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# Peptide catalyzed regio- and enantioselective $\epsilon$ -alkylation of $\gamma$ -branched 2,4-dienals *via* trienamine activation†

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**The regio- and enantioselective  $\epsilon$ -alkylation of  $\gamma$ -branched 2,4-dienals was successfully achieved *via* trienamine catalysis. N-Terminal prolyl pentapeptide with a turn structure was effective as a catalyst for this transformation.**

The vinylogous reactivity of enolate equivalents derived from  $\alpha,\beta$ -unsaturated aldehydes and their higher conjugated analogues is of interest from the perspective of regio- and stereoselectivity.<sup>1</sup> Enamine catalysis is a powerful method for generating such nucleophiles from a variety of aldehydes, including unsaturated ones.<sup>2</sup> The merit of enamine catalysis lies in its ability to elevate the HOMO energy level and provide efficient stereocontrol due to the nature of covalent catalysis. In this context, numerous regio- and enantioselective reactions have been reported for chiral dienamines derived from enals (Fig. 1, left).<sup>3</sup>

In 2006, Jørgensen's group reported the dienamine catalysis for the regio- and enantioselective  $\gamma$ -amination of enals using azodicarboxylate esters.<sup>4</sup> This finding prompted researchers to study the reaction of dienamines with a variety of substrates. In some cases, the reaction preferentially proceeds at the  $\alpha$ -position,<sup>5</sup> yielding products as either  $\alpha,\beta$ -unsaturated<sup>6</sup> or  $\beta,\gamma$ -unsaturated aldehydes.<sup>7</sup> For the former type of the products, while the dienamine mechanism is plausible, the possibility of a Morita–Baylis–Hillman (MBH)-type mechanism cannot be excluded.<sup>5</sup>  $\gamma$ -Selectivity for the reaction of enals *via* dienamine catalysis has also been observed in alkylation, aldol reaction, and the reaction with metal-activated electrophiles.<sup>3b,8</sup> For the alkylation of dienamines with a cation precursor 4,4'-bis(dimethylamino)benzhydrol (BDAB), regioselectivity is influenced by the substituents on the dienamine (Scheme 1a).<sup>7b,9</sup> The enantiofacial selectivity of dienamines can be controlled either by steric repulsion from the bulky substituent on the amine catalyst<sup>9b,10</sup> or through attracting interactions between

the electrophile and the catalyst molecule.<sup>11</sup> Through theoretical calculation, Jørgensen's group demonstrated that the mechanism of the  $\gamma$ -selective amination of dienamine is the consecutive Diels–Alder reaction and the hydrolysis of the resulting amins rather than the simple nucleophilic addition.<sup>4</sup> Inspired by this finding, the cycloaddition chemistry of dienamines has also been widely explored.<sup>12</sup>

In the study of trienamine reactivity (Fig. 1, right), early investigations focused on [4+2] cycloadditions occurring at the  $\beta$ - and  $\epsilon$ -positions.<sup>13</sup> As a result, the cycloaddition chemistry of trienamines with various dienophiles has been extensively investigated.<sup>12,14</sup> In contrast, studies on one-bond-forming reactions remain relatively limited. In 2015, Albrecht's group demonstrated that 5-alkyl furfurals undergo dearomative trienamine formation, which then reacts with electrophiles in an  $\epsilon$ -selective manner.<sup>15</sup> Several variants of this reaction have since been developed.<sup>16</sup> Two studies have explored one-bond-forming reaction of simple linear trienamines derived from dienals. Melchiorre's group demonstrated a photocatalytic C–C bond formation of aldehydes *via* enamine catalysis, where a trienamine derived from diarylprolinol silyl ether and 2,4-heptadienal reacted with complete  $\epsilon$ -selectivity but no enantioselectivity (Scheme 1b).<sup>17</sup> Later, Appayee's group showed that, using pyrrolidine or its derivatives, the alkylation of the trienamine *via* an  $S_N1$  mechanism selectively occurred at the  $\alpha$ -position, yielding MBH-type products without creating a chiral center (Scheme 1c).<sup>18</sup> Currently, there are no reported examples of a reaction that achieves both regio- and enantioselective one bond formation in trienamines.

Our group previously reported a regioselective 1,6-addition to 2,4-dienals *via* an iminium ion intermediate, utilizing an

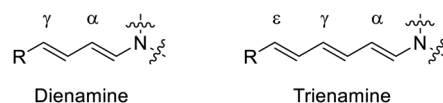
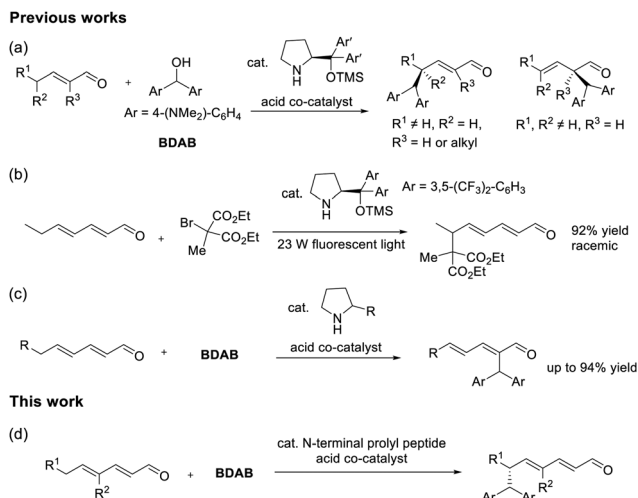


Fig. 1 Molecular structure of dienamine and trienamine derived from unsaturated aldehydes.

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Scheme 1 Alkylation via di- and trienamine catalysis.

N-terminal prolyl peptide with a turn structure as a catalyst.<sup>19</sup> We envisaged that a similar directing effect of the peptide catalyst could facilitate the regioselective reaction of diene-derived trienamines. Herein, we report the regio- and enantioselective  $\epsilon$ -alkylation of 2,4-dienals *via* trienamine activation using a peptide catalyst under mild conditions (Scheme 1d).

According to our previous work, we initially attempted the alkylation of linear dienal **1** with **BDAB** using the peptide catalyst **C1**, H-Pro-D-Pro-Aib-Trp-Trp-PEG-PS resin,<sup>20</sup> in the presence of an acid co-catalyst.<sup>9a,18</sup> Although the yield was low,  $\epsilon$ -product was predominantly obtained (Table 1, entry 1).<sup>21</sup> The minor component was the  $\alpha$ -product with an MBH-type structure, which is consistent with a previous report by Appayee's group.<sup>18</sup>

Encouraged by this result, we carried out catalyst screening. As for the co-catalyst, an excess of weak acid was required for

optimal selectivity (Table 1, entries 1–4). The fifth amino acid residue from the N-terminus of the peptide was scanned because, according to our previous results,<sup>20</sup> the residue is likely to be positioned near the  $\epsilon$ -position of the trienamine intermediate. Substituting Trp with either a small (Ala) or bulky (Pya) residue reduced  $\epsilon$ -selectivity (entries 5 and 6). Notably, the acid co-catalyst remained effective when it was incorporated within the peptide chain (entry 7), showing only a slightly lower  $\epsilon$ -selectivity. Catalysts **C5** and **C6** only gave  $\alpha$ -products (entries 8 and 9). The low yields are primarily attributed to self-condensation of substrate **1**, leading to multiple side products. In all cases, no  $\gamma$ -substituted product was detected.

From the results of catalyst screening, it is suggested that the fifth Trp residue plays an important role for the  $\epsilon$ -selectivity. As the alkylation with **BDAB** is known to proceed through the intermediacy of benzylic cation species,<sup>9b</sup> attractive interaction of the cation and the electron rich indole ring on the Trp residue could be the driving force.<sup>22</sup> DFT calculations, using 3-methylindole (a model for the catalyst substructure) and the **BDAB**-derived cation, show a significant stabilization energy of 32 kJ mol<sup>-1</sup> upon complex formation. This stabilization is accompanied by a close contact (3.42 Å) between the aromatic rings of the two molecules (Fig. S1, ESI<sup>†</sup>). This strong intermolecular interaction may facilitate the delivery of the cation to the  $\epsilon$ -position.<sup>23</sup>

As for the enantioselectivity, despite extensive screening of the peptide catalysts and the reaction conditions, the enantiomeric excess (ee) value remained low at the maximum of 13%. A previous NMR study indicated that the trienamine made of diphenylprolinol trimethylsilyl ether and nona-2,4-dienal adopts a 1.4 : 1 mixture of (1*E*,3*E*,5*E*) and (1*E*,3*E*,5*Z*) isomers.<sup>24</sup> The result of DFT calculations on a model trienamine, 1-(hepta-1,3,5-trien-1-yl)-*N*-methyl prolinamide were in accordance with the NMR observation (Table S2, ESI<sup>†</sup>). This configurational heterogeneity may be responsible for the low enantioselectivity.

Related to this, an NMR study on the configuration of dienamines has been reported, where a similar configurational isomerism was observed.<sup>25</sup> In this context, Melchiorre's research group demonstrated that the introduction of  $\alpha$ -branching to the enal induced the preference for the (1*E*,3*E*) isomer of the dienamine.<sup>9b</sup> Accordingly, we presumed that the  $\gamma$ -branching structure could similarly impact trienamine configurations, potentially enhancing enantioselectivity.

To investigate this hypothesis, we selected dienal **2a** as a nucleophile precursor. To our delight, the regioselectivity remained largely unchanged, while the ee value increased to 72% under the same reaction conditions (Table 2, entry 1). The major enantiomer of the  $\epsilon$ -product was determined to have (*R*) configuration (Scheme S2, ESI<sup>†</sup>). Screening on peptide sequences revealed that the highest selectivity was achieved when Trp or its derivatives occupied the fifth position (Table S3, ESI<sup>†</sup>). Moreover, regioselectivity correlated positively with the electron density of the indole ring on the Trp derivatives. Conducting the reaction in toluene significantly improved outcomes (76% yield for 2 days at room temperature), affording the  $\epsilon$ -product with an  $\epsilon$ : $\alpha$  ratio of 97:3 and 89% ee (entry 6). Interestingly, the  $\alpha$ -product was obtained as 3,5-dienals.<sup>18</sup>

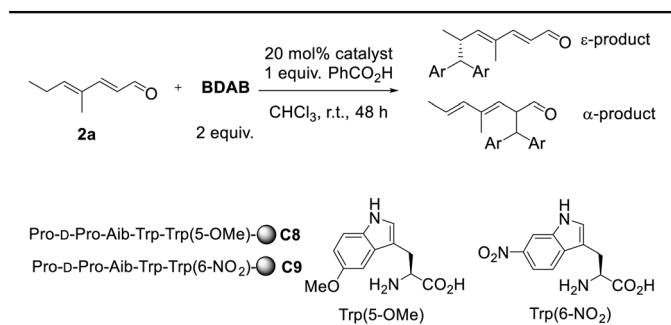
Table 1 Catalyst screening of regioselective alkylation of dienal **1**

Pro-D-Pro-Aib-Trp-Trp-● **C1**    **C5**    **C6**    ● : PEG-PS resin  
 Pro-D-Pro-Aib-Trp-Ala-● **C2**  
 Pro-D-Pro-Aib-Trp-Pya-● **C3**    Pya  
 Pro-D-Pro-Aib-Trp-Asp-● **C4**    Aib

Entry	Catalyst	Acid (equiv.)	Yield <sup>a</sup> (%)	$\epsilon$ : $\alpha$ <sup>a</sup>
1	<b>C1</b>	AcOH (0.2)	18	89 : 11
2	<b>C1</b>	AcOH (1.0)	30	90 : 10
3	<b>C1</b>	TFA (1.0)	21	71 : 29
4	<b>C1</b>	PhCO <sub>2</sub> H (1.0)	59	87 : 13
5	<b>C2</b>	PhCO <sub>2</sub> H (1.0)	22	36 : 64
6	<b>C3</b>	PhCO <sub>2</sub> H (1.0)	27	48 : 52
7	<b>C4</b>	—	29	86 : 14
8	<b>C5</b>	PhCO <sub>2</sub> H (1.0)	42	0 : 100
9	<b>C6</b>	PhCO <sub>2</sub> H (1.0)	24	0 : 100

<sup>a</sup> Determined by <sup>1</sup>H NMR spectra of the crude mixture.



**Table 2** Catalyst screening of regioselective alkylation of  $\gamma$ -branched dienal **2a**

Entry	Catalyst	Yield <sup>a</sup> (%)	$\epsilon$ : $\alpha$ <sup>a</sup>	ee <sup>b</sup> (%)
1	<b>C1</b>	45	89 : 11	72
2	<b>C3</b>	32	69 : 31	39
3	<b>C5</b>	31	0 : 100	—
4	<b>C8</b>	44	93 : 7	70
5	<b>C9</b>	48	77 : 23	66
6 <sup>c</sup>	<b>C1</b>	<b>78</b>	<b>97 : 3</b>	<b>89</b>
7 <sup>c</sup>	<b>C6</b>	24	0 : 100	—

<sup>a</sup> Determined by <sup>1</sup>H NMR spectra of the crude mixture. <sup>b</sup> ee of  $\epsilon$ -products. <sup>c</sup> Toluene was used as a solvent.

Subsequently, we applied the peptide catalyst to the  $\epsilon$ -alkylation of several  $\gamma$ -branched 2,4-dienals. As shown in Table 3, the  $\epsilon$ -products were obtained with high enantio- and regioselectivity. Furthermore, we also investigated the feasibility of extending regioselective  $\epsilon$ -alkylation to 3-(1-cyclohexen-1-yl)-2-propenal **2f** (Table 3, entry 6).

DFT calculations on 1-(4-methylhepta-1,3,5-trien-1-yl)-*N*-methyl prolinamide, which is a model compound of the trienammine from **2a**, revealed that the energy difference of (1*E*,3*E*,5*E*) and (1*E*,3*E*,5*Z*) isomers was 19.3 kJ mol<sup>-1</sup> and this value is significantly larger than that of the non- $\gamma$ -methylated counterpart (4.4 kJ mol<sup>-1</sup>, see Table S2, ESI†). This configurational preference for the trienammine, along with the conformational advantage for the (*s-trans*, *s-trans*, *s-trans*) structure, might serve as the enhancement of enantioselectivity.

**Table 3** Regioselective  $\epsilon$ -alkylation of  $\gamma$ -branched 2,4-dienals

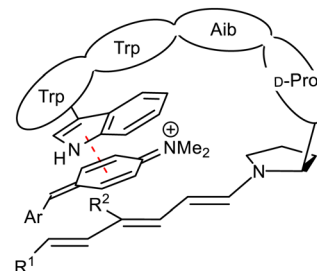
H-Pro-D-Pro-Aib-Trp-Trp  $\bullet$   
20 mol%  
1 equiv. PhCOOH  
toluene, r.t., 48 h

**2**

**3**

Entry	<b>2</b>	R <sup>1</sup>	R <sup>2</sup>	$\epsilon$ : $\alpha$ <sup>a</sup>	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	<b>2a</b>	Me	Me	97 : 3	72	89
2	<b>2b</b>	Et	Et	85 : 15	72	84
3	<b>2c</b>	Pr	Pr	78 : 22	46	83
4	<b>2d</b>	Bn	Bn	> 95 : 5	80	92
5	<b>2e</b>	Bn	Me	> 95 : 5	71	87
6	<b>2f</b>			> 95 : 5	49	71

<sup>a</sup> Determined by <sup>1</sup>H NMR spectra of the crude mixture. <sup>b</sup> Isolated yield of  $\epsilon$ -products. <sup>c</sup> ee of  $\epsilon$ -products.

**Fig. 2** Proposed mechanistic model.

It is interesting to mention that the present peptide catalyzed  $\epsilon$ -alkylation of the trienammines showed an opposite sense for the enantiofacial selectivity compared to the  $\gamma$ -alkylation of dienamines brought by diphenylprolinol silyl ether, even though both catalysts are derived from *L*-proline.<sup>9b</sup> This might be attributed to the difference in the interaction of the electrophile and the catalyst; in the reaction of dienamine, the stereochemical course was controlled by the steric repulsion with the substituent on the catalyst, whereas the peptide chain behaved as a carrier of the electrophile based on the strong interaction between the Trp and the cation (Fig. 2).<sup>11</sup>

In this study, we have successfully developed the first catalytic asymmetric  $\epsilon$ -alkylation of 2,4-dienals. This novel transformation provides functionalized compounds amenable to further modifications at  $\alpha$  to  $\delta$  positions, including intriguing cascade sequences. Our research highlights the unique capability of peptide catalysis in imparting distinctive reactivity profiles to challenging compound classes, exemplified by  $\gamma$ -branched 2,4-dienals *via* the trienammine intermediate.

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## Data availability

The data supporting this article have been included as part of the ESI.†

## Conflicts of interest

There are no conflicts to declare.

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