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Highly enantioselective Michael-cyclization cascade promoted by synergistic asymmetric aminocatalysis and Lewis acid catalysis

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ABSTRACT

The novel dual cooperative asymmetric aminocatalysis and Lewis acid catalysis has been successfully developed for promoting cascade Michael-cyclization reaction with high enantio-, regio- and chemo-selectivity. The simple and practical process affords a one-pot approach to synthetically useful cyclopentenes.

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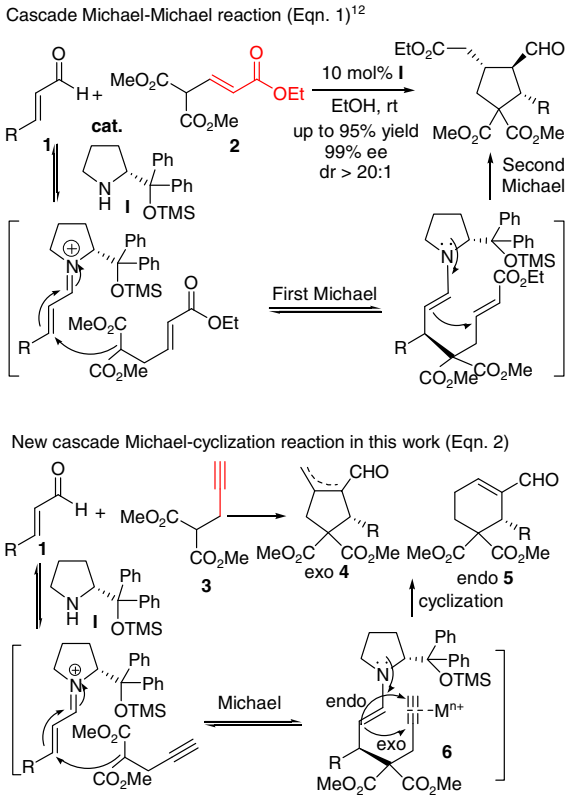
Cascade reactions are unrivaled in their power to rapidly construct complex molecular frameworks with high synthetic efficiency and atom economy.[1] While asymmetric cascade organocatalysis has received considerable attention recently,[2,3] particularly chiral second amines—the most widely used catalytic systems,[4] it is realized that in these cases, only the 'classical' electrophilic partners such as appendant aldehydes, ketones, enones, α,β-unsaturated esters, and alkyl halides can be employed for trapping nucleophilic enamine. Clearly, an important direction with goal of expanding the scope of the powerful synthetic strategy should go beyond the current territory.

Given the great success of Lewis acid catalysis and aminocatalysis, we question whether it might be possible to merge the two catalytic systems[5] for developing new enantioselective cascade processes. However, to our knowledge, no asymmetric protocols using the strategy have been reported.[6,7] Herein we describe the development of the first combined aminocatalysis and Lewis acid catalysis in an asymmetric Michael-cyclization cascade to afford highly enantioenriched (89–99% ee) versatile cyclopentenes.[8,9]

In the past decade, Lewis acid complexes with π-bonds (termed 'π-acids' or 'π-ligands')[10] such as alkynes[11] have been demonstrated to be valuable electrophiles in organic transformations. We envision that incorporation of the moiety instead of a classic electrophilic partner α,β-unsaturated ester (e.g., **2**, Scheme 1, Eq. 1)[12] into a nucleophilic malonate generates a new bifunctional dimethyl propargylmalonate **3** (Eq. 2). The newly designed substance can potentially



Scheme 1. Enantioselective cascade reactions.

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engage in a new binary catalytic asymmetric Michael-cyclization process to create synthetically useful chiral cyclopentenes in one-pot operation. In the proposed cascade, chiral amine **I** activates an enal **1** to form an iminium, which is subject to the Michael addition to form an enamine **6**. Activation of the alkyne by a Lewis acid enables an intramolecular cyclization. Such corporative catalysis may improve the reaction efficiency (yields and/or enantioselectivity). The working hypothesis looks simple on paper. However, the implementation of the strategy faces significant barriers. The primary and most obvious issue is the compatibility of a chiral amine base and a Lewis acid in one-pot and their interference may affect the enantioselectivity significantly. Second, in the subsequent cyclization reaction, possible exo- and endo- enamine attack of the Lewis acid activated triple bond (e.g., π-acid) could result in multiple products **4** and **5**. It is conceived that the steric and kinetic effects favor the 5-exo-dig process.

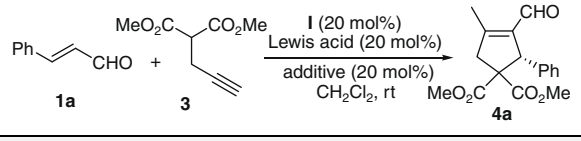
Initial validation of the hypothesis was carried out with a reaction between cinnamaldehyde **1a** and dimethyl propargylmalonate **3** in CH_2Cl_2 at rt in the presence of organocatalyst **I** (20 mol %) and a Lewis acid (20 mol %) (Table 1). Mixed but encouraging results were produced. The reaction proceeded cleanly with only the formation of highly regio-selective conjugated cyclopentene aldehyde **4a** with excellent ees (95–99%) albeit very low yields (6–13%) due to slow conversion when $PdCl_2$ (entry 1), $Pd(OAc)_2$ (entry 2), $ZnCl_2$ (entry 3), and AgOTf (entry 7) were employed. This finding indicates that these soft acids have a limited effect on the chiral amine initiated asymmetric conjugate addition reaction. Moreover, the cascade process is highly chemo- and regio-selective. No reaction occurred for other screened metal complexes including Au(I) and Au(III) (entries 5 and 6). We chose $PdCl_2$ as Lewis acid for further optimization of reaction conditions, mainly aimed at improving reaction yields since it co-catalyzed the reaction more efficiently. The dramatic improvement in yield arose from the addition of acid additives without sacrificing the enantioselectivity (entries 8–10). Notably, the reaction yield (63%) was improved dramatically with $PhCO_2H$ (entry 9). Screening of reaction solvents revealed that CH_2Cl_2 was the choice of the cascade process (see Supplementary data for details). Tuning the ratio of **I** and $PdCl_2$ had an impact on the reaction yield (entries 10 and 11). Reducing the amount of $PdCl_2$ led to improvement. We decided to select the use of 10 mol % $PdCl_2$ to probe the scope of the cascade reaction due to much shorter reaction time (entry 10).

The binary catalytic system promoted asymmetric Michael-cyclization reaction serve as a viable approach to the chiral cyclopentenes with significant structural variation (Table 2). The facile production of the cyclopentene products is especially noteworthy given that one quaternary carbon and one stereogenic center are created in the one-pot operation. It appears that the electronic nature has little influence on both reaction yield and enantioselectivity. The aromatic ring bearing electron-neutral (entry 1), -withdrawing (entries 2–6), and -donating (entries 7–9) groups and a combination of electron-withdrawing and -donating substituents (entry 10) can be readily accommodated. Furthermore, heteroaromatic furanyl enal can effectively participate in the process as well (entries 11). Finally, we also found that the steric effect on the cascade process is limited too (entries 2, 5, and 9). It is also realized the limitation of the cascade reaction. When aliphatic pent-2-enal was employed, no desired Michael-cyclization product was obtained. 2-Ethyl-3-methyl benzaldehyde was isolated, in addition to other unidentified products. It was believed that the substituted benzaldehyde product was formed through a possible [4+2] process.[13] The absolute configuration of the products compounds is determined by single X-ray crystal structure analysis from a derivative **7** from **4b** (Fig. 1).[14]

The preliminary mechanistic studies show that the synergistic effect of the two catalysts contributes to the high reaction yields and high enantioselectivity. In the absence of $PdCl_2$, only the Michael reaction occurred with poor ee (67%) and in a very low yield (17%) under the same reaction conditions and at the same reaction time (36 h) (Scheme 2, Eq. 3 vs Table 2, entry 1). The absence of catalyst **I** resulted in no reaction. Finally, the Michael adduct **8** can be efficiently transformed into the cyclic product **4a** in the presence of catalyst **I** and $PdCl_2$ (Eq. 4). In a control, without **I**, the cyclization reaction did not occur, indicative of an enamine involved.

In conclusion, we have developed an unprecedented asymmetric Michael-cyclization protocol for one-pot preparation of highly enantioenriched cyclopentenes under mild reaction conditions. A catalytic strategy features the combination of widely used aminocatalysis and Lewis acid catalysis to achieve high enantioselectivity and high yields in a cooperative manner for the first time. Further

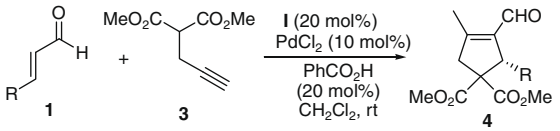
Table 1
Exploration of combined aminocatalysis and Lewis acid catalysis in asymmetric Michael-cyclization cascade[a]



Entry	Lewis acid	Additive	*t* (h)	Yield[b] (%)	ee[c] (%)
1	$PdCl_2$	None	24	13	95
2	$Pd(OAc)_2$	None	24	6	95
3	$ZnCl_2$	None	40	13	97
4	CuOTf·½Tol	None	24	0	—
5	AuCl	None	50	0	—
6	$AuCl_3$	None	50	0	—
7	AgOTf	None	40	11	99
8	$PdCl_2$	TEA	58	2	—
9	$PdCl_2$	$PhCO_2H$	48	63	99
10	**$PdCl_2$**[d]	**$PhCO_2H$**	**36**	**81**	**95**
11	$PdCl_2$[e]	$PhCO_2H$	96	80	99

[a] Unless stated otherwise, the reaction was carried out with **1a** (0.1 mmol) and **3** (0.1 mmol) in the presence of 20 mol % organocatalyst **I**, 20 mol % $PdCl_2$ and additive (0.2 equiv) in CH_2Cl_2 (0.5 mL) was added a and the resulting solution was stirred for specified time at rt. The reaction mixture was directly purified by silica gel chromatography without work-up.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralpak IC).
[d] 10 mol % $PdCl_2$ used.
[e] 1 mol % $PdCl_2$ used.

Table 2
Scope of **I** and $PdCl_2$ promoted cascade Michael-cyclization reactions[a]



Entry	R	*t* (h)	Yield[b] (%)	ee[c] (%)
1	Ph, **4a**	36	81	95
2	4-BrC_6H_4, **4b**	96	64	95
3	3-FC_6H_4, **4c**	108	63	97
4[d]	2-FC_6H_4, **4d**	36	83	99
5[d]	2-$NO_2C_6H_4$, **4e**	36	77	99
6	4-$NO_2C_6H_4$, **4f**	60	86	93
7	4-MeC_6H_4, **4g**	36	91	99
8	4-$MeOC_6H_4$, **4h**	72	61	92
9	2-$MeOC_6H_4$, **4i**	60	76	99
10	4-Ac-3-MeO-C_6H_4, **4j**	60	73	97
11	furanyl, **4k**	108	65	89

[a] Unless specified, see footnote a in Table 1 and Supplementary data.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralpak IC).
[d] 30 mol % **I** used in 0.25 mL of CH_2Cl_2.

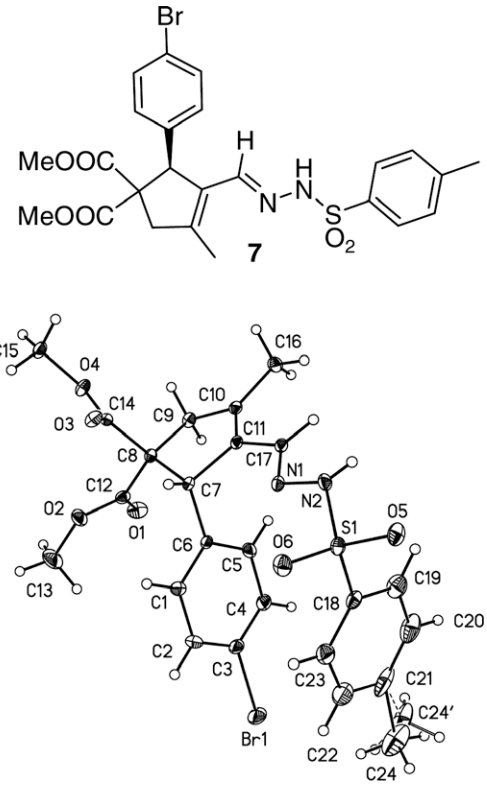
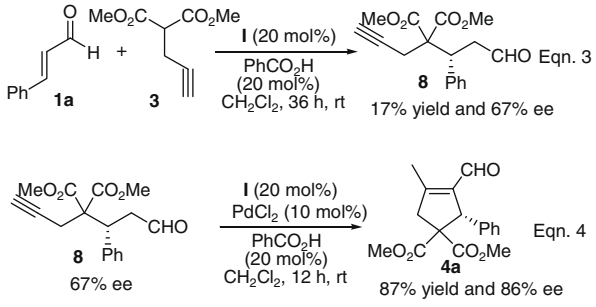


Figure 1. X-ray crystallographic structure **7**.



Scheme 2.

investigation of this powerful and general approach aimed at expanding the scope of asymmetric cascade catalysis and the mechanism of the cascade process is under way in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.096.

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