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Proline-mediated dimerization of cinnamaldehydes via 1,3-dipolar cycloaddition reaction with azomethine ylides. A rapid access to highly functionalized hexahydro-1*H*-pyrrolizine

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ABSTRACT

1,3-Dipolar cycloaddition reaction of cinnamaldehyde with azomethine ylides generated through decarboxylation of iminium or oxazolidinone intermediate formed by the reaction of L-proline with cinnamaldehydes is reported. The stereoselective reaction provides an efficient access to the highly functionalized hexahydro-1*H*-pyrrolizine.

Following several decades of dormancy,[1] organocatalysis has recently received overwhelming attention and led to many advancements.[2] The broad utility of α,β-unsaturated aldehydes in organic synthesis has attracted great attention for developing new reactions of these compounds. Successes in organocatalysis include nucleophilic conjugate addition,[3] asymmetric conjugate reduction,[4] Diels–Alder reaction,[5] reductive Michael cyclization,[6] triple cascade reaction,[7] iminium cyclization,[8] cyclopropanation,[9] Friedel–Crafts alkylation,[10] γ-butylactone formation,[11] 1,3-dipolar cycloaddition,[12,13] tandem Michael-aldol,[14] [3+3] cycloaddition,[15] sequential conjugate addition aldol-dehydration reaction,[16] intramolecular Michael reaction,[17] β-hydroxylation,[18] domino oxa-Michael-aldol reaction,[19] asymmetric γ-amination,[20] oxy-Michael addition,[21] and vinylogous Michael addition.[22]

Recently, we reported an enantioselective organocatalytic formal [3+3] cycloaddition of crotonaldehyde and its application in the asymmetric synthesis of (−)-isopulegol hydrate and (−)-cubebaol. The methodology was subsequently extended to the synthesis of aromatic aldehydes by organocatalytic [4+2] and [3+3] cycloaddition of α,β-unsaturated aldehydes and, more recently, applied to the synthesis of (+)-palitantin.[23] In addition, we observed the organocatalytic direct self-trimerization of acrolein, which was applied to the total synthesis of a marine natural product, montiporyne F.[24] In continuing our search for new cycloadditions of the α,β-unsaturated aldehydes,[25] we report here our observation of the proline-mediated 1,3-dipolar cycloaddition of cinnamaldehydes.

Initially, in a background blank study for the organocatalysis reaction, cinnamaldehydes (**1a**) and L-proline (0.2 equiv) in CH_3CN were stirred at ambient temperature for 24 h. Surprisingly, the novel products **2a** and **3a**,[26] separated by flash column chromatography, were obtained in trace amount, apparently arising from the reaction of two molecules of cinnamaldehyde and proline[27,28] followed by extrusion of CO_2.

The yield was increased to 50% after reaction for 24 h when 2 equiv of L-proline was applied. Interestingly, adducts **2a** and **3a** share the same skeleton of hexahydropyrrolizine. Pyrrolozidine alkaloids are widespread in nature and many of them have important biological activities (see Scheme 1).[29] For example, 3′-acetyltrachelanthamine is a strong antifeedant against *Leptinotarsa decemlineata* with low toxicity, while floridinine exhibits moderate antifungal activity against *Fusarium monoliforme*.[30] SC-53116, a potent and selective 5-HT_4 receptor agonist, has been shown to promote antral contractions and gastric emptying in canine models.[31] The broad biological activities and structural novelties of pyrrolozidine alkaloids have received great attention and have made them popular targets for showcasing new synthetic methodologies,[32] such as in the synthesis of (−)-trachelanthamidine,[33] isoretronecanol,[34] macronecine,[35] and (+)-petasinecine.[36] The structures of **2a** and **3a** were assigned based on IR, ^1H, ^{13}C NMR, COSY, DEPT, HMQC, HMBC, and INADEQUATE analysis. Unfortunately, the adducts **2a** and **3a** were obtained with no enantioselectivity. Higher temperature (60 °C) shortened the reaction time (24 h vs 2 h) in ca. 1:1 ratio of **2a** and **3a** with 53% yield (Table 1, entry 2). However, further increasing the reaction temperature (80 °C) gave complicated mixtures (Table 1, entry 3). A survey of solvents revealed that the reaction medium significantly affects the yield of this process. For example, the reaction carried out in CH_3CN and DMF gave the highest yields, 53% and 51%, respectively (Table 1, entries 2 and 4), whereas lower yields were observed for the reactions in toluene, CH_2Cl_2, and DMSO (Table 1, entries 5–7). Microwave-assisted organic reactions (MOREs) are faster and more efficient than their conventional counterparts.[37] For some reactions, microwave irradiation not only enhances the rates of reaction, but can also give rise to products that do not form under

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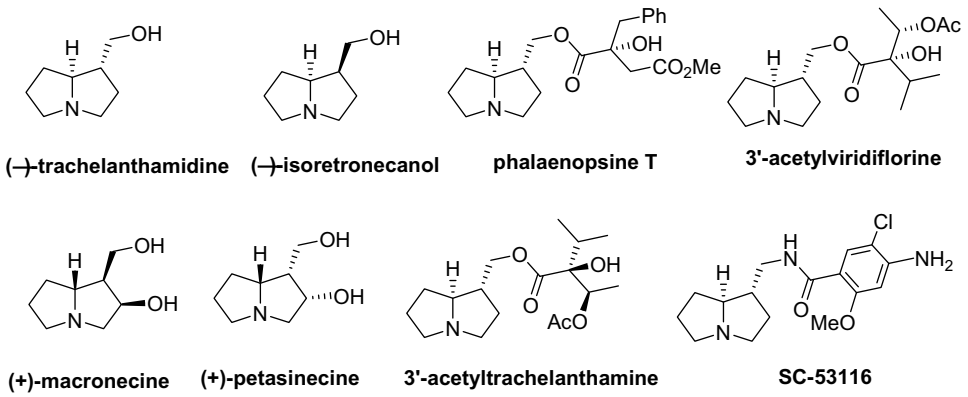
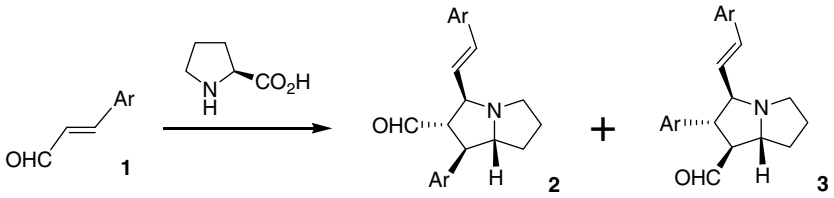


Scheme 1. Examples of biologically active natural occurring hexahydropyrrolizine alkaloids and pharmaceutics agents.

Table 1
Reactions of cinnamaldehyde derivatives with L-Pro



Entry	Aldehydes (**1**)	Solvent	Meth.	*T* (h)	*T* (°C)	Ratio[a] (**2**:**3**)	Yield[b] (%)
1	**1a**, Ar = Ph	CH_3CN	A	24	25	4:3	50
2	**1a**, Ar = Ph	CH_3CN	A	2	60	1:1	53
3	**1a**, Ar = Ph	CH_3CN	A	1	80	n.a.	~0[c]
4	**1a**, Ar = Ph	DMF	A	1	60	5:4	51
5	**1a**, Ar = Ph	Toluene	A	1.5	60	n.a.	0[c]
6	**1a**, Ar = Ph	CH_2Cl_2	A	3	40	4:3	42
7	**1a**, Ar = Ph	DMSO	A	1	60	0:1	24
8	**1a**, Ar = Ph	CH_3CN	B	0.1	60	5:4	61
9	**1a**, Ar = Ph	DMF	B	0.1	60	5:4	63
10	**1a**, Ar = Ph	Toluene	B	2	60	6:1	28
11	**1a**, Ar = Ph	CH_2Cl_2	B	0.75	40	5:2	47
12	**1a**, Ar = Ph	DMSO	B	0.1	60	5:4	52
13	**1b**, Ar = Furanyl	CH_3CN	A	7	25	2:3	65
14	**1b**, Ar = Furanyl	DMF	B	0.1	60	4:3	68
15	**1b**, Ar = Furanyl	CH_3CN	B	1.5	60	2:1	69
16	**1c**, Ar = 4-$MeOC_6H_4$	CH_3CN	A	18	25	1:1	52
17	**1c**, Ar = 4-$MeOC_6H_4$	DMF	B	0.25	60	3:2	55
18	**1c**, Ar = 4-$MeOC_6H_4$	CH_3CN	B	1	60	1:1	71
19	**1d**, Ar = 2-$NO_2C_6H_4$	CH_3CN	A	3	25	1:1	35[c]
20	**1d**, Ar = 2-$NO_2C_6H_4$	DMF	B	0.1	60	~0:1	57
21	**1d**, Ar = 2-$NO_2C_6H_4$	CH_3CN	B	0.2	60	~0:1	61
22	**1e**, Ar = 4-$Me_2NC_6H_4$	CH_3CN	A	72	25	7:6	30
23	**1e**, Ar = 4-$Me_2NC_6H_4$	DMF	B	1	60	4:3	61
24	**1e**, Ar = 4-$Me_2NC_6H_4$	CH_3CN	B	3	60	n.a	~0[d]

Method A: stirred at 25–80 °C. Method B: microwave.
[a] The ratios were determined by ^1H NMR.
[b] Isolated yields.
[c] With complicate mixtures.
[d] Almost no reaction and removed starting aldehyde; reaction at 80 °C gave the complicate mixtures.

conventional thermolytic conditions.[38] In this study, reactions of L-proline and cinnamaldehyde in DMF and CH_3CN at 60 °C under microwave conditions[39] gave the highest yields, with much shorter reaction times (a few hours vs 6 min; Table 1, entries 8–12). A series of cinnamaldehyde derivatives reacted with L-proline at ambient temperature and under microwave conditions, respectively, gave products **2** and **3** in similar yields and selectivity (Table 1, entries 13–24). Most of the reactions under microwave conditions were completed in a few minutes. Interestingly, in the reaction with **1d**, much higher selectivity was observed under microwave conditions than at ambient temperature (Table 1, entries 19–21). Noteworthily, reaction of **1e** in CH_3CN under microwave conditions gave almost no reaction after 3 h, whereas 61% yield was obtained when reacted in DMF for 1 h. The structure of **3d** was assigned unambiguously by single-crystal X-ray analysis of its derivatives. Reduction of **3d** ($NaBH_4$, MeOH, 25 °C; 15 min; 85% yield) to alcohol **4** followed by esterification with 4-nitrobenzoic acid (EDCI, DMAP, 4-$NO_2C_4H_4CO_2H$, CH_2Cl_2, 25 °C, 1 h; 80% yield) gave **5**. The ORTEP structure of **5** is shown in Figure 1.[40]

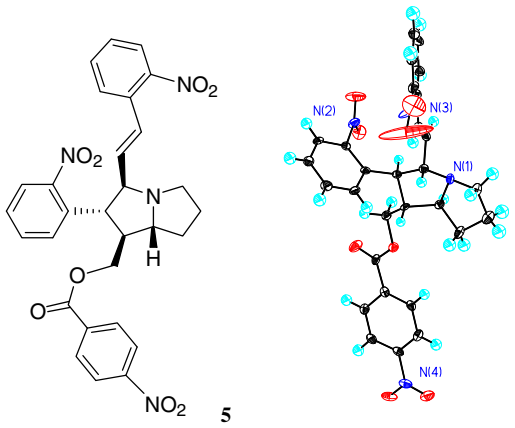


Figure 1. ORTEP plots for X-ray crystal structures of 5.

The high diastereoselectivity (two from the eight possible diastereoisomers) of this dipolar cycloaddition can be realized in a plausible mechanism, as illustrated in Scheme 2. Initial formation of iminium **A** or oxazolidinone **B**[41] by cinnamaldehyde and proline provides a non-stabilized cyclic azomethine ylides **C**,[42] followed by 1,3-dipolar cycloaddition[43] with another cinnamaldehyde to give the adducts **2a** and **3a**. While the dipole **C** approaches cinnamaldehyde, all the substituents, including CHO, CH=CHPh, and Ph, tend to be away from each other, but aligned with H on the same side for less steric hindrance, giving **2a** and **3a**. In Scheme 2, *syn* and *anti* approaches are described for the orientation of the Ph group on the cinnamaldehyde relative to the CH=CHPh group on the dipolar zwitterions **C**. *Endo* and *exo* approaches denote the orientation of the aldehyde group relative to the pyrrolidine ring on the dipole **C**. The small differences in the head-to-head[44] versus head-to-tail selectivity of Ph and CHO groups toward CH=CHPh cause the subtle differences in the regioselectivity of **2a**/**3a**.[45]

Natural products present in dimeric form are common in nature. Moreover, symmetry plays a crucial role in a variety of biological processes.[46] Many efforts have been made to develop new methodologies in the dimerization synthesis.[47] The proline-mediated dimerization of cinnamaldehyde described herein provides an efficient route to the highly functionalized hexahydro-1*H*-pyrrolizine. The simple synthetic procedures and high diastereoselectivity give great potential for the synthetic versatility of the products. Further applications of this methodology toward total synthesis of natural products are currently underway.

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Supplementary data

Supplementary data (experimental procedures and characterization data for the new compound (**2**–**5**)) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.039.

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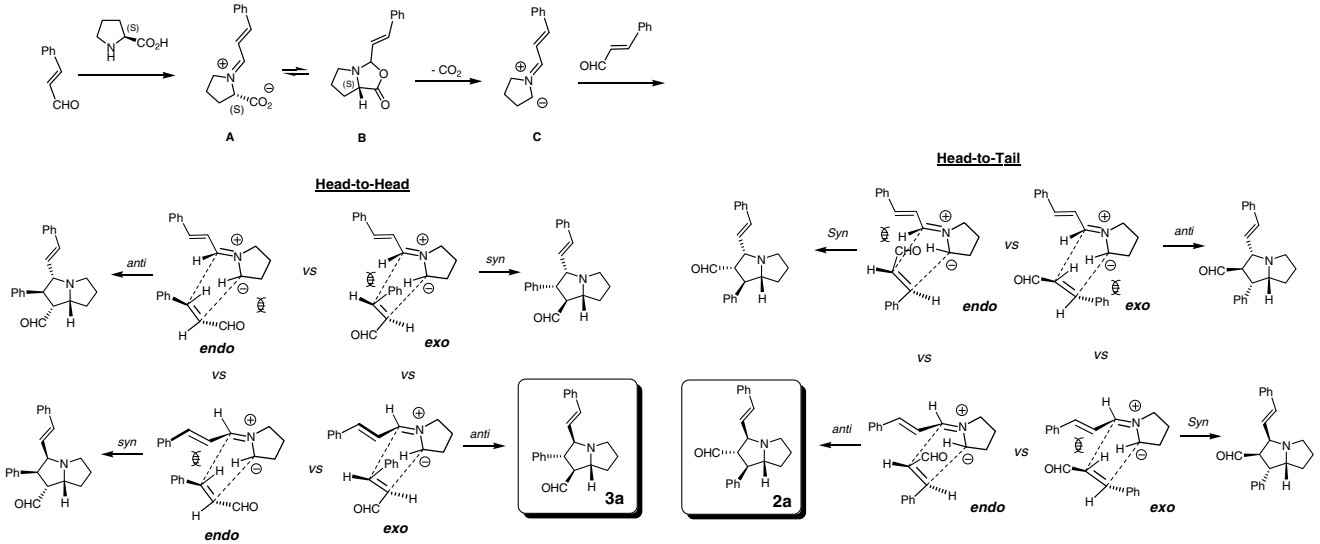

Scheme 2. Proposed mechanism for the dipolar cycloaddition.

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