2, 4.2 Hz, 1H×0.5), 3.88–3.83 (m, 1H×0.5), 3.75 (s, 3H×0.5), 3.74 (s, 3H×0.5), 3.36 (dd, $J$=10.0, 7.2 Hz, 1H×0.5), 3.28 (dd, $J$=10.0, 7.2 Hz, 1H×0.5), 3.15 (dd, $J$=10.0, 4.2 Hz, 1H×0.5), 3.08–3.03 (m, 1H×0.5). $^{13}$C (100 MHz, DMSO-$d_6$): $\delta$ 173.1, 172.3, 159.2, 158.7, 132.9, 130.7, 128.5, 128.3, 113.8, 113.5, 71.5, 70.9, 65.3, 64.8, 55.11, 55.07, 38.5, 37.8. HRMS: calcd for $C_{11}H_{14}NO_3S$ ($MH^+$) 240.0689, found 240.0698.

*4.7.1.5. 2-(4-Ethynylphenyl)thiazolidine-4-carboxylic acid (**7e**).* Colorless amorphous solid, 54 mg, 66%, dr 61:39. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.54–7.43 (m, 2H), 5.71 (s, 1H×0.61), 5.52 (s, 1H×0.39), 4.20 (s, 1H×0.39), 4.18 (dd, $J$=6.8, 4.8 Hz, 1H×0,61), 4.16 (s, 1H×0.61), 3.91 (dd, $J$=8.8, 7.2 Hz, 1H×0.39), 3.36 (dd, $J$=10.0, 7.2 Hz, 1H×0.39), 3.29 (dd, $J$=10.0, 6.8 Hz, 1H×0.61), 3.13–3.05 (m, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.8, 172.1, 142.6, 140.0, 131.8, 131.6, 127.6, 127.1, 121.5, 120.7, 83.3, 83.1, 81.1, 80.8, 71.1, 70.4, 65.5, 64.9, 38.3, 38.0. HRMS: calcd for $C_{12}H_{12}NO_2S$ ($MH^+$) 234.0583, found 234.0591.

*4.7.1.6. 2-(4-Phenylethynylphenyl)thiazolidine-4-carboxylic acid (**8a**).* Reaction was performed on a 26%-scale of the general procedure. Colorless amorphous solid, 22 mg, 77%, dr 61:39. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.57–7.42 (m, 9H), 5.73 (s, 1H×0.61), 5.54 (s, 1H×0.39), 4.20 (dd, $J$=6.8, 5.2 Hz, 1H×0.61), 3.91 (dd, $J$=8.8, 7.2 Hz, 1H×0.39), 3.40–3.07 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.8, 172.1, 142.4, 139.8, 131.42, 131.36, 131.28, 131.25, 128.8, 128.7, 127.7, 127.2, 122.2, 122.1, 122.0, 121.3, 89.6, 89.3, 89.2, 89.0, 71.2, 70.4, 65.6, 64.9, 38.3, 38.0. HRMS: calcd for $C_{18}H_{16}NO_2S$ ($MH^+$) 310.0896, found 310.0904.

*4.7.1.7. 2-(4-(4-Cyanophenylethynyl)phenyl)thiazolidine-4-carboxylic acid (**8b**).* Pale yellow amorphous solid, 93 mg, 80%, dr 1:1. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.92–7.49 (m, 8H), 5.74 (s, 1H×0.5), 5.56 (s, 1H×0.5), 4.19 (dd, $J$=6.8, 5.2 Hz, 1H×0.5), 3.92 (dd, $J$=8.8, 6.8 Hz, 1H×0.5), 3.40–3.06 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.8, 172.0, 143.3, 140.6, 132.6, 132.12, 132.09, 131.7, 131.5, 127.8, 127.3, 127.1, 127.0, 121.1, 120.4, 118.4, 111.0, 110.9, 93.2, 93.0, 88.2, 88.0, 71.1, 70.3, 65.6, 64.9, 38.3, 38.0. HRMS: calcd for $C_{19}H_{15}N_2O_2S$ ($MH^+$) 335.0854, found 335.0869.

*4.7.1.8. 2-(4-(4-Methylphenylethynyl)phenyl)thiazolidine-4-carboxylic acid (**8c**).* Colorless amorphous solid, 89 mg, 77%, dr 1:1. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.58–7.22 (m, 8H), 5.72 (s, 1H×0.5), 5.54 (s, 1H×0.5), 4.20 (dd, $J$=6.8, 4.8 Hz, 1H×0.5), 3.92 (dd, $J$=8.8, 7.2 Hz, 1H×0.5), 3.38 (dd, $J$=10.0, 7.2 Hz, 1H×0.5), 3.31 (dd, $J$=10.2, 6.8 Hz, 1H×0.5), 3.13 (dd, $J$=10.2, 4.8 Hz, 1H×0.5), 3.12–3.07 (m, 1H×0.5), 2.34 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.8, 172.1, 142.1, 139.5, 138.6, 138.5, 131.32, 131.27, 131.24, 131.15, 129.3, 127.7, 127.2, 122.2, 121.5, 119.2, 119.1, 89.8, 89.5, 88.6, 88.4, 71.2, 70.5, 65.5, 64.9, 38.3, 38.0, 21.0. HRMS: calcd for $C_{19}H_{18}NO_2S$ ($MH^+$) 324.1053, found 324.1065.

*4.7.1.9. 2-(4-(4-Methoxyphenylethynyl)phenyl)thiazolidine-4-carboxylic acid (**8d**).* Colorless amorphous solid, 85 mg, 72%, dr 59:41. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.56–6.96 (m, 8H), 5.72 (s, 1H×0.59), 5.54 (s, 1H×0.41), 4.20 (dd, $J$=6.9, 4.9 Hz, 1H×0.59), 3.91 (dd, $J$=8.8, 7.0 Hz, 1H×0.41), 3.79 (s, 3H), 3.37 (dd, $J$=10.0, 7.0 Hz, 1H×0.41), 3.31 (dd, $J$=10.2, 6.9 Hz, 1H×0.59), 3.13 (dd, $J$=10.2, 4.9 Hz, 1H×0.59), 3.09 (dd, $J$=10.0, 8.8 Hz, 1H×0.41). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.8, 172.1, 159.6, 159.5, 141.9, 139.3, 132.94, 132.90, 131.2, 131.0, 127.6, 127.2, 122.5, 121.7, 114.4, 114.14, 114.06, 89.8, 89.5, 87.8, 87.7, 71.2, 70.5, 65.5, 64.9, 55.2, 38.3, 38.0. HRMS: calcd for $C_{19}H_{18}NO_3S$ ($MH^+$) 340.1002, found 340.1011.

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## Supplementary data

Data of the initial rate determination (Tables S1 and S2, Fig. S1); NMR spectra; full authorship of Gaussian 09; Cartesian coordinates and absolute energies of stationary points (Tables S3 and S4). Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.03.056.

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