

Asymmetric  $\delta$ -Lactam Synthesis with a Monomeric Streptavidin Artificial MetalloenzymeIsra S. Hassan,<sup>†,§</sup> Angeline N. Ta,<sup>‡,§</sup> Michael W. Danneman,<sup>†,‡,§</sup> Natthawat Semakul,<sup>†,‡,§</sup> Matthew Burns,<sup>†,‡</sup> Corey H. Basch,<sup>†</sup> Vanessa N. Dippon,<sup>†</sup> Brian R. McNaughton,<sup>\*,‡,§</sup> and Tomislav Rovis<sup>\*,†,‡,§</sup><sup>†</sup>Department of Chemistry, Columbia University, New York, New York 10027, United States<sup>‡</sup>Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

## S Supporting Information

**ABSTRACT:** Reliable design of artificial metalloenzymes (ArMs) to access transformations not observed in nature remains a long-standing and important challenge. We report that a monomeric streptavidin (mSav) Rh(III) ArM permits asymmetric synthesis of  $\alpha,\beta$ -unsaturated- $\delta$ -lactams via a tandem C–H activation and [4+2] annulation reaction. These products are readily derivatized to enantioenriched piperidines, the most common *N*-heterocycle found in FDA approved pharmaceuticals. Desired  $\delta$ -lactams are achieved in yields as high as 99% and enantiomeric excess of 97% under aqueous conditions at room temperature. Embedding a Rh cyclopentadienyl (Cp\*) catalyst in the active site of mSav results in improved stereocontrol and a 7-fold enhancement in reactivity relative to the isolated biotinylated Rh(III) cofactor. In addition, mSav-Rh outperforms its well-established tetrameric forms, displaying 11–33 times more reactivity.

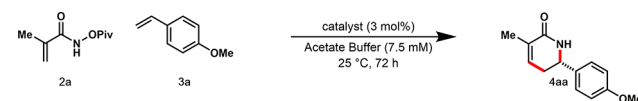
Piperidines are the most common *N*-heterocycle found in FDA approved drugs.<sup>1</sup> Strategies to assemble this important structural motif are common but often involve cyclization, which necessitates the preassembly of an acyclic precursor.<sup>2</sup> Two-component approaches such as cycloadditions or annulations are inherently more attractive. A handful of recent [4+2] cycloaddition approaches have been devised, using *N*-heterocyclic carbene,<sup>3–5</sup> cinchona alkaloid,<sup>6</sup> chiral phosphoric acid<sup>7</sup> or metal catalysis.<sup>8,9</sup> Although each strategy is useful, they are limited to specific classes of precursors and substitution patterns. An alternative approach is to develop a methodology that enables access to  $\alpha,\beta$ -unsaturated- $\delta$ -lactams from simple precursors under mild conditions.<sup>10,11</sup> In this context, the coupling of acrylamides with abundant  $\alpha$ -olefins via C–H activation and annulation would provide direct access to  $\alpha,\beta$ -unsaturated- $\delta$ -lactams in a single step.

Rh(III) catalysis has been extensively demonstrated to mediate C–H activation reactions involving C(sp<sup>2</sup>)–H bonds proximal to a directing group.<sup>12</sup> The subsequent functionalization with alkenes is less well-developed but has been documented for benzhydroxamate esters<sup>13</sup> and unsaturated oxime esters<sup>14</sup> delivering *N*-heterocycles in good yield. The

direct union of acrylamide hydroxamate esters with alkenes has not been disclosed.<sup>15</sup>

In collaboration with the Ward group,<sup>16</sup> we have previously described a tetrameric streptavidin (tSav) system containing a biotinylated Rh(III) cofactor for the asymmetric synthesis of dihydroisoquinolones using benzhydroxamate esters and acrylate partners (Figure 1ii).<sup>17</sup> In concurrent work, Cramer reported a small-molecule chiral Rh(III) catalyst for a complementary coupling reaction involving styrene partners (Figure 1iii).<sup>18</sup>

Table 1. Reaction Optimization and Controls



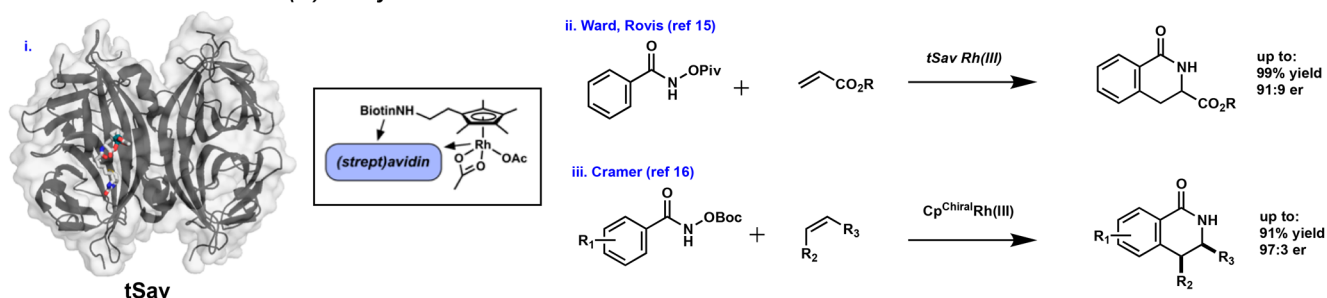
| entry          | catalyst   | NMR yield (%) <sup>a</sup> | enantiomeric excess (%) <sup>b</sup> |
|----------------|--|----------------------------|--------------------------------------|
| 1              | Cp*RhCl <sub>2</sub>                                     | 25                         | 0                                    |
| 2              | Cp* <sup>biotin</sup> RhCl <sub>2</sub>                  | 15                         | 0                                    |
| 3              | wt-tSav:Cp* <sup>biotin</sup> RhCl <sub>2</sub>          | 9                          | –26                                  |
| 4 <sup>c</sup> | N118K-K121E-tSav:Cp* <sup>biotin</sup> RhCl <sub>2</sub> | 3                          | 0                                    |
| 5 <sup>d</sup> | wt-mSav:Cp* <sup>biotin</sup> RhCl <sub>2</sub>          | 44                         | 92                                   |
| 6              | wt-mSav:Cp* <sup>biotin</sup> RhCl <sub>2</sub>          | 99                         | 91                                   |
| 7              | wt-mSav:Cp* <sup>biotin</sup> RhCl <sub>2</sub>          | 58                         | 82                                   |

2a (3.0  $\mu$ mol), 3a (1.5  $\mu$ mol), catalyst, in 200  $\mu$ L of acetate buffer (62.5 mM NaOAc, 100 mM NaCl, pH 7.4) with 3  $\mu$ L of MeOH. <sup>a</sup>Conversion and yield determined by <sup>1</sup>H NMR analysis relative to a trimethyl(phenyl)silane internal standard. <sup>b</sup>Enantiomeric excess determined by HPLC analysis. <sup>c</sup>1 mol % catalyst. <sup>d</sup>200  $\mu$ L of NaCl buffer (100 mM NaCl, pH 7.4) used.

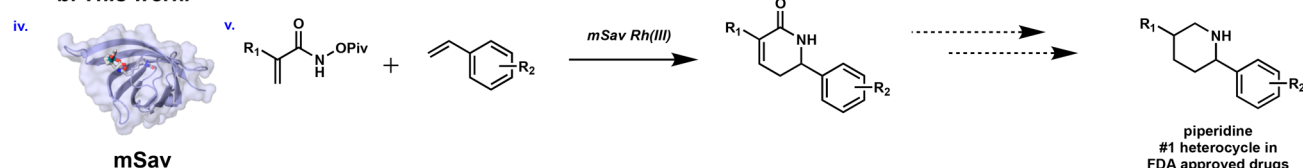
The most common ArM platform developed to date is the biotin-tetrameric (strept)avidin (biotin-tSav) system, pioneered by Whitesides<sup>19</sup> and Ward<sup>20</sup> (Figure 1a). These ArMs utilize high affinity (up to  $K_D \sim 10^{-14}$  M) interactions between tSav and biotin–metal conjugates. tSav-based ArMs have been utilized in an increasing number of transition-metal mediated transformations.<sup>14</sup> Herein, we introduce a new ArM platform based on monomeric streptavidin (mSav) and demonstrate its use in the direct enantioselective coupling of

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## a. Previous ArM for Rh(III) catalysis:

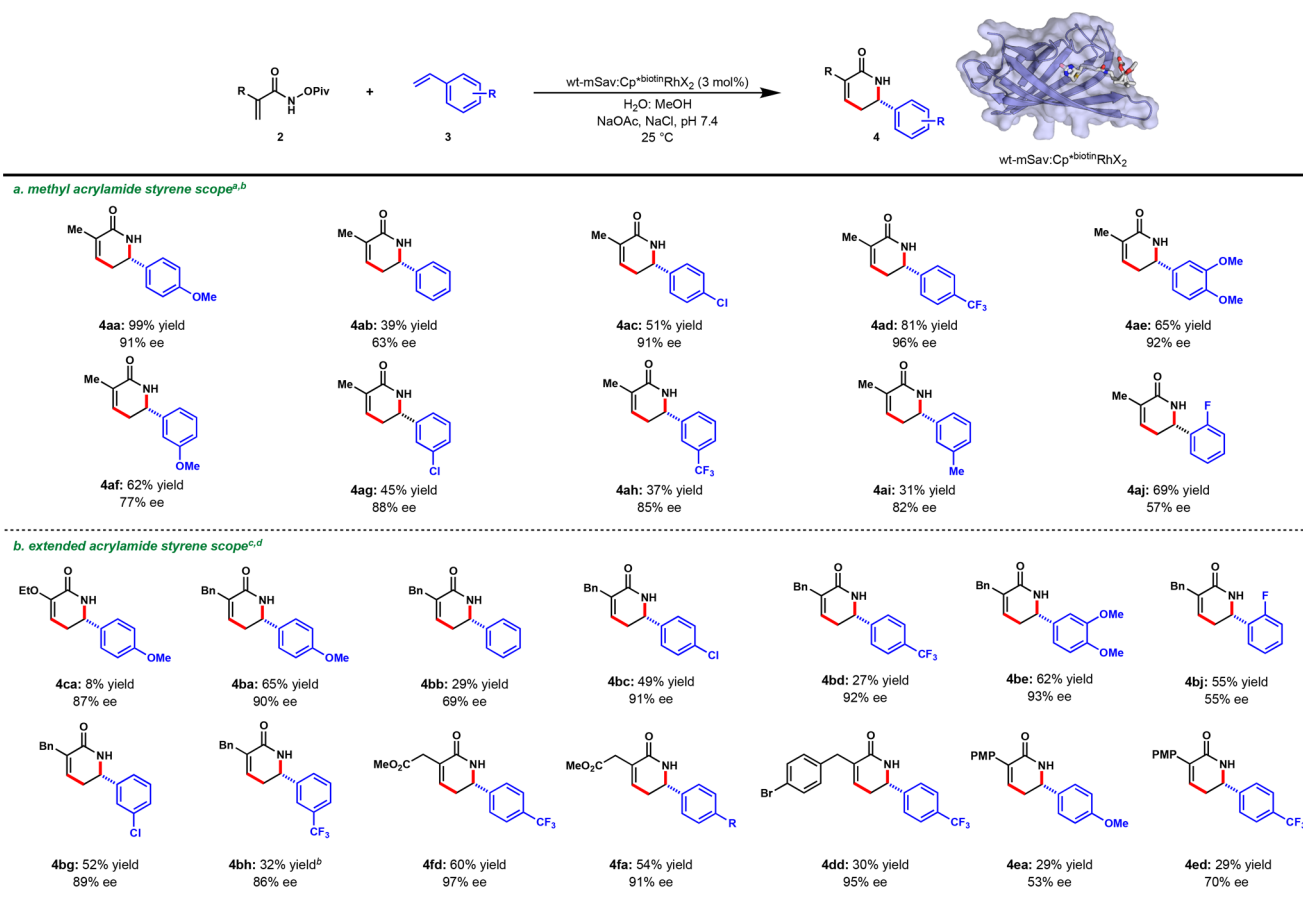


## b. This work:



**Figure 1.** (a) i. tetrameric streptavidin (tSav) ArM; ii. Previously developed tSav Rh(III) benzhydroxamate coupling; iii. Cramer's enantioselective Chiral Cp variant. (b) iv. monomeric streptavidin (mSav) ArM. v. Target transformation (this work). [tSav (PDB ID: 3RY1) and mSav (PDB ID: 4JNJ) were complexed with the biotin cofactor in AutoDock and rendered in PyMOL.]

## Scheme 1. (a) Methyl Acrylamide Styrene Scope; (b) Extended Acrylamide Styrene Scope



<sup>a</sup>Reaction conditions: **2a** (3.0  $\mu\text{mol}$ ), **3** (1.5  $\mu\text{mol}$ ), catalyst, in 200  $\mu\text{L}$  of acetate buffer (62.5 mM NaOAc, 100 mM NaCl, pH 7.4) with 3  $\mu\text{L}$  MeOH, at 25  $^\circ\text{C}$  for 72 h. <sup>b</sup>Yields determined by  $^1\text{H}$  NMR analysis relative to a trimethyl(phenyl)silane internal standard. Enantiomeric excess determined by HPLC analysis. PMP = *para*-methoxyphenyl.

acrylamide hydroxamate esters and styrenes (Figure 1v). The reaction allows rapid access to piperidines, the most common *N*-heterocycle found in FDA-approved pharmaceuticals.<sup>1,21</sup>

Initial investigations examined the coupling of methacrylamide **2a** with styrene **3a**.<sup>22</sup> The use of Cp\*Rh(III) as a catalyst under aqueous buffer conditions delivers **4aa** in modest yield

(entry 1, Table 1).<sup>23</sup> The use of biotinylated Rh cofactor as catalyst provides **4aa** in 15% yield. Incorporation of the cofactor into wt tSav leads to further diminished yields and very low selectivities (entry 3, Table 1). Similarly, a mutant tSav (N118 K/K121E) that proved to be a highly reactive ArM in our previous work<sup>14</sup> did not provide the desired  $\delta$ -lactam (**4aa**) in appreciable yield (Table 1, entry 4). In an effort to improve the reaction, we turned our attention to monomeric streptavidin (mSav, Figure 1-iv). We reasoned that the use of mSav, with a more exposed Rh binding site relative to tSav, could serve as a competent ArM template, and may simplify ArM tuning and analysis. Like tSav, biotin is bound tightly by mSav ( $K_D \sim 2 \text{ nM}$ <sup>24–26</sup>) but has been engineered to resist tetramerization by replacing hydrophobic amino-acid residues at the barrel–barrel interface with charged ones.

In the event, 1 mol % wt-mSav:Cp<sup>\*biotin</sup>RhCl<sub>2</sub> ArM in acetate buffer enables the coupling of acrylamide (**2a**) and *para*-methoxystyrene (**3a**) to provide the desired  $\delta$ -lactam (**4aa**) in 44% yield and 92% enantiomeric excess (ee), (Table 1, entry 5).<sup>27</sup> A modest increase in metalloenzyme catalyst loading results in substantially higher yield and virtually identical selectivity, delivering the desired  $\delta$ -lactam (**4aa**) in 99% yield and 91% ee (Table 1, entry 6). The use of 100 mM NaCl in place of acetate buffer leads to 58% yield (Table 1, entry 7).

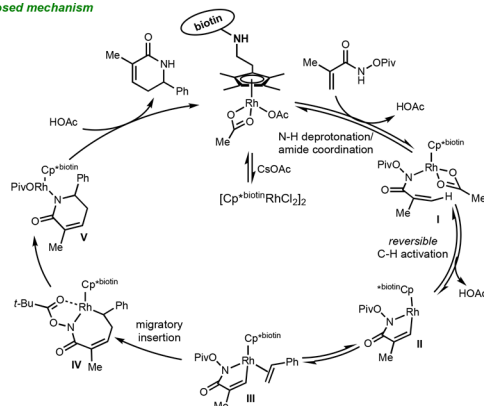
The wt-mSav:Cp<sup>\*biotin</sup>RhCl<sub>2</sub> catalyzed reaction proved broadly tolerant to the coupling partners employed (Scheme 1). With respect to the styrene partner (Scheme 1a), enantioselectivities are best with *para*-substituted styrenes, regardless of electronic character. Meta-substituted styrenes are also tolerated, affording good to high enantioselectivities, while a single *ortho*-substituted styrene leads to somewhat decreased selectivity. Styrene itself is a poor substrate, proceeding in modest selectivity and yield (**4ab**). Importantly, all substrates give the desired  $\delta$ -lactam products as single regioisomers. Substitution on the acrylamide is well tolerated regardless of steric demand affording product with enantioselectivities that match the corresponding methacrylamide system (Scheme 1b). However, aryl- and alkoxy- substitution results in diminished yields (**4ca**, **4ea** and **4ed**).

A plausible catalytic cycle for this reaction<sup>28</sup> is proposed in Scheme 2. Metalation of the amide by rhodium generates intermediate **I**. C–H activation occurs, presumably via a concerted-metalation deprotonation (CMD) mechanism, providing five-membered rhodacycle **II**. A deuterium labeling experiment illustrates that the C–H activation step is reversible, suggesting that the concerted metalation/deprotonation (CMD) is not the turnover limiting step (Scheme 2b). Subsequent alkene coordination and migratory insertion would give seven-membered rhodacycle **IV**. Available evidence suggests this step is the enantiodetermining event. N–O bond cleavage and reductive elimination then occurs to form transient Rh(III) intermediate **V**. Protodemetalation regenerates the Rh(III) catalyst and closes the catalytic cycle.

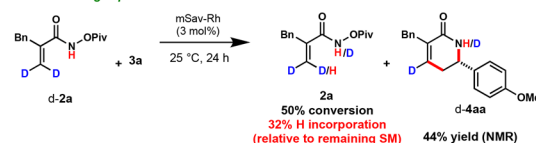
While the Cp<sup>\*biotin</sup>RhCl<sub>2</sub> cofactor alone delivers the desired  $\delta$ -lactam (**4aa**) with no appreciable selectivity (0% ee, Table 1, entry 2), its significantly reduced reactivity was a surprise (15% yield with 3 mol % catalyst loading, compared to 99% yield with an equivalent of the mSav artificial metalloenzyme). To begin to evaluate the molecular dictates of reactivity and stereocontrol, we determined that mutation of tyrosine 112 (Y112), which neighbors the putative Cp<sup>\*biotin</sup>Rh pocket has a significant effect on the transformation. In comparison to the

## Scheme 2. (a) Proposed Mechanism; (b) Labelling Experiment; (c) Mutational Study

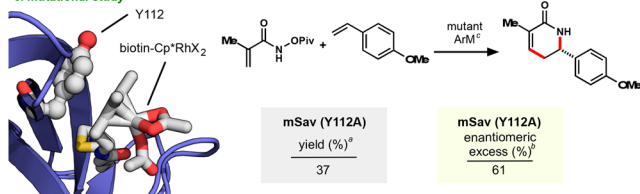
### a. proposed mechanism



### b. deuterium labeling experiment<sup>a,b</sup>



### c. mutational study



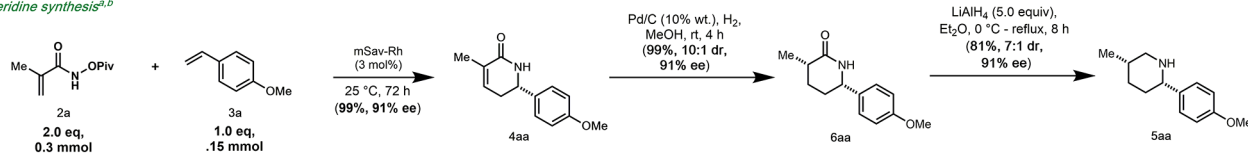
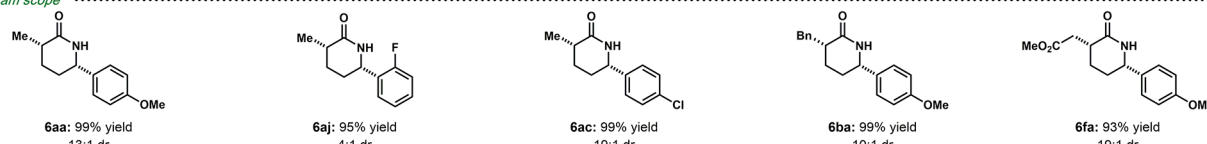
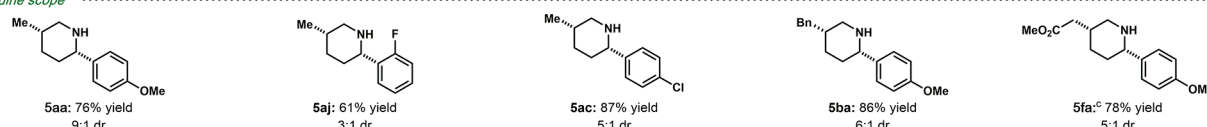
<sup>a</sup>Reaction conditions: **2a** (3.0  $\mu\text{mol}$ ), **3** (1.5  $\mu\text{mol}$ ), catalyst, in 200  $\mu\text{L}$  of acetate buffer (62.5 mM NaOAc, 100 mM NaCl, pH 7.4) with 3  $\mu\text{L}$  of MeOH, at 25  $^{\circ}\text{C}$  for 72 h. <sup>b</sup>Yields determined by  $^1\text{H}$  NMR analysis relative to a trimethyl(phenyl)silane internal standard.

ArM featuring wt-mSav, the Y112A mutant provides the desired product in low yield and enantiomeric excess (37% and 61%, respectively). This observation is consistent with its likely role as a rigidifying element through  $\pi$ -stacking to the Cp framework on the catalyst.<sup>17,29</sup> Despite significant decreases in reactivity and selectivity, Y112A maintains affinity for biotin (see Supporting Information).

In order to derivatize the resulting  $\delta$ -lactam products into piperidines, the coupling of **2a** and **3a** to provide **4aa** was performed at a 0.15 mmol scale providing identical results to the reaction performed on a 1.5  $\mu\text{mol}$  scale (99% yield, 91% ee) (Scheme 3a). Hydrogenation of **4aa** affords the reduced lactam **6aa** in 99% yield and 10:1 dr. Subsequent reduction of **6aa** with  $\text{LiAlH}_4$  furnishes the desired piperidine **5aa** in 81% yield and 7:1 dr (Scheme 3).

Indeed, the derivatization can proceed under exceedingly mild reduction conditions. Treatment of a range of  $\delta$ -lactams (**6**) formed in good diastereoselectivity following hydrogenation with  $\text{BH}_3\cdot\text{SMe}_2$  provides the corresponding piperidines in good yield and comparable diastereoselectivity to the  $\text{LiAlH}_4$  reduction (Scheme 3b,c). Notably, these reduction conditions are tolerant of ester functionalities (**5fa**) with a slight erosion of diastereoselectivity, likely due to competitive imine/enamine tautomerization of an intermediate.

In conclusion, we have developed an artificial metalloenzyme that efficiently catalyzes an enantioselective tandem C–H activation and [4+2] annulation reaction to afford  $\delta$ -

Scheme 3. (a) Preparative Scale  $\delta$ -Lactam Synthesis and Piperidine Derivatization; (b) Lactam Scope; (c) Piperidine Scopea. Piperidine synthesis<sup>a,b</sup>b. Lactam scope<sup>b</sup>c. Piperidine scope<sup>b</sup>

<sup>a</sup>Reaction conducted at a 0.15 mmol scale. <sup>b</sup>Derivatization performed on racemic products. Diastereoselectivity determined by <sup>1</sup>H NMR analysis relative to a trimethyl(phenyl)silane internal standard. Isolated yields. <sup>c</sup>Reaction conducted with 5 equiv BH<sub>3</sub>·SMe<sub>2</sub> and 5 equiv *n*-PrNH<sub>2</sub>.

substituted lactams. This metalloenzyme accepts a diverse array of acrylamide and styrene coupling partners. The mSav metalloenzyme platform demonstrates superior reactivity relative to its tSav counterpart and the free cofactor alone. Efforts to understand the crucial factors responsible for improved reactivity are currently underway.

## ■ ASSOCIATED CONTENT

## ● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b01596.

Detailed experimental procedures, characterization data, copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for all isolated compounds (PDF)

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<sup>§</sup>These authors contributed equally.

## Notes

The authors declare the following competing financial interest(s): A provisional patent has been filed on aspects of this work.

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- (22) The solid acrylamide needs to be administered as a solution in methanol. Both the acrylamide and styrene are only slightly soluble in water. The metalloenzyme reaction starts out clear in appearance and gradually turns cloudy as the reaction progresses.
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