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Enantioselective Organocatalytic Formal [3 + 3]-Cycloaddition of α,β-Unsaturated Aldehydes and Application to the Asymmetric Synthesis of (–)-Isopulegol Hydrate and (–)-Cubebaol†

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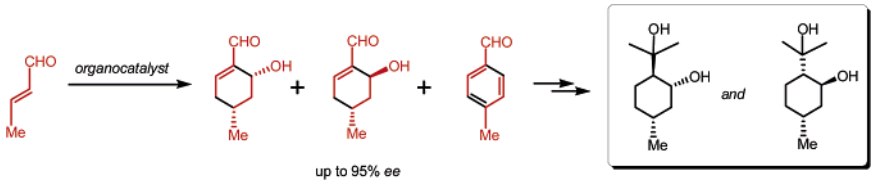
ABSTRACT



The first highly enantioselective organocatalyzed carbo [3 + 3] cascade cycloaddition of α,β-unsaturated aldehydes is reported. Using this methodology, crotonaldehyde is converted to 6-hydroxy-4-methylcyclohex-1-enecarbaldehyde, which is used in the synthesis of (–)-isopulegol hydrate, (–)-cubebaol, and *p*-tolualdehyde as well as (–)-6-hydroxy-4-methyl-1-cyclohexene-1-methanol acetate, an intermediate in the total synthesis of lycopodium alkaloid magellanine. Other α,β-unsaturated aldehydes give rise to chiral cyclohexadienes via formal [4 + 2] reactions.

Cycloadditions, such as Diels−Alder reactions, have been the most important and versatile reactions in organic chemistry for the synthesis of six-membered rings. Recently, considerable advances have been made in the development of other new types of cycloadditions for the six-membered ring synthesis, such as [6 + 3],[1] oxa-[3 + 3],[2] and aza-[3 + 3],[3] etc. Notwithstanding the success of these formal [3 + 3]-cycloadditions and the pioneering work by Hsung et. al.,[4] an efficient all-carbon [3 + 3]-cycloaddition for the synthesis of cyclohexenes has never been realized. Herein, we report the first example of an enantioselective carbo [3 + 3]-cycloaddition in the presence of organocatalyst.[5] Organocatalyzed reactions have been an important subject in modern synthetic chemistry.[6] Among them, proline, MacMillan catalyst, and Jørgensen catalyst can promote Michael addition by iminium ion formation with the acceptor enal.[7] Alterna-

† Dedicated to Prof. J. D. Winkler on the occasion of his 50th birthday.

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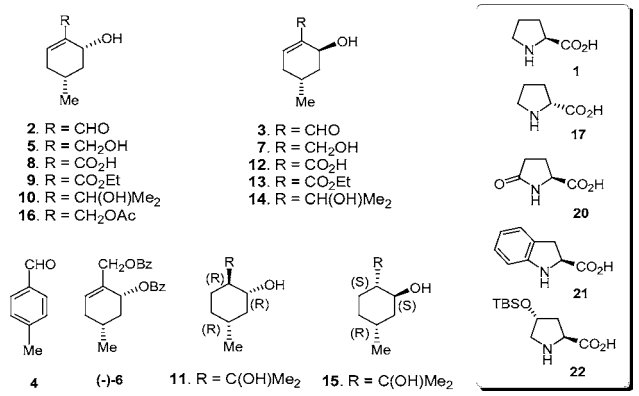
tively, the secondary amine on proline can activate a carbonyl donor via an enamine formation and facilitate the ensuing Michael reaction.[8] Whereas these two types of recently discovered reactions proceed according to an iminium ion mechanism or intermediate enamine formation, observation of both mechanisms in one reaction has not been reported. As part of our ongoing studies in cycloadditions,[9] and organocatalysis,[10] we were inspired to investigate whether the all-carbon [3 + 3] reaction might be accomplished by the combination of these two aforementioned mechanistic pathways.

We initially explored the reaction of crotonaldehyde with 50 mol % of L-proline (**1**) in CH_3CN at room temperature for 4 h. To our delight, the reaction afforded the two diasteromeric [3 + 3] adducts **2** and **3** in a ratio of 1.8:1, along with some *p*-tolualdehyde (**4**), Scheme 1. These

Scheme 1



adducts may be produced through a stepwise cascade reaction and equilibrium process as shown in Scheme 2. It is likely that the proline-catalyzed Michael reaction of crotonaldehyde proceeds via transition state (*E*)-**T**[11] and affords the (*S*)-Michael adduct,[12] which subsequently adds to the aldehyde (enamine aldol reaction) to yield the cyclohexenes product. To our knowledge, this is the first example of carbo [3 + 3]-cycloaddition of α,β-unsaturated aldehyde. The structure of **2** was assigned unambiguously by its single-crystal X-ray analysis. Reduction of **2** to **5** ($LiAlH_4$, THF; 90%) followed by benzoation (PhCOCl, CH_2Cl_2, Et_3N, cat. DMAP; 85%) afforded (−)-**6**, which proved to be identical to the product obtained from the reduction **3** to **7** followed by Mitsunobu reaction with benzoic acid. Chlorite oxidation of **2** to **8** ($NaClO_2$, *t*-BuOH, 2-methyl-2-butene, NaH_2PO_4, 25 °C; 84%), followed by esterification (EtOH, cat. TsOH, 25 °C) afforded **9** in 80% yield.[13] Alkylation of ester **9** with MeLi (THF, 0 °C, 80%) provided **10**, which was hydrogenated (Pd−C, H_2, EtOAc; 75%) to give (−)-isopulegol hydrate (**11**). Using the same reaction sequence, **3** was transformed to (−)-cubebaol (**15**) via compounds **12**, **13**, and **14**. The enantiomer of **15**, (+)-cubebaol, has been used for the synthesis of the HIV-1 protease inhibitive didemnaketals.[14] These 8-hydroxy menthols, *p*-menthane-3,8-diols, have been reported to have biological activities, e.g., plant growth inhibition, allelopathic effect, and strong mosquito repellent activity.[15] The cyclohexenol subunit is also quite prevalent in various natural isolates and therapeutic agents. In a further demonstration of the application of this methodology, **5** was acetylated (Ac_2O, CH_2Cl_2, Et_3N, cat. DMAP; 85%) to **16**, an important intermediate for the total synthesis of lycopodium alkaloid magellanine.[16] The reaction has been examined under various conditions, and selected results are summarized in Table 1.[17] Reaction in MeOH and THF gave many unstable and unidentifiable compounds, and the reaction rate decreases in the following order: DMF > DMSO > CH_3CN > CH_2Cl_2 > MeOH ∼ THF.

In CH_3CN, the reaction is insensitive to substrate concentrations varying from 0.2 to 1.5 M. The enantioselectivity of the reaction did not change in the presence of more catalyst (20 versus 50 mol % of L-proline); however, the reaction rate was slightly higher at 50 mol %. Prolonged reaction times in CH_3CN (8 days) led to the formation of **4**. Reactions catalyzed by D-proline gave the opposite enantiomers of **2** and **3**. Lowering the temperature decreased the rate and the yield of **4** but increased the enantioselectivity of **2** and **3**, and the best results were obtained in DMF at −10 °C (80% ee for **2** and 95% ee for **3)**. Below −20 °C, L-proline gave no reaction after a few days. In the presence of pyrrolidine or (*S*)-indoline-2-carboxylic acid hydrochloride (**21**), the reaction gave a complicated mixture. However, a mixture of pyrrolidine (**18**) and acetic acid (**19**) afforded **4** exclusively (10% yield after 3 h, 78% yield after 48 h), without any trace of **2** or **3**. Reaction with 5-oxo-L-proline (**20**) at room temperature gave no reaction after 48 h, most likely due to the unfavorable formation of the amide iminium ion. Reaction with (4*S*)-4-(*tert*-butyldimethylsilyloxy)-L-proline (**22**) gave lower enantioselectivity.

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(9) For an example of [6 + 2] cycloaddition, see: Hong, B.-C.; Shr, Y.-J.; Wu, J.-L.; Gupta, A. K.; Lin, K. J. *Org. Lett.* **2002**, *4*, 2249.

(10) Chen, S.-H.; Hong, B.-C.; Su, C.-F.; Sarshar, S. *Tetrahedron Lett.* **2005**, *46*, 8899.

(11) For the directed electrostatic activation with (Z)-proline-derived iminium, see: Kunz, R. K.; MacMillan D. W. C.*J. Am. Chem. Soc.* **2005**, *127*, 3240.

(12) For (*R*)-selective Michael addition by L-proline derivative, see: Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710.

(13) For an alternative preparation of the methyl ester (mixture of isomers) by a tandem Morita−Baylis−Hillman (MBH) and ring-closing-metathesis (RCM) sequence, see: Krafft, M. E.; Song, E.-H.; Davoile, R. J. *Tetrahedron Lett.* **2005**, *46*, 6359.

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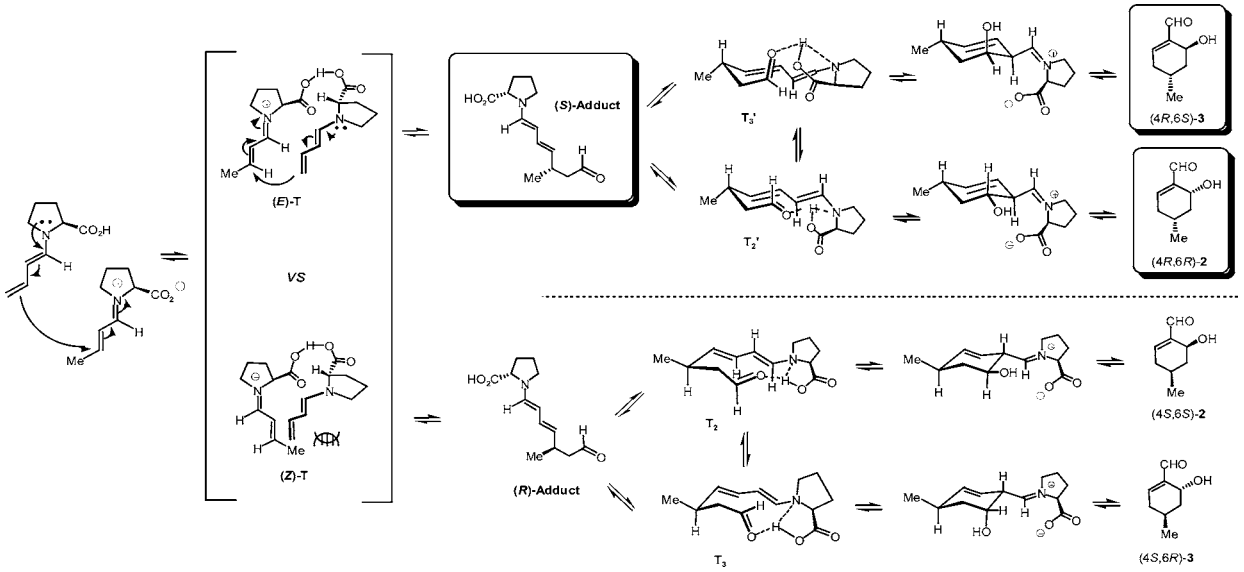
(16) ±)-**16** was used in the synthesis; see: Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053.

(17) Hydroxyaldehydes **2** and **3** are volatile; hence the reported yields are those of the corresponding alcohols (**5**, **7**, and tolylmethanol) obtained from in situ $NaBH_4$ reduction.

Scheme 2. Proposed Mechanism of the Cascade Catalysis of [3 + 3]-Cycloaddition of Crotonaldehyde



The Michael-type reaction is involved in many biosynthetic pathways.[18] The current organocatalyzed [3 + 3] reaction has never been reported under conventional conditions. Since crotonaldehyde,[19] **2** (or **3**) derivatives,[20] and *p*-tolualdehyde[21] have been isolated from natural sources, it is interesting to speculate—about whether this type of [3 + 3] process is a biotransformation and can be observed in nature.

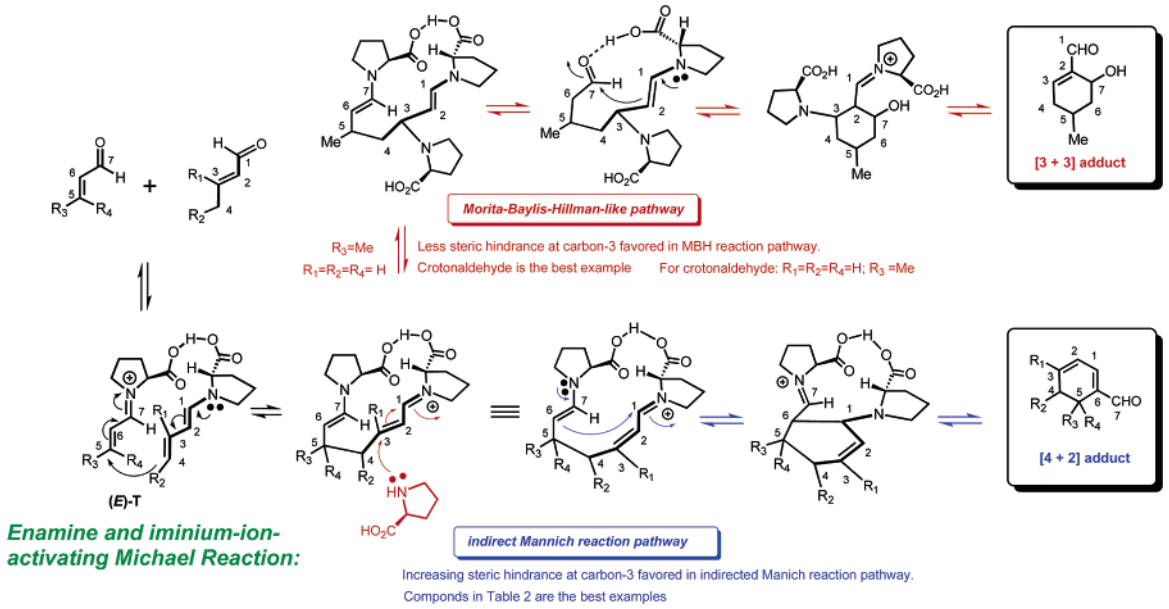
A series of homologous α,β-unsaturated aldehydes were then reacted with L-proline in CH_3CN to afford the corresponding adducts (Table 2). Unlike crotonaldehyde, these aldehydes give the diene products **23**−**30** via formal [4 + 2] reactions, and whenever possible, less than 5% of the corresponding aromatic adduct. These [4 + 2] adducts may be produced through an indirect Mannich reaction pathway as shown in Scheme 3. Reaction of 4-oxobut-2-enyl acetate with L-proline in CH_3CN at 0 °C for 8 h afford the diene adduct (**23**) in 68% yield with 94% ee (entry 1, Table 2). Reaction of 3-methyl-2-butenal with L-proline at 25 °C for

Table 1. Miscellaneous Effects of the [3 + 3]-Cycloaddition of Crotonaldehyde

entry	cat.[a]	solvent	concn[b] (M)	*T* (°C)	time (h)	product ratio (%)[c] **4/2/3**	yield[d] (%)	ee for **2** (config)[e]	ee for **3** (config)[e]
1	1	MeOH	0.4	26	4	complex mixture	0		
2	1	THF	0.4	26	4	complex mixture	0		
3	1	CH_2Cl_2	0.4	26	4	0:62:38	38	8 (4*R*,6*R*)	62 (4*R*,6*S*)
4	1	DMSO	0.4	26	4	29:45:26	40	2 (4*R*,6*R*)	66 (4*R*,6*S*)
5	1	DMF	0.4	26	4	40:41:19	62	23 (4*R*,6*R*)	73 (4*R*,6*S*)
6	1	CH_3CN	0.4	26	4	13:56:31	75	9 (4*R*,6*R*)	65 (4*R*,6*S*)
7	1	CH_3CN	0.2	26	4	12:55:33	63	12 (4*R*,6*R*)	60 (4*R*,6*S*)
8	1	CH_3CN	0.8	26	4	13:60:27	58	10 (4*R*,6*R*)	62 (4*R*,6*S*)
9	1	CH_3CN	1.5	26	4	29:48:23	54	33 (4*R*,6*R*)	70 (4*R*,6*S*)
10	1[f]	CH_3CN	0.4	26	6	8:63:29	72	9 (4*R*,6*R*)	62 (4*R*,6*S*)
11	1	CH_2Cl_2	0.4	0	48	6:39:55	42	30 (4*R*,6*R*)	55 (4*R*,6*S*)
12	1	DMF	0.4	0	8	28:43:29	68	76 (4*R*,6*R*)	91 (4*R*,6*S*)
13	1	DMF	0.4	−10	16	6:50:44	73	80 (4*R*,6*R*)	95 (4*R*,6*S*)
14	1	CH_3CN	0.4	−5	48	3:42:55	78	69 (4*R*,6*R*)	71 (4*R*,6*S*)
15	17	CH_3CN	0.4	0	48	5:47:48	70	62 (4*S*,6*S*)	82 (4*S*,6*R*)
16	17	DMF	0.4	−10	24	11:52:37	70	61 (4*S*,6*S*)	94 (4*S*,6*R*)
17	18	CH_3CN	0.4	26	8	complex mixture	0		
18	18, 19	CH_3CN	0.4	26	3	100:0:0	10[g]		
19	20	DMF	0.4	26	48	no reaction	0		
20	21	DMF	0.4	0	4	complex mixture	0		
21	22	DMF	0.4	−10	24	0:62:38	60	38 (4*R*,6*R*)	55 (4*R*,6*S*)

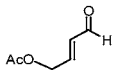
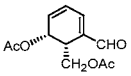
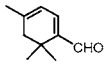
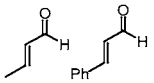
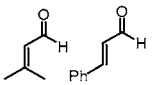
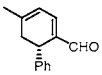
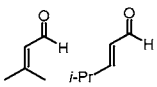
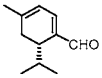
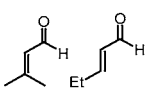
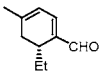
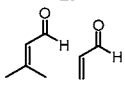
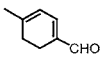
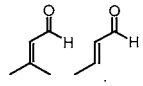
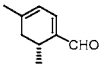
[a] 50 mol % of catalyst was used unless otherwise stated. [b] Concentration of crotonaldehyde. [c] Ratio determinated by ^1H NMR. [d] Yields refer to the isolated alcohols from in situ $NaBH_4$ reduction. [e] Enantiomeric excesses (ee) were measured by GC−MS (Shimadzu QP 5000, chiral capillary column, γ-cyclodextrin trifluoroacetyl, Astec Type G-TA, size 30 m × 0.25 mm, flow rate 24 mL/min, temperature range 60−120 °C, gradient 3 °C/min). Absolute configuration was assigned by transforming the product to *p*-methane-3,8-diol and comparison with the literature. [f] 20 mol % of catalyst was used. [g] Yield of 4-methylbenzene alcohol after in situ $NaBH_4$ reduction.

Scheme 3



3 h afford the diene adduct (**24**) in 82% yield (entry 2, Table 2). The capacity of proline to catalyze asymmetric cross reactions between nonequivalent α,β-unsaturated aldehydes was next examined (entries 3−8, Table 2). For all examples, the reactions gave the corresponding diene adducts in good yield and slightly lower enantioselectivity.

Table 2. Formal [4 + 2]-Cycloaddition of α,β-Unsaturated Aldehydes

entry	aldehydes	product	temp (°C)	time (h)	yield[a] % (*ee*)[b]
1		 **23**	0	8	68[c] (94)
2		 **24**	25	3	82[d]
3		 **25**	0	36	61 (63)
4		 **26**	-20	48	72 (32)
5		 **27**	-20	96	78 (56)
6		 **28**	-20	90	76 (45)
7		 **29**	25	8	71[d]
8		 **30**	-20	48	82 (41)

[a] Isolated yield. [b] Enantiomeric excesses (ee) were measured by GC−MS; absolute stereochemistry not determined. [c] Isolated yield of the cis adduct; trans/cis = 1:9. [d] Achiral product.

In conclusion, we have developed an enantioselective [3 + 3]-cycloaddition of crotonaldehyde catalyzed by proline derivatives. The process provides a significant addition to the arsenal of cycloaddition-based methodologies, which provide practical tool for rapid and efficient access to six-membered ring systems, and is practical for large scale synthesis. Further applications of this methodology along with mechanistic studies and synthetic extensions (e.g. [3 + 3] *vs.* [4 + 2]) are under active investigation in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for the new compounds (**2**−**30**) and X-ray crystallographic data for compound **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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