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Crossed Intramolecular Rauhut−Currier-Type Reactions via Dienamine Activation

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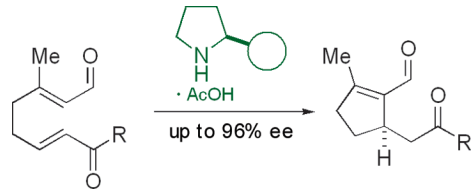
ABSTRACT

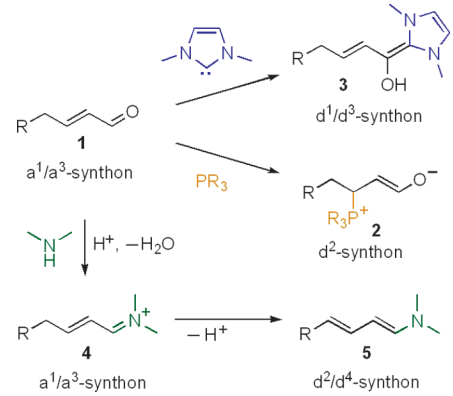


The intramolecular Rauhut−Currier reaction creates a carbon−carbon bond between two tethered Michael acceptors. Previous asymmetric versions have relied on 1,4-additions of chiral nucleophilic catalysts. Herein, we investigate a novel strategy that involves the formation of electron rich dienamines as key intermediates. Our methodology provides an efficient entry to the iridoid framework.

The use of functionalized chiral scaffolds as switches for biological signaling pathways has spurred the development of new reactions for their rapid assembly by means of asymmetric synthesis.[1] In this context, organocatalysis[2] complements existing transition metal-based catalysis allowing for the enantioselective synthesis of densely functionalized hetero- and carbocyclic motifs with often orthogonal chemoselectivity.[3]

While α,β-unsaturated aldehydes[4] **1** are traditionally used as a^1/a^3-synthons (Scheme 1), organocatalysis has added new value to this important structural class. In addition to the long-known 1,4-addition of nucleophilic catalysts (**1** → **2**) such as tertiary phosphines, 1,2-additions have recently allowed for new chemoselective transformations. *N*-Heterocyclic carbenes have converted **1** into homoenolate equivalents[5] **3** and secondary amines have been shown to convert

Scheme 1. Activation of α,β-Unsaturated Aldehydes with Different Nucleophilic Catalysts



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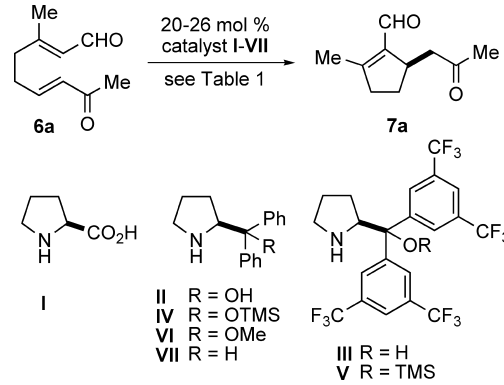
1 into electron-rich dienamines[6] **5** via iminium ion **4**, a key intermediate in iminium ion catalysis.[7]

The intramolecular Rauhut−Currier (RC) reaction[8] generates chiral cycloalkenes from acyclic precursors bearing two tethered Michael acceptors. Surprisingly, a transannular version of this reaction by Moore[9] preceded thorough investigations of Krische[10] and Roush[11] of intramolecular RC reactions using alkyl phosphines as catalyst. In 2007, Miller[12] and shortly after Gladysz[13] reported enantioselective intramolecular RC reactions of bis(enones). While Miller used cysteine derivatives as catalyst, Gladysz employed phosphines associated with a chiral rhenium complex. Recently, Scheidt[14] made progress in the intermolecular RC reaction using silyloxyallenes. There is also evidence for the involvement of RC-type processes in biosynthesis of iridodials.[15]

Our previous work[6h] in the area of dienamine catalysis was concerned with the d^4-reactivity of α,β-unsaturated aldehydes (**1** → **5**). Herein, we report the potential of **5** as a d^2-synthon in a mechanistically distinct RC-type reaction. Since the Jørgensen−Hayashi catalyst (**IV**) is specific toward aldehydes, selective activation over other Michael acceptors such as α,β-unsaturated ketones might be attainable. More importantly, this mode of activation should allow the activation of β-disubstituted alkenes, thereby providing an entry into the iridoid class[16,17] of natural products, found widely in plants and insects which possess important pharmacological activities.[18] We started our investigations using compound **6a** as the test substrate in order to explore the viability of an enantioselective cyclization to give cyclopentene **7a**. An initial screening of catalysts **I**−**V** in the absence of any additives revealed catalyst **IV** to be best in terms of both reactivity and enantioselectivity (Table 1, entries 1−5).

Table 1. Catalyst and Solvent Screening[a]



entry	catalyst	additive	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	**I**		CH_2Cl_2	72	22	6
2	**II**		CH_2Cl_2	72	n.d.	79
3	**III**		CH_2Cl_2	72		-
4	**IV**		CH_2Cl_2	72	60	88
5	**V**		CH_2Cl_2	72	32	94
6	**IV**	AcOH	CH_2Cl_2	3	57	89
7[d]	**IV**	AcOH	CH_2Cl_2	24	41	93
8	**IV**	AcOH	PhMe	28	29	44
9	**IV**	AcOH	MeCN	28	32	93
10	**IV**	AcOH	$CHCl_3$	3	57	87
11[e]	**IV**	AcOH	CH_2Cl_2	4	58	91
12[e]	**VI**	AcOH	CH_2Cl_2	4	58	76
13[e]	**VII**	AcOH	CH_2Cl_2	4	53	54
14[e,f]	**IV**	AcOH	CH_2Cl_2	5	63	91

[a] Experimental conditions: to a solution of aldehyde **6a** (0.19 mmol) and additive (26 mol %) in 0.5 mL of solvent, 26 mol % of catalyst **I**−**VII** in 1 mL of solvent was added at room temperature. The product was purified by flash chromatography. [b] Yield of isolated product. [c] Determined by HPLC methods. [d] Reaction was carried out at +5 °C. [e] Slow addition (5−10 min) of aldehyde **6a** in CH_2Cl_2 (1.0 mL) to a solution of the catalyst (20 mol %) and the additive (20 mol %) in CH_2Cl_2 (0.5 mL). [f] 0.36 mmol scale.

The use of acetic acid as an additive led to a considerable increase in the reaction rate without impairing the enantioselectivity (entry 6). Lowering the temperature to 5 °C improved the enantioselectivity at the expense of reactivity and yield (entry 7). Switching solvents to toluene or acetonitrile (entries 8 and 9) again had a negative influence on the reactivity whereas the use of chloroform gave comparable results (entry 10). Slow addition of the substrate to a solution of the catalyst **IV** was the key to lowering the

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(9) Erguden, J. K.; Moore, H. W. *Org. Lett.* **1999**, *1*, 375.

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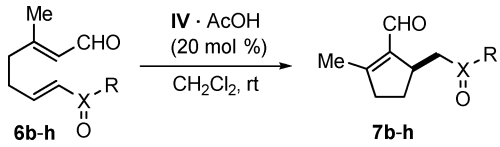
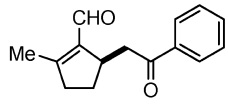
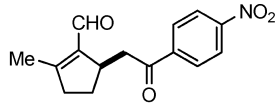
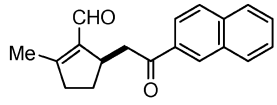
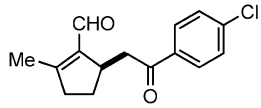
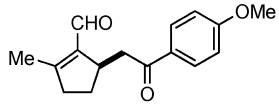
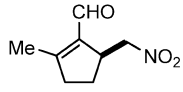
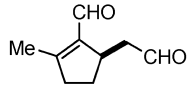
catalyst loading down to 20 mol %, which was accompanied by a slight increase in the asymmetric induction (entry 11).

However, employing catalysts **VI** and **VII** in this manner offered no improvements (entries 12 and 13). Finally, at 0.36 mmol scale we were able to increase the yield to 63% and 91% ee (entry 14). In order to evaluate the scope of this new cyclization, various aldehydes (**6b**−**h**) were allowed to react under the optimized conditions. The desired iridoid aldehydes (**7b**−**h**) were obtained in good yields and enantioselectivities up to 96% ee as shown in Table 2.

Table 2. Substrate Scope[a]



entry	product	time (h)	yield[b] (%)	ee[c] (%)
1	 **7b**	20	68	89
2	 **7c**	5	73	96 (99)[d]
3	 **7d**	7	71	88
4	 **7e**	7	53	91 (99)[d]
5	 **7f**	40	45	90
6	 **7g**	1.5	51	68
7	 (+)-rotundial (**7h**)	22	36	86

[a] Experimental conditions: to a solution of **IV**·AcOH (20 mol %) in CH_2Cl_2 (1 mL) was slowly added (5−10 min) a solution of aldehydes **6b**−**h** (0.36 mmol) in CH_2Cl_2 (2 mL) at room temperature. The products (**7b**−**h**) were isolated by flash chromatography. [b] Isolated yield. [c] Determined by HPLC methods. [d] After one recrystallization.

The electronic environment at the acceptor strongly influences the reaction rate and the enantioselectivity. Electron-withdrawing groups in the aromatic ring increase the reaction rate (entries 2−4), whereas the electron-donating 4-methoxy substituent reduced the reaction rate significantly (entry 5). Other Michael acceptors such as nitroalkenes can be employed but the reaction proceeds with somewhat lower enantioselectivity (entry 6). The presence of a methyl group in the β-position of the aldehyde was crucial to the enantioselectivity and the reaction rate. We speculate that the methyl substituent renders the dienamine more nucleophilic and lowers the relative energy of the required 3*Z*-configuration (vide infra). In order to determine the stereochemical outcome of the cyclization, single crystals were obtained from **7e**, and the absolute configuration was determined to be *R* (Figure 1).

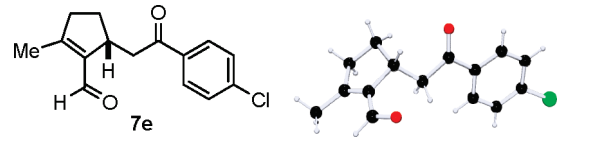


Figure 1. X-ray crystal structure of (*R*)-**7e**.

To further demonstrate the utility of our methodology, we identified (+)-rotundial (**7h**, entry 7), a powerful mosquito repellent from *Vitex rotundifolia*,[19] as target molecule for the application of an asymmetric RC-type cyclization. The precursor dialdehyde **6h** was obtained in five steps from geranyl acetate. The yield of the cyclization step (36%, 86% ee) was hampered by the sensitivity of rotundial to degradation.[20] The overall yield (25%) compares favorably with previous syntheses,[21] and the sign of the optical rotation was in agreement with the assumed (*R*)-configuration.

Based on our previous experience, we propose the following catalytic cycle which is in agreement with our observations although further experiments will be necessary to support this working hypothesis (Scheme 2).

The first step is the condensation of the substrate **6a** with the catalyst **IV** to form an iminium ion **8**.[22] Jørgensen has shown using NMR studies that the iminium ion exists in an equilibrium with the electron-rich dienamine **9**.[23] Previous work has focused on its reactivity as d^4-synthon. In this instance, we were able to exploit the d^2-reactivity with the aid of sterics. It is conceivable that acetic acid assists in the formation of the carbon−carbon bond by activating the acceptor. In our model system, the tentative intermediate is

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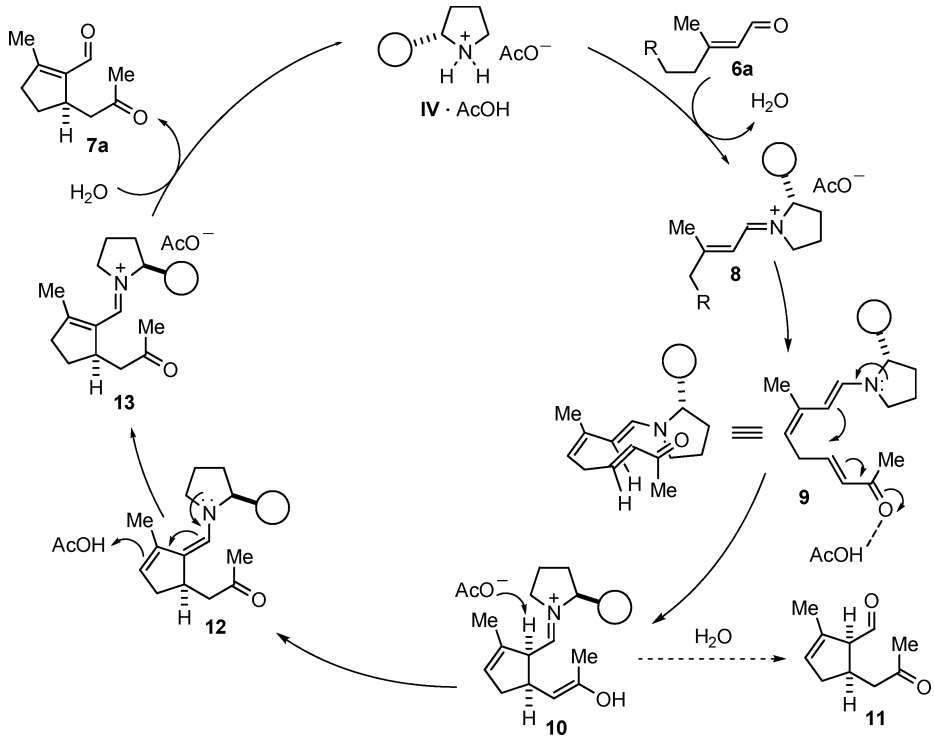
(20) Another possible explanation is capture of the catalyst as described by Unelius (ref 16).

(21) For the first synthesis of (*R*)- and (*S*)-rotundial, see: Takikawa, H.; Yamazaki, Y.; Mori, K. *Eur. J. Org. Chem.* **1998**, 229.

(22) (a) Seebach, D.; Grošelj, U.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2008**, *91*, 1999. (b) Grošelj, U.; Schweizer, W. B.; Ebert, M.-O.; Seebach, D. *Helv. Chim. Acta* **2009**, *92*, 1.

(23) For theoretical discussions concerning dienamine intermediates, see ref 6d and: Duarte, F. J. S.; Cabrita, E. J.; Frenking, G.; Santos, A. G. *Chem.—Eur. J.* **2009**, *15*, 1734.

Scheme 2. Proposed Reaction Mechanism



cis-**10**.[24] Hydrolysis of the iminium ion would lead to compound *cis*-**11**.[25] However, it should be noted that each step in the catalytic cycle is reversible and proton abstraction (**10** → **12**) and reprotonation (**12** → **10**) could easily lead to *trans*-**10**. Presumably, hydrolysis of **10** is slow; therefore, protonation of **12** in the γ-position leads to iminium ion **13**, which upon hydrolysis releases **7a** to regenerate the catalyst.

In summary, we have developed an enantioselective organocatalytic RC-type cyclization of α,β-unsaturated aldehydes catalyzed by the commercially available Jørgensen−Hayashi catalyst **IV**. The iridoid products, cyclopentene derivatives bearing a tetra-substituted olefin, were obtained in moderate to good yields and with good enantioselectivity. Due to the unprecedented mode of activation in RC-processes (1,2- vs 1,4-activation), complementary chemoselectivity can be achieved. The extremely simple operational procedure and the synthetic versatility of the products render this new approach highly appealing for the synthesis of optically active iriods, such as (+)-rotundial.

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Supporting Information Available: Experimental procedures, NMR spectra, and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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(24) The possibility of the enone to adopt an *s-cis* conformation and participate in a formal [4 + 2]-process leading to Unelius-type intermediates followed by hydrolytic cleavage of the catalyst cannot be ruled out completely.

(25) *EZ*-Isomerization of the enol moiety of **10** could lead to an intramolecular attack of the iminium ion and to a dead end in the catalytic cycle .