Asymmetric Synthesis

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Amine-Catalyzed Cyclizations of Tethered α,β-Unsaturated Carbonyl Compounds**

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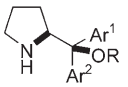
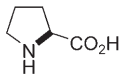
Dedicated to Professor Thomas R. Hoye

Intramolecular reactions of linked α,β-unsaturated carbonyl compounds provide an elegant entry to mono- and bicyclic ring systems. Most cyclizations are initiated by the addition of electrons,[1] hydride[2] or other nucleophiles[3] to one of the Michael acceptors and subsequent attack of the activated species to the other Michael acceptor. If the nucleophile is eliminated, the overall process is commonly dubbed a Rauhut–Currier reaction.[4] Moreover, carbene organocatalysts[5] have been demonstrated to activate α,β-unsaturated carbonyl compounds.[6] Scheidt and co-workers have used carbenes to transform α,β-unsaturated aldehydes into ester enolate equivalents, which were used in Michael-type cyclizations.[7]

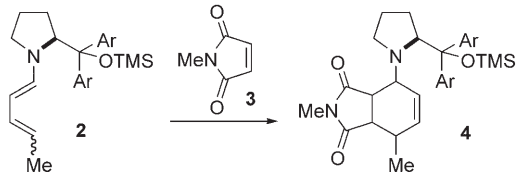
Triggered by the enal annulations of Hong and co-workers,[8] we investigated vinylogous reactivity on tethered α,β-unsaturated aldehydes by using an organocatalytic[9,10] approach. Already in the 1970s Yamada et al.[11] used proline derived vinylogous enamines in stoichiometric asymmetric C–C bond-forming reactions. Nowadays, diarylprolinol silyl ethers (**1**)[12] have proven to be an excellent class of organocatalysts for the activation of saturated and unsaturated aldehydes.[13]





1a: $Ar^1 = Ar^2$ = Ph, R = H (*S*)-proline
1b: $Ar^1 = Ar^2$ = Ph, R = TBS
1c: $Ar^1 = Ar^2$ = Ph, R = TMS
1d: Ar^1 = Ph, Ar^2 = 3,5-$C_6H_3(CF_3)_2$, R = TMS
1e: $Ar^1 = Ar^2$ = 3,5-$C_6H_3(CF_3)_2$, R = TMS

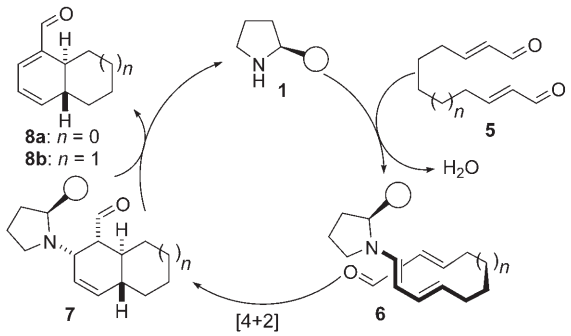
In their seminal γ-amination work, Jørgensen and co-workers[14] observed the electron-rich dienamine[15] **2** by NMR spectroscopy. Trapping of this species was possible with maleimide **3** (Scheme 1) to afford cycloadduct **4**, which was incapable of eliminating the catalyst **1e** and therefore constituted a dead end in a possible catalytic cycle.



Scheme 1. Jørgensen's [4+2] addition of dieneamine **2** and maleimide **3**. TMS = trimethylsilyl.

At this point it is important to emphasize the mechanistic complementarity to iminium catalysis. In the latter, small organic molecules are used to activate the dienophile by covalent binding, and this concept has been applied successfully in intermolecular[16] and intramolecular Diels–Alder (IMDA) reactions[17] as well as conjugate additions of preformed dienolates (silylketene acetals) to α,β-unsaturated aldehydes.[18] Herein, we use an organic catalyst to generate chiral electron-rich dienes, which in turn direct the facial approach of the α,β-unsaturated carbonyl moiety.

Our investigations started with dialdehydes **5**, which we previously used in a diversity-oriented synthesis of lepidopteran sex pheromones.[19] Assuming that vinylogous enamine activation is operative (Scheme 2), a rapid IMDA reaction



Scheme 2. Proposed catalytic cycle for the cyclization of unsaturated dialdehydes **5**.

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[+] X-ray structure analysis.

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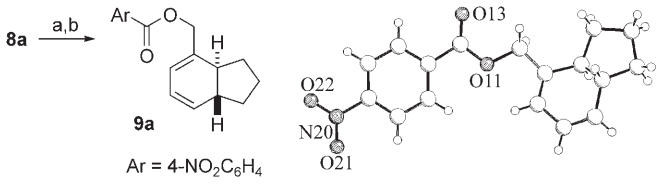
(**6**→**7**) and subsequent elimination of catalyst **1** leads to **8**. In a tentative catalytic cycle, **5** condenses with catalyst **1** to form the electron-rich diene **6**. This intermediate presumably adopts a conformation that minimizes repulsion with the bulky aryl substituents and exposes the unshielded face of the π system to an *endo* approach of the enal.

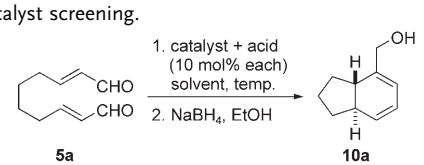
The cycloadduct **7**, in contrast to **4**, is prone to β-hydride elimination to regenerate catalyst **1**. It is conceivable that a second catalyst molecule assists this elimination through formation of an iminium ion with the remaining aldehyde functionality, either prior to or after the cycloaddition step. In a preliminary screen, 10 mol% of **1c** proved sufficient to convert the dialdehydes (**5**) into the bicyclic products **8**. The aldehydes were reduced and converted into the corresponding nitrobenzoates **9a** and (not depicted) **9b** (Scheme 3). Their relative and absolute configurations were confirmed by X-ray crystallographic analysis, and the results support our stereochemical rationale.



Scheme 3. Crystallography results support the suggested mechanism. a) $NaBH_4$, EtOH, RT, 85% (87% from **8b**); b) 4-$NO_2C_6H_4COCl$, pyridine, RT, 100% (80% for **9b**).

Upon this foundation, we investigated reaction parameters such as solvent, catalyst, and acid additive and explored the substrate scope. In addition to (*S*)-proline, the cyclization reaction can be promoted by a variety of diarylprolinol silyl ethers (Table 1). We found that increasing bulk in the diarylsilyloxy moiety (**1c** < **1b**; **1c** < **1d**[20] < **1e**) lowers the reaction rate. Interestingly, hydrogen bond donors in the catalyst (**1a**, proline) led to the opposite enantiomer, albeit with lower selectivity. These findings suggest that precautions have to be taken to avoid acidic removal of the catalyst's silyl protecting groups in order to prevent erosion of the enantiomeric excess during the reaction. We therefore screened for

Table 1: Catalyst screening.



Entry	Catalyst[a]	*t* [h]	*ee* [%]
1	(*S*)-proline	22	−14
2	**1a**	24	−60[b]
3	**1b**	20	88
4	**1c**	3	90
5	**1d**	48	94
6	**1e**	2	–

[a] Catalyst·BzOH in toluene (0.1 M) at room temperature. [b] 50% conversion.

mild carboxylic acids as the cocatalyst (Table 2).[21] The data indicate a strong, but not yet understood correlation between the pK_a value and the reaction rate. Accordingly, the acid cocatalyst must be involved in an intricate enamine–iminium–dienamine equilibrium, but it may also play a role in the activation of the dienophile/Michael acceptor. The reactions can be run in a variety of solvents with comparable results (Table 3). Toluene is the preferred solvent over benzene and halogenated solvents, although chloroform and methylene chloride led to slightly faster reaction times.

Table 2: Acid screening.

Entry	Acid[a]	pK_a	*t* [h]	*ee* [%]
1	none	–	144	80[b]
2	CH_3CO_2H	4.76	12	82
3	*p*-$MeOC_6H_4CO_2H$	4.47	12	84
4	$C_6H_5CO_2H$ (BzOH)	4.20	3	90
5	*p*-$ClC_6H_4CO_2H$	3.99	4	88
6	*p*-$NO_2C_6H_4CO_2H$	3.44	2	86

[a] **1c**·acid in toluene (0.1 M) at room temperature. [b] 50% conversion.

Table 3: Solvent screening.

Entry	Solvent[a]	*t* [h]	*ee* [%]
1	$C_6H_5CH_3$	3	90
2	C_6H_6	4	85
3	$CHCl_3$	2	86
4	CH_2Cl_2	1	29
5	THF	96	–[b]
6	MeCN	5	67

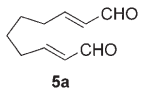
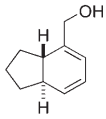
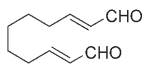
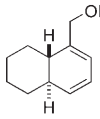
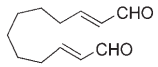
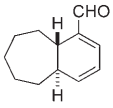
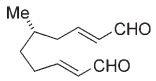
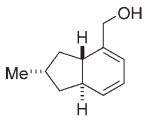
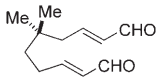
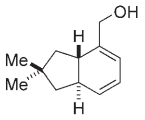
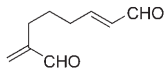
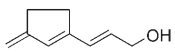
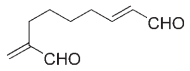
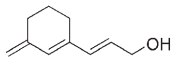
[a] **1c**·BzOH in solvent (0.1 M) at room temperature. [b] No conversion.

Whereas **10a** and **10b** (Table 4) were accessible in good yield and high enantioselectivity, larger bicyclic ring systems (**10c**) could not be isolated. Compounds **5d** and **5e** were chosen to test the limits of position selectivity. It can be speculated that the rate of dienamine formation determines the ratio of two regioisomeric products, which is 2:1 for the methyl derivative **10d** and 4:1 for the *gem*-dimethyl derivative **10e** favoring the less hindered position. Therefore we conclude that site-specific enamine and iminium formation remains a difficult task.[22]

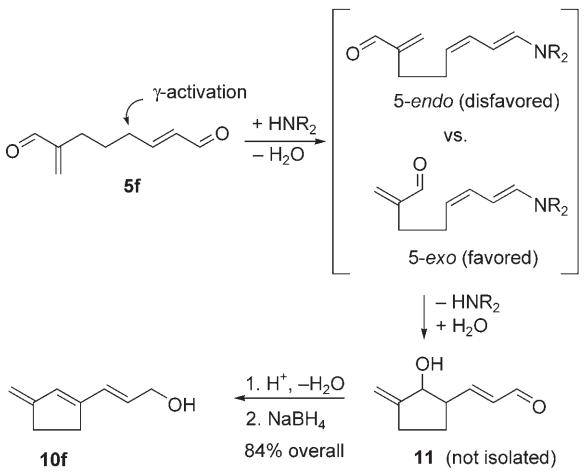
The substrates **5f** and **5g** each bearing an α-methylene group,[23] were synthesized by using the Pihko methylenation.[24] In Baldwin's terminology,[25] the intramolecular Michael addition of **5f** is a disfavored 5-*endo-trig* process, whereas the 5-*exo-trig* vinylogous aldol condensation pathway is allowed, leading to alkylidenecyclopentene **10f** (Scheme 4). Alternatively, the formation of **10f** can be explained by a vinylogous Mannich condensation,[26] which might also explain the fast 6-*exo* ring closure to afford **10g**.

When one of the aldehyde functions is replaced by an α,β-unsaturated ketone as the acceptor (**12**), no formal [4+2] cycloaddition was observed; instead, a direct enantioselective vinylogous Michael addition[27] lead to **13** (Scheme 5).[28] Ketoaldehyde **13** has orthogonal reactive functionality for subsequent transformations. Organocatalytic cyclization cas-

Table 4: Substrate scope.

Entry	Substrate	Product
1[a]	 **5a**	 **10a** (60%, 94% *ee*)
2[b]	 **5b**	 **10b** (60%, 95% *ee*)
3[b]	 **5c**	 **10c** (0%)
4[b]	 **5d**	 **10d** (65%)[c]
5[b]	 **5e**	 **10e** (73%, 98% *ee*)[d]
6[b]	 **5f**	 **10f** (84%)
7[b]	 **5g**	 **10g** (84%)

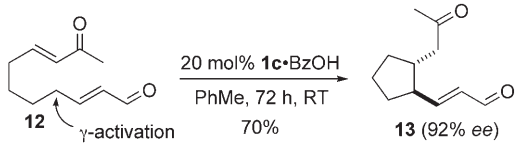
[a] **1c**·BzOH in CH_2Cl_2 (0.1 M) at −18 °C, 2 days. [b] **1c**·BzOH in toluene (0.1 M) at room temperature. [c] 2:1 mixture of regioisomers. [d] 4:1 mixture of regioisomers.



Scheme 4. Cyclization of α-methylene aldehydes.

cades[29] with **13** and related molecules are subject of ongoing efforts.

We have investigated the enantioselective addition of in situ formed dienolate equivalents to Michael acceptors.



Scheme 5. Intramolecular vinylogous Michael addition. Bz = benzoyl.

Our results complement previous organocatalytic approaches by installing the transient chiral directing group at the diene moiety. As a demonstration, novel mono- and bicyclic scaffolds were synthesized by γ-activation of tethered unsaturated dicarbonyl precursors. The products were obtained in good yield and excellent selectivity, and their conversion into biologically relevant natural products[30] will be reported in due course.

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Keywords: aldehydes · cyclization · Diels–Alder reactions · Michael addition · organocatalysis

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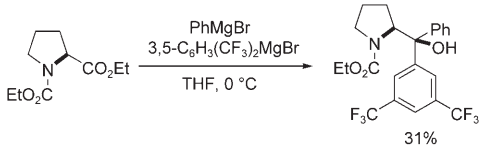

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