Communication

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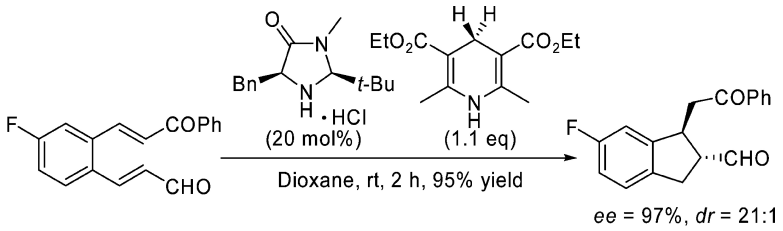

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Catalytic Asymmetric Reductive Michael Cyclization

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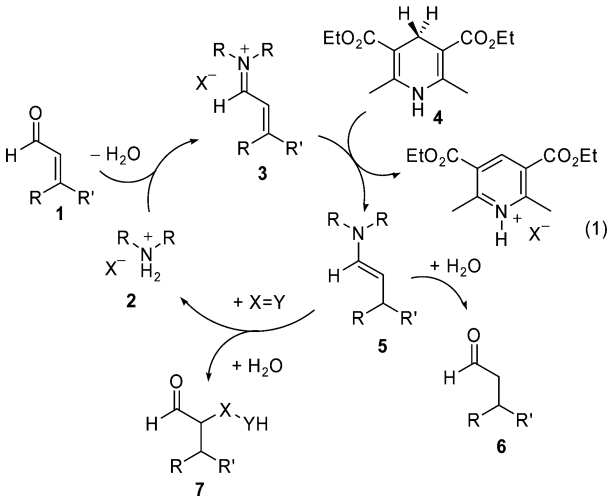
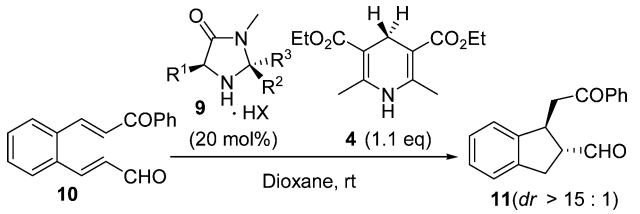
Asymmetric catalysis of carbonyl transformations using amines or ammonium salts as catalysts has recently gained considerable attention.[1] While enamine catalysis has been used mostly in the context of carbonyl α-substitution reactions,[2] iminium catalysis is typically employed in conjugate and cycloadditions of enals.[3] The two strategies are closely related, and the same catalysts can often be utilized in both approaches. In fact, enamine catalysis generally proceeds via iminium ion formation, while iminium catalysis often leads to an enamine intermediate. Combining the two catalysis principles in tandem sequences using a single catalyst is obviously attractive but has rarely been realized. Here we disclose an efficient asymmetric in situ iminium catalytic conjugate reduction followed by an enamine catalytic intramolecular Michael reaction. Our process gives five- and six-membered carbacycles in excellent yields and enantioselectivities.

We have previously developed an organocatalytic, metal-free asymmetric transfer hydrogenation of α,β-unsaturated aldehydes.[4] In this reaction, an enal (**1**) is activated with a MacMillan imidazolidinium salt (**2**) via iminium ion formation (**3**). A subsequent hydride transfer to intermediate **3** from Hantzsch ester **4a** presumably gives enamine intermediate **5**. In situ hydrolysis then provides saturated aldehyde **6**, usually in high yields and enantioselectivities (eq 1). We reasoned that the reductively generated enamine intermediate **5**, in addition to hydrolysis, should also be able to react in situ with various electrophiles (X = Y) to give an α-modified aldehyde **7**. To the best of our knowledge, such a combination of iminium and enamine catalysis has not been realized before.



The tandem sequence would be related to previously developed metal-mediated reductive enolate generation−electrophile trapping processes.[5] For example, catalytic inter- and intramolecular reductive aldol and Michael reactions of unsaturated carbonyl compounds via metal enolates have been developed.[6] While asymmetric catalytic reductive aldol reactions have been described,[7] the corresponding reductive Michael reactions are unknown.[8]

Table 1. Catalyst Screening for the Reductive Michael Cyclization



catalyst	R^1	R^2	R^3	X	time [h]	yield [%]	ee [%]
9a	H	*t*-Bu	H	CF_3CO_2	2	82	93
9b	H	*t*-Bu	H	Cl	12	90	95
9c	H	2,6-Ph_2Ph	H	Cl	12	75	16
9d	Bn	*t*-Bu	H	Cl	3	98	96
9e	*p*-BnOBn	*t*-Bu	H	Cl	6	91	95
9f	*p*-*t*-BuOBn	*t*-Bu	H	Cl	6	90	95
9g	Bn	Me	Me	Cl	24	<10	

We have developed an imidazolidinone-catalyzed Michael cyclization of formyl enones to give useful cyclic keto aldehydes in high yields and enantiomeric excesses.[9,10] Since these reactions are catalyzed with the same type of catalyst that is used in our organocatalytic conjugate reduction, we expected the two reactions to work well in an in situ tandem sequence. Indeed, when we treated enal enone **10** with Hantzsch ester **4** in the presence of different imidazolidinone salts (**9**), clean reductive Michael cyclization to keto aldehyde **11** was observed (Table 1). Independent of the catalyst, the reaction furnished the *anti*-product highly diastereoselectively. Moreover, excellent yield and enantioselectivity was obtained when we used commercially available imidazolidinone catalyst **9d**. Catalyst **9g**, which we have previously used in the intermolecular Michael reaction, proved ineffective.

We have also screened different Hantzsch esters as hydrogen donors and found commercially available Hantzsch ester **4** to give the best results (see Supporting Information).

After identifying suitable reaction conditions for the reductive Michael cyclization of substrate **10**, we set up a study toward exploring the scope of the process. The results are shown in Table 2. The Michael acceptor portion tolerates both aromatic and aliphatic enones giving the products in comparable yields and stereoselectivities (entries 1−6). Substituents at the aromatic portion are well tolerated (entries 5 and 6). We have also investigated an alkylidene malonate Michael acceptor (**22**) and obtained reasonably good results when we used catalyst **9c**.

Diastereoselectivities are generally high, and products resulting from the conjugate reduction of the enone were not observed. Our tandem reaction constitutes a nonasymmetric conjugate reduction followed by an asymmetric Michael cyclization. The alternative sequence consisting of an asymmetric conjugate reduction of a β,β-disubstituted enal followed by its diastereoselective Michael cy-

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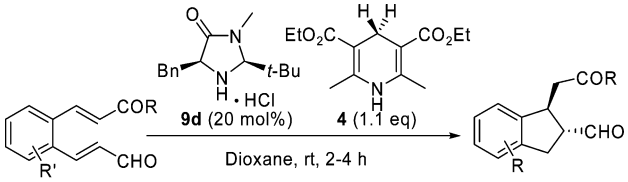
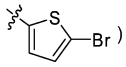
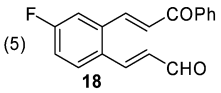
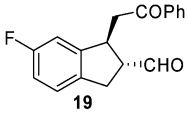
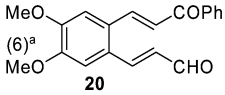
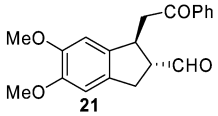
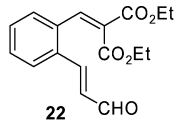
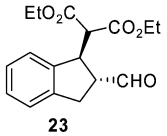
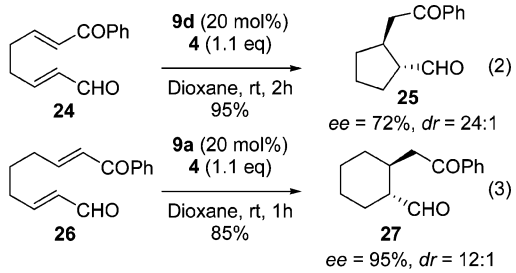
Table 2. Organocatalytic Reductive Michael Cyclization



Entry	Starting Material	Product	Yield [%]	*dr*	*ee* [%]
(1)	**10** (R = Ph)	**11**	98	15:1	96
(2)	**12** (R = 2-Naphthyl)	**13**	94	50:1	94
(3)	**14** (R = )	**15**	91	40:1	92
(4)	**16** (R = Me)	**17**	91	>50:1	91
(5)	 **18**	 **19**	95	21:1	97
(6)[a]	 **20**	 **21**	88	23:1	96
(7)[b]	 **22**	 **23**	86	>50:1	86

[a] Using catalyst **9a**. [b] Using catalyst **9c**.

clization is likely to proceed equally and will be reported in the future. The spacer between the enal and the Michael acceptor portion is not limited to a (substituted) benzene ring. As expected from our previous studies, the cyclization of aliphatic enal **24** with catalyst **9d** gives product **25** in somewhat reduced enantioselectivity (eq 2). In contrast, the corresponding higher homologue **26** provides the product (**27**) in excellent enantiomeric excess when we used catalyst **9a** (eq 3).



In summary, we have developed a highly enantioselective organocatalytic reductive Michael cyclization of enal enones. We assume that the reaction proceeds via an iminium catalytic conjugate reduction followed by an in situ enamine catalytic asymmetric Michael cyclization. Notable features of our reaction include (a) the high selectivity (chemo-, regio-, diastereo-, and enantioselectivity); (b) the not fully explored but already broad scope; (c) the practical and user-friendly reaction conditions; and (d) potential application in the synthesis of natural products.

With the proof of concept being made, a variety of different single flask, tandem enamine−iminium catalysis sequences seem possible and will be investigated.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and HPLC traces (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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