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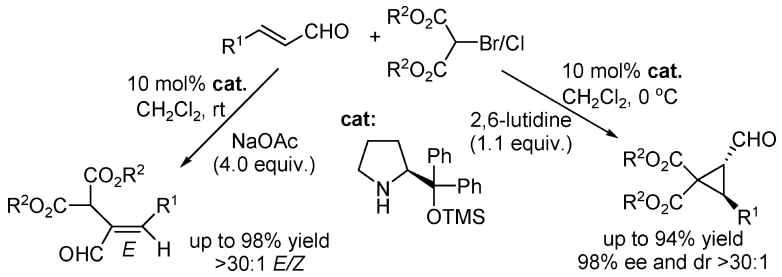

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Organocatalytic Enantioselective Cascade Michael-Alkylation Reactions: Synthesis of Chiral Cyclopropanes and Investigation of Unexpected Organocatalyzed Stereoselective Ring Opening of Cyclopropanes

Hexin Xie, Liansuo Zu, Hao Li, Jian Wang, and Wei Wang*

Contribution from the Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001

Received May 8, 2007; E-mail: wwang@unm.edu

Abstract: The development of efficient methods for the facile construction of important molecular architectures is a central goal in organic synthesis. An unprecedented organocatalytic asymmetric cascade Michael-alkylation reaction of α,β-unsaturated aldehydes with bromomalonates has been developed. The process, efficiently catalyzed by chiral diphenylprolinol TMS ether in the presence of base 2,6-lutidine, serves as a powerful approach to the preparation of synthetically and biologically important cyclopropanes in high levels of enantio- and diastereoselectivities. Remarkably, the power of the cascade process is fueled by its high efficiency of the production of two new C−C bonds, two new stereogenic centers, and one quaternary carbon center in one single operation, which otherwise is difficult to achieve by traditional strategies. Moreover, the beauty of the cascade process is further underscored by the nature of the product formation depending on the reaction conditions. With the alternation of base from 2,6-lutidine (1.1 equiv), which is effective for the cyclopropanations, to NaOAc (4.0 equiv), the spontaneous ring-opening of cyclopropanes takes place to lead to stereoselective (*E*) α-substituted malonate α,β-unsaturated aldehydes. A possible reaction mechanism, which involves a Michael-alkylation−retro-Michael pathway, is proposed and verified by experimental studies. This investigation represents the first example of an organocatalyst-promoted ring opening of the cyclopropanes, whereas such reactions have been intensively explored by Lewis acid-based catalysis.

1. Introduction

The identification of new synthetic methodologies that enable facile construction of complex molecular scaffolds in an efficient way from readily available starting materials remains a challenging goal in chemical synthesis. Cascade processes, in which several bond-forming steps take place in a single operation, have received much attention in this regard because they address one of the fundamental issues related to synthetic efficiency. Consequently, cascade reactions have been the subject of intense research in recent years, as evidenced by the number of reviews that have appeared.[1] The catalytic asymmetric version of cascade reactions is particularly appealing as a result of more atom economy. However, the state-of-the-art of cascade reactions is that there are a limited number of catalytic enantioselective cascade reactions developed thus far.

The efficient preparation of three-membered ring systems is of considerable synthetic interest. The rigid cyclopropane scaffolds are important molecular architectures of a large number of biologically and medicinally relevant substances.[2−4] Moreover, the strained three-membered ring can undergo a variety of ring-opening reactions to generate new molecular skeletons.[2,5] Therefore, the cyclopropanes have long served as a valuable platform for the design of new asymmetric technologies. The currently available methods for synthesis of cyclopropanes include intensively studied organometallic-based catalysis[3,4,6] and asymmetric versions of the Simons−Smith reaction.[7] Significant advances also have been made in the development of catalytic methods based on the reaction of ylides for electron-deficient alkenes since the pioneering work by Corey.[8] Notably,

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recently Aggarwal and Dai,[9] Gaunt[10] and MacMillan[11] have independently described elegant, organocatalyzed asymmetric cyclopropanations using the ylide chemistry.

In contrast to the use of the specific type of sulfur ylides, the employment of readily available alkyl halides for a catalytic Michael-alkylation reaction with α,*β*-unsaturated aldehydes to produce cyclopropanes is an extremely challenging task.[12−14] It is fully realized that the development of general catalytic asymmetric α-alkylation processes has been a long-standing challenge to organic chemists.[15] Such processes are plagued by the tendency of the nucleophilic Lewis- or Brønsted-base catalyst toward an undesirable alkylation reaction with the electrophilic α-alkyl halides that consequently kills the catalyst activity.[16] This is particularly problematic using amine-promoted α-alkylation of enolizable carbonyl compounds with alkyl halides.[17] The high tendency of *N*-alkylation of the secondary amino group of the catalyst with alkyl halides leads to poisoning the catalyst. However, it is noteworthy that there is no such a problem in the case of MacMillan's amine-catalyzed cyclopropanation process using sulfur ylides.[11] Moreover, several side reactions and the racemization of the product further complicate the process.[16] To date, very few catalytic asymmetric α-alkylation methods have been described. Asymmetric phase-transfer catalyzed alkylation of a glycine derivative with alkyl halides has been intensively studied with great success.[18] Koga and co-workers employed chiral oligoamines as catalysts for the indirect α-benzylation of preformed cyclohexanone lithium enolates.[19] List et al. reported a study of an (*S*)-α-methyl proline-promoted intramolecular alkylation of halo aldehydes.[17] More recently, MacMillan[20] and Sibi[21] have independently described new elegant organocatalytic enantioselective α-alkylation of aldehydes and ketones using radial chemistry.

In this paper, we detail a new amine-catalyzed cascade Michael-alkylation process to generate highly functionalized chiral cyclopropanes in one-pot transformation.[22−26] By the careful design of the substrates and optimization of the reaction conditions, we have demonstrated that the use of bromomalonates as nucleophile and electrophile (eg., alkylation reagent) reacting with α,*β*-unsaturated aldehdyes and chiral diphenylprolinol TMS ether as promoter in the presence of 2,6-lutidine as acid scavenger, enables the cascade Michael-alkylation process to proceed efficiently. The tandem reactions afford chiral cyclopropanes with high levels of enantio- (90−98% ee) and diastereoselectivities (≥30:1 dr) and in high yields without intoxicating the catalyst. Significantly, the cascade reactions

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(13) To the best of our knowledge, prior to our initial investigation, only a single study was described by Arai and co-workers using chiral phase-transfer catalyst for cyclopropanation from α,*β*-ketones but with modest enantioselectivity: Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, 4215.

(14) During our investigation, Hansen and co-workers reported an organocatalyzed asymmetric cyclopropanation reaction of α,*β*-unsaturated ketones with bromonitromethane but with modest enantioselectivities and yields: Hansen, H. M.; Longbottom, D. A.; Ley, S. V. *Chem. Commun.* **2006**, 4838 and McCooey and co-workers described an organocatalyzed asymmetric cyclopropanation reaction of nitro-olefins with chloromalonate but with modest enantioselectivities and yields using H-bonding mediated catalysis: McCooey, S. H.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494. However, the utilization of α,*β*-unsaturated aldehydes reactions halostabilized carbanions for cyclopropanations have not yet reported.

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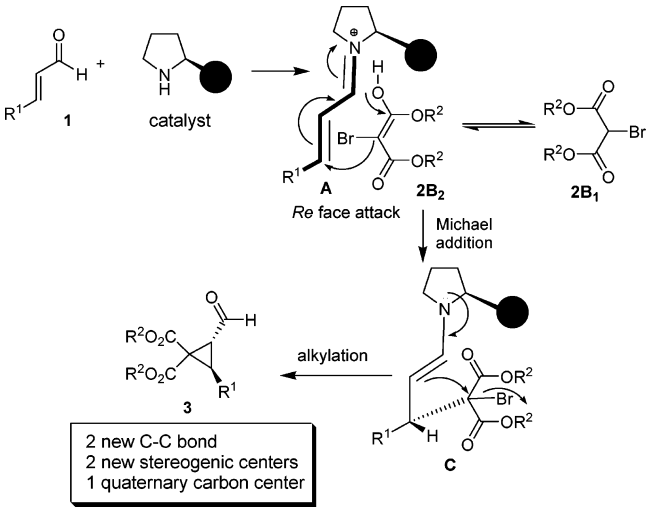
provide fully substituted and highly functionalized chiral cyclopropanes, which contain two stereogenic centers and one quaternary carbon center. Moreover, surprisingly, in the optimization of reaction conditions of the organocatalytic cascade Michael-alkylation reaction, a significant amount of the byproducts, α-substituted malonate α,β-unsaturated aldehydes, are observed when NaOAc is used as base. Through an intensive study aimed at the optimization of reaction conditions, we were able to develop a novel one-pot process for the synthesis of the (*E*) α-substituted malonate α,β-unsaturated aldehydes in high stereoselectivity. A mechanistic investigation reveals that the α,β-unsaturated aldehydes are generated from the subsequent ring opening of cyclopropanes via a retro-Michael reaction. The studies also show that both the organocatalyst diphenylprolinol TMS ether and the base NaOAc play essential roles in the formation of the products.

2. Results and Discussion

2.1. Organocatalytic Asymmetric Cyclopropanation. 2.1.1 Design Plan. In order to successfully develop an amine-promoted asymmetric cascade Michael-alkylation reaction of α,β-unsaturated aldehydes with alkylhalides, we surmise that the key issue is to design alkylhalides. In the cascade conjugate addition−alkylation, the alkylhalides have an ambiphilic function (Scheme 1). They serve as nucleophile for the initial Michael addition reaction with α,β-unsaturated aldehydes. They also function as the electrophile for the subsequent alkylation process. As discussed above, in view of the challenges associated with the tendency of *N*-alkylation, other side reactions, and diastreoselectivity, we envision that the utilization of bromomalonates **2** will kill two birds with one stone (Scheme 1). The favorable enol form **2B$_2$** renders the −Br to be a very poor leaving group as a result of the p−π conjugation with the sp^2-hybridized carbon and thus overcomes the problem of the possible *N*-alkylation with an amine catalyst, whereas serving as nucleophile, it enables participation in the conjugate addition to an activated α,β-unsaturated aldehyde by an amine catalyst through an iminium **A** (Scheme 1). On the other hand, once the nucleophilic enamine **C** is produced, it undergoes the second catalytic cycle alkyaltion reaction. The resulting tertiary bromide from the Michael addition process cannot form an enol form, which should readily undergo an intramolecular α-alkylation reaction to produce a cyclopropane. On the basis of our previous studies, we presume that the use of amine organocatalysts consisting of sterically bulky side chains such as diarylprolidinol diaryl ethers **I**−**III**[23,27] and MacMillan's imidazolidinone **IV**[22e] would be ideal promoters for the cascade process (Figure 1). It has been demonstrated that they are effecitve activators to efficently promote cascade reactions through iminium and enamine chemistry with high stereoselectivity.[23,27] Furthermore, their steric hindrance may prevent the *N*-alkylation of the pyrrolidine ring with bromomalonates **2**. It is expected that the initial enantioselective Michael addition reaction, well-controlled by the chiral diarylprolidinol diaryl ether, should lead to a highly enantiomeric enriched nucleophile enamine **C**, which is intramolecularly trapped by the resulting electrophile alkylbromide to form a cyclic three-membered ring. This enables achievment of high levels of stereoselectivity for the entire process since we believe that the catalyst is involved in both iminium and enamine steps, as shown in Scheme 1.

Scheme 1. Organocatalytic, Enantioselective Cascade Michael-Alkylation Reactions



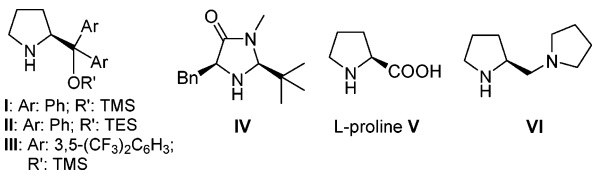


Figure 1. Structures of organocatalysts screened.

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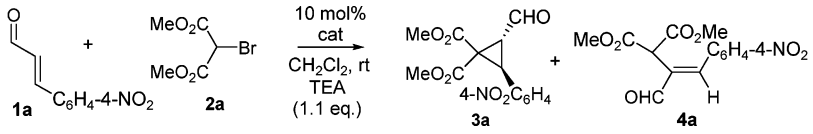
(27) For a review of diaryl prolinol ethers catalysis, see: (a) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. And leading references using chiral diaryl prolinol ethers, see: (b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (d) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253. (e) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *118*, 6804. (f) Chi, Y.; English, E. P.; Pomerantz, W. C.; Horne, W. S.; Joyce, L. A.; Alexander, L. R.; Fleming, W. S.; Hopkins, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *127*, 6050.

Table 1. Catalyst Screening for the Enantioselective Cascade Michael-Alkylation Reaction of *trans*-4-Nitro Cinnamaldehyde (**1a**) with Dimethyl α-Bromomalonate (**2a**)[a]



entry	cat.	t (h)	% yield[b]	% ee[c]	dr[d]	ratio **3a**:**4a**[d]
1	**I**	9	88	92	>30:1	17:1
2	**II**	9	85	89	>30:1	14:1
3	**III**	28	20	nd[e]	>30:1	nd[e]
4	**IV**	28	<5	nd[e]	nd[e]	nd[e]
5	**V**	4	79	26	>30:1	>30:1
6	**VI**	2	89	35	>30:1	>30:1

[a] Reaction conditions: unless otherwise specified, a mixture of **2a** (0.12 mmol), and **1a** (0.14 mmol, 1.2 equiv), TEA (0.13 mmol, 1.1 equiv) and catalyst (0.012 mmol, 0.1 equiv) in CH_2Cl_2 was stirred for a specified time period at rt; also see Experimental Section and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Determined by ^{1}H NMR. [e] Not determined.

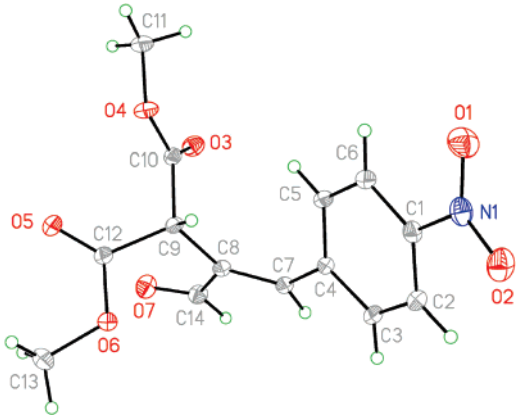


Figure 2. X-ray crystal structure of compound **4a**.

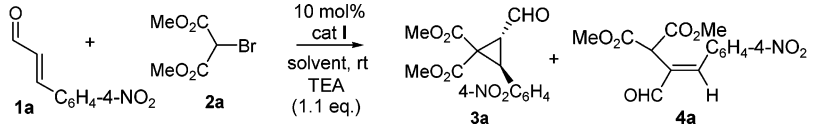
2.1.2. Optimization of Reaction Conditions. As discussed above, a critical issue, which needs to be addressed in developing a catalytic asymmetric approach to the cascade Michael-alkylation reaction, is the identification of proper organocatalysts. Consequently, our initial studies focus on screening different amine-based organocatalysts. On the basis of the previous successful experience in the use of chiral diarylprolinol silyl ethers, which are effective promoters for activation of α,β-unsaturated aldehydes for cascade reactions,[23,25,27] we initially explored a model reaction of *trans*-4-nitro cinnamaldehyde (**1a**) with dimethyl α-bromomalonate (**2a**) in CH_2Cl_2 using (*S*)-diphenylprolinol TMS ether **I** as a catalyst (Table 1, entry 1). A base TEA (1.1 equiv) is used as a HBr scanvager. Remarkably, it is found that the process proceeds smoothly to give cyclopropanation product **3a** as a major product. The reaction is completed within 9 h in 88% yield and high enantioselectivity (92% ee) and excellent diastereoselectivity (>30:1 dr). Unexpectedly, we observe that in addtion to the desired product **3a**, a byproduct **4a** with *E*-stereoconfiguration is obtained with a ratio of 17:1. The structure of compound **4a** is determined by X-ray crystal structural analysis (Figure 2).[28] Encouraged by the promising results, we probe prolinol ethers **II** and **III** for the cascade reaction under the same reaction conditions. While the (*S*)-diphenylprolinol TES ether (**II**) affords comparable results, no reaction proceeds poorly for the more steric (*S*)-bis-[3,5-difluoromethylphenyl]prolinol TMS ether (**III**) (entries 2 and 3). MacMillan's chiral imidazolidinone **IV**-promoted reaction is also sluggish (entry 6). Even after 28 h, only a small amount of product (<5%) is observed based on ^{1}H NMR analysis. These results are consistent with the general observation that the diarylprolinol silyl ethers[23,27] are better promoters for cascade reactions than MacMillan's chiral imidazolidinone, presumbably because the imidazolidinones, possessing bulky side chains at each end, are more sterically hindered. The same reason may be for the more bulky (*S*)-bis[3,5-difluoromethylphenyl]prolinol TMS ether (**III**). Interestingly, when catalysts L-proline **V** and (*S*)-pyrrolidine diamine **VI** are exploited, the cascade processes take place very rapidly and are accomplished within 4 h with excellent diastereoselectivity (>30:1) (entries 10 and 11). Remarkably, desired product **3a** is obtained almost exclusively, but with poor ee (26 and 35%, respectively). The low enantioselectivity is probably due to the small side chains of the catalysts, which cannot effectively block one face over the other. The above studies show that (1) the catalyst activities vary significantly and (2) the steric effect imposed by these catalysts plays a key role in catalytic activity and stereoselectivity, which is why catalysts **I** and **II** are identified in the list of catalysts probed as the best promoters for the cascade reactions.

On the basis of the outcomes obtained from the above investigation, we choose (*S*)-diphenylprolinol TMS ether, **I**, as the catalyst used in further studies of the cascade Michael-alkylation process aimed at optimizing reaction conditions by focusing on surveying the reaction medium, the nature of bases, and the reaction temperature.

Solvents play an important role in governing the rates and enantio- and diastereoselectivity of a reaction. Therefore, we probe the effects of reaction medium on the **I**-promoted cascade Michael-alkylation process (Table 2). We observe that the solvents have a meaningful impact on the efficiencies of these reactions. Reactions performed in less polar halogenated solvents such as CH_2Cl_2 and $Cl(CH_2)_2Cl$ (entries 1 and 2) generally afford the better results in terms of reaction yield, ee, and dr, and significantly only a minimal amount of compound **4a** is formed. However, a pronounced amount of bypoduct **4a** is obtained when the reactions are carried out in toluene and xylenes (entries 3 and 4). The outcomes vary dramatically with the utilization of polar solvents. No reaction occurs in DMF (entry 6), whereas the processes take place in CH_3CN and EtOH (entries 5 and 7) with high dr (>30:1) and a higher ratio of

(28) The X-ray crystal structure of compound **4a** is also available from CCDC-631930. These data can be obtained free of charge via www.ccdc.cam.ac.uk.

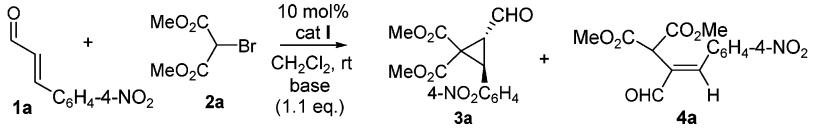
Table 2. Solvent Effect on the **I**-Catalyzed Enantioselective Domino Michael-Alkylation Reaction of *trans*-4-Nitro Cinnamaldehyde (**1a**) with Dimethyl α-Bromomalonate (**2a**)[a]



entry	solvent	*t* (h)	% yield[b]	% ee[c]	dr[d]	ratio **3a**:**4a**[d]
1	CH_2Cl_2	9	88	92	>30:1	17:1
2	$Cl(CH_2)_2Cl$	8	93	91	>30:1	17:1
3	toluene	24	70	92	>30:1	5:1
4	xylenes	24	71	91	>30:1	7:1
5	CH_3CN	8	54	73	>30:1	>30:1
6	DMF	48	nr	nd[e]	nd[e]	nd[e]
7	EtOH	6	90	82	>30:1	25:1

[a] Reaction conditions: unless specified, see footnote *a* of Table 1 and Experimental Section and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Determined by ^{1}H NMR. [e] Not determined.

Table 3. Organocatalytic Enantioselective Domino Michael-Alkylation Reaction of *trans*-4-Nitro Cinnamaldehyde (**1a**) with Dimethyl α-Bromomalonate (**2a**)[a]



entry	base	*t* (h)	% yield[b]	% ee[c]	dr[d]	ratio **3a**:**4a**[d]
1	TEA	9	88	92	>30:1	17:1
2	DIPEA	36	<5	nd[e]	nd[e]	nd[e]
3	2,6-lutidine	23	90	91	>30:1	>30:1
4[f]	2,6-lutidine	5.5	93	94	>30:1	>30:1
5	DABCO[g]	9	65	94	>30:1	25:1
6[h]	NaOAc[i]	5.5	93[j]	nd[e]	nd[e]	1:3

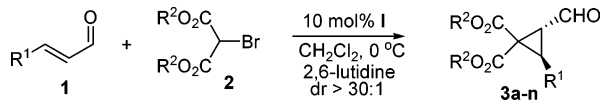
[a] Reaction conditions: unless specified, see footnote *a* of Table 1 and Experimental Section and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Determined by ^{1}H NMR. [e] Not determined. [f] At 0 °C. [g] 0.7 equiv used. [h] **1a**:**2a** with ratio of 1.5:1 used. [i] 2.0 equiv used. [j] Referred to a mixture of **3a** and **4a**.

3a:**4a** but with a lower ee than those of nonpolar solvents employed (entries 1−4).

The effect of bases on the processes is evaluated next. In general, the organic bases except DIPEA furnish the products with respected results (Table 3, entries 1−5). It is unclear why no reaction occurs when DIPEA is used as a base (entry 2). Among the bases probed, 2,6-ludidine is the best choice for the process (entry 3). In this instance, high yield (90%) and high ee (91%) is achieved without formation of product **4a**. Lowering the reaction temperature to 0 °C leads to further imporvement in both yield (93%) and enantioselectivity (94% ee) (entry 4). However, interestingly, the reaction time is significantly shortened. More surprisingly, when 2 equiv of base NaOAc is used, the major product obained is byproduct **4a** with a ratio of 3:1 (entry 6).

2.1.3. Scope of the Cascade Michael-Alkylation Reactions. The optimal reaction conditions, uncovered in the exploratory effort, are exploited to probe the scope of the organocatalyst **I**-catalyzed cascade Michael-alkylation reactions. As revealed in Table 4, the tandem process serves as a general approach to the preparation of highly functionalized chiral cyclopropanes. Remarkably, in the cascade process two new C−C bonds, two new stereogenic centers, and one quaternary carbon center are efficiently assembled in a single operation with high levels of enantioselectivities (90−98% ee) and excellent diastereoselectivities (>30:1 dr in all cases). Moreover, under the optimized reaction conditions, no byproducts **4** are observed. The study of the steric effect of the malonate ester components **2** reveals that generally high yields and outstanding enantioselectivities are obtained. A sole exception is a highly hindered *i*-Pr ester, which requires a longer reaction time and gives the product in lower than usual yield but without deteriorating enantio- and diastereoselectivities (entry 4). Significant structural variation of α,*β*-unsaturated aldehydes can be applicable to the powerful cascade processes to furnish the desired products **3** with highly respected results (entries 1 and 5−14). The electronic nature of the substituents of aromatic systems of α,*β*-unsaturated aldehydes **1** apparently has limited influence on the stereochemical outcome (entries 1, and 5−12). Independent of the electronic characteristics of the substituents [electron withdrawing (entries 1, and 5−8), donating (entries 9−10), neutral (entry 11), and heterocyclic (entry 12)] are the reaction yields and enantio- and diastereoselectivities. The similar trend is observed for the steric effect as well (entries 5, 7, and 10). Also significant is that the **I**-promoted domino processes tolerate the less reactive alkyl α,*β*-unsaturated aldehydes (entries 13 and 14). Both good yields (68 and 74%) and excellent levels of enantioselectivities (95 and 96% ee) are seen, albeit with relatively longer reaction times. Finally, we probe the structural effect of **2** on the cascade process (entries 15 and 16). Switching the leaving group from −Br to −Cl does not influence the yield (95%), ee (94%), and dr (>30:1) (entry 15). A relative longer reaction time (16 h) is expected since -Cl is a poorer leaving group than -Br. The use of ketone ester $CH_3COCHBrCO_2Bn$ instead of malonates for

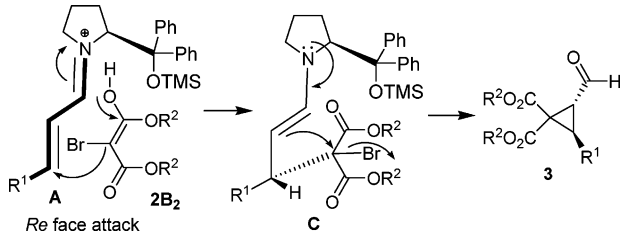
Table 4. Catalyst **I** Promoted Domino Michael-Alkylation Reactions of α,β-Unsaturated Aldehydes (**1**) with α-Bromomalonates (**2**)[a]



entry	R^1	R^2	**3**	*t* (h)	% yield[b]	% ee[c]
1	4-$NO_2C_6H_4$	Me	**3a**	5.5	93	94
2	4-$NO_2C_6H_4$	Et	**3b**	6.5	87	94
3	4-$NO_2C_6H_4$	Bn	**3c**	8	88	93
4	4-$NO_2C_6H_4$	*i*-Pr	**3d**	34	42	90
5	2-$NO_2C_6H_4$	Me	**3e**	20	89	96[d]
6	4-FC_6H_4	Me	**3f**	16	84	97[d]
7	2-ClC_6H_4	Me	**3g**	20	94	98[d]
8	4-$CF_3C_6H_4$	Me	**3h**	16	84	95[d]
9	4-$MeOC_6H_4$	Me	**3i**	24	85	94
10	2-$MeOC_6H_4$	Me	**3j**	24	72	96
11	Ph	Me	**3k**	21	88	96
12	2-furanyl	Me	**3l**	43	87	92
13	Et[e]	Me	**3m**	52	68	95[d]
14	*n*-C_5H_{11}[e]	Me	**3n**	52	74	96[d]
15[f]	4-$NO_2C_6H_4$	Me	**3a**	16	95	94
16[g]	4-$NO_2C_6H_4$	Bn	**3o**	37	66	96[h]

[a] Reaction conditions: unless specified, see Experimental Section and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H and Chiralcel OD−H) and dr by ^{1}H NMR. [d] Ee determined after converted to corresponding enone with $Ph_3P{=}CHCOPh$. [e] 2 equiv of **1** used. [f] Dimethyl α-chloromalonate used. [g] Ketone ester $CH_3COCHBrCO_2Bn$ used. [h] 4:1 dr and the major isomer is COOBn *cis* to CHO group.

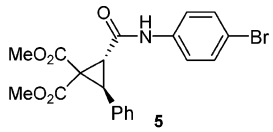
Scheme 2. Proposed Model for the Rationalization of Observed Stereochemistry of Products **3**



the cascade Michael-alkylation reaction shows that the variant can participate in the process with the achievement of high enantioselectivity (96% ee) and respected yield (66%) (entry 16). It is noted that a new chiral center is produced with 4:1 dr and the product of COOBn and CHO group with a *cis* relationship is a major one. The result is consistent with that obtained from Cordova's work.[26]

2.1.4. Outcome of Stereoconfiguration of Cyclopropanation Products 3. A model, as shown in Scheme 2, is proposed to rationalize the observed stereochemistry of the products **3** resulting from the (*S*)-diphenylprolinol TMS ether **I**-catalyzed cascade Michael-alkylation reactions. Reaction of (*S*)-**I** with the α,β-unsaturated aldehyde affords the iminium ion **A**, which allows for *re* face attack of the enol $\mathbf{2B_2}$, leading to formation of enamine **C** with an (*S*)-configured stereocenter. This is consistent with the observations of the earlier studies.[23,25,27] The diastereotopic differentiation of the nucleophile is directed from the catalyst, yielding a diastereomeric ratio of >30:1. Experimentally, the absolute configuration of the product **3k** is determined and confirmed by a single-crystal X-ray analysis based on its derivative **5** (Figure 3).[29]

(29) The X-ray crystal structure of compound **5k** is also available from CCDC-640204. These data can be obtained free of charge via www.ccdc.cam.ac.uk.



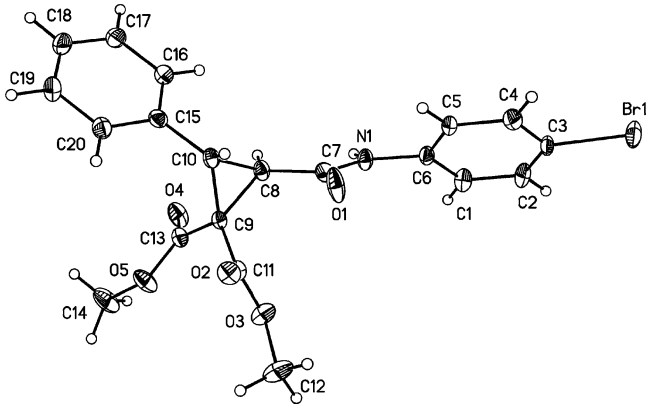


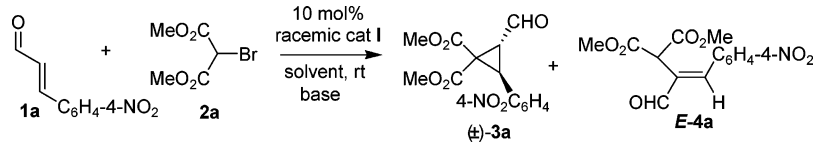
Figure 3. The X-ray crystal structure of compound **5** derived from **3k**.

2.2. Investigation of Organocatalytic Ring Opening of Cyclopropanes. 2.2.1. Optimization of Reaction Conditions for One-Pot Synthesis of α-Substituted Malonate α,β-Unsaturated Aldehydes 4. As mentioned above, in the study of base effects on the catalytic cascade Michael-alkylation reactions, we serendipitously discovered that the use of NaOAc (2.0 equiv) as base in the presence of 10 mol % catalyst **I** results in byproduct α,β-unsaturated aldehyde **4a** as a major product (Table 5, entry 1). The surprising observation prompts us to conduct a detailed investigation of the process since this could result in a new approach to the preparation of synthetically interesting functionalized α,β-unsaturated aldehydes **4**. We hypothesize that the optimization of reaction conditions of the cascade process may lead to α,β-unsaturated aldehydes **4** as desired major product with cyclopropanes **3** as byproduct.

Based on our previous study, our first notion is that the types of bases and their amounts might govern the fate of products **3** and **4**. Accordingly, we carry out experiments of screening several bases and their amounts using a reaction of *trans*-4-nitro cinnamaldehyde (**1a**) with dimethyl α-bromomalonate (**2a**) in the presence of 10 mol % catalyst (Table 5). When 4 equiv of NaOAc is used under the same reaction conditions in CH_2Cl_2 using a racemic diphenylprolinol TMS ether **I**, we find that the ratio of **4a**:**3a** is dramatically increased from 3:1 to >30:1 in almost quantitative yield (entry 2). As a matter of fact, we do not observe product **3a**. More significantly, the process is highly stereoselective and affords the product **4a** favorably with (*E*) geometry. Encouraged by the results, we screen other inorganic bases including K_2CO_3 and Na_2CO_3, and the outcomes turn out to be interesting (entries 3 and 4). The major product obtained is **3a** rather than **4a**. We find that K_2CO_3 and Na_2CO_3 have poorer solubility in CH_2Cl_2 than NaOAc. This indicates that the nature of the base is important for the ring-opening reactions.

We choose the use of NaOAc as the base for further evaluation of the process. Examination of other organocatalysts **V**−**VIII** (Figure 1 and Table 5, entries 5−8) indicates that the catalysts play a crucial role in the cascade process. No reaction occurs when **VIII** with −OH group is used (entry 8). The result

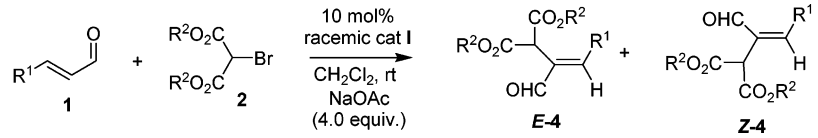
Table 5. Optimization of Reaction Conditions for One-Pot Synthesis of α,β-Unsaturated Aldehydes **4**[a]



entry	catalyst	base (equiv)	solvent	*t* (h)	% yield of **4a**[b]	ratio of **3a**:**4a**[c]	ratio of ***E*-4a**:***Z*-4a**[c]
1	racemic **I**	NaOAc (2.0)	CH_2Cl_2	9	70	1:3	nd
2	racemic **I**	NaOAc (4.0)	CH_2Cl_2	8	98	<1:30	19:1
3	racemic **I**	K_2CO_3 (4.0)	CH_2Cl_2	24	<10	>10:1	nd[d]
4	racemic **I**	Na_2CO_3 (4.0)	CH_2Cl_2	24	<10	13:1	nd[d]
5[e]	racemic **V**	NaOAc (4.0)	CH_2Cl_2	8	0	nd[d]	nd[d]
6[e]	**VI**	NaOAc (4.0)	CH_2Cl_2	8	<5	>30:1	nd[d]
7[e]	**VII**	NaOAc (4.0)	CH_2Cl_2	8	<5	>30:1	nd[d]
8	**VIII**	NaOAc (4.0)	CH_2Cl_2	19	0	nd[d]	nd[d]
9	racemic **I**	NaOAc (4.0)	toluene	18	77	8:1	7:1
10	racemic **I**	NaOAc (4.0)	CH_3CN	18	31	1:1.7	20:1

[a] Reaction conditions: unless specified, a mixture of **2a** (0.12 mmol), and **1a** (0.13 mmol), a base and catalyst (0.012 mmol) in CH_2Cl_2 was stirred for a specified time period at rt. [b] Isolated yields. [c] Determined by ^1H NMR. [d] Not determined. [e] The major product obtained is the cyclopropanation product (±)-**3a**.

Table 6. Catalyst **I**-Catalyzed One-Pot Synthesis of α,β-Unsaturated Aldehydes **4**[a]



entry	R^1	R^2	4	*t* (h)	% yield (*E*)[b]	*E*:*Z*[c]
1	4-$NO_2C_6H_4$	Me	**4a**	8	98	19:1
2	4-$NO_2C_6H_4$	Et	**4b**	20	90	10:1
3	4-$NO_2C_6H_4$	Bn	**4c**	32	76	8:1
4	4-$NO_2C_6H_4$	*i*-Pr	**4d**	120	72	9:1
5	2-$NO_2C_6H_4$	Me	**4e**	41	95 (*E*/*Z* mixture)	2.3:1
6	4-FC_6H_4	Me	**4f**	22	91	15:1
7	4-CNC_6H_4	Me	**4g**	48	81	14:1
8	4-$CF_3C_6H_4$	Me	**4h**	22	87	20:1
9	4-$MeOC_6H_4$	Me	**4i**	24	85	>30:1
10	2-$MeOC_6H_4$	Me	**4j**	24	45 (*E*) and 55 (*Z*)	1:1.1
11	3-MeO-4-$AcOC_6H_3$	Me	**4k**	24	95	20:1
12	Ph	Me	**4l**	24	90	15:1
13[e]	H	Me	**4m**	24	<5	nd[d]
14[e]	*n*-C_5H_{11}	Me	**4n**	48	<5	nd[d]

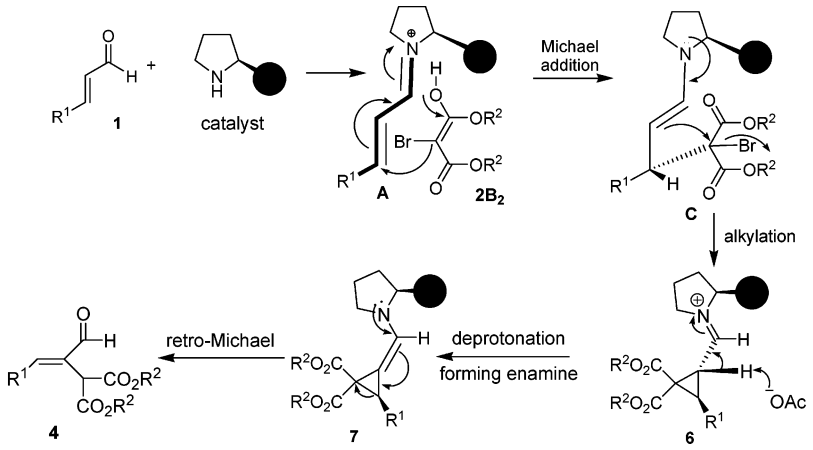
[a] Reaction conditions: unless specified, see Experimental Section and Supporting Information. [b] Isolated yields. [c] Determined by ^1H NMR. [d] Not determined. [e] Major product is cyclopropanes, and we also perform the experiments of their corresponding pure cyclopropanes for ring-opening reactions in the presence of NaOAc (2 equiv) and catalyst **I** (10 mol %). No ring-opening reactions for both cases are observed.

implies that the TMS group has an important role in the activity of α,β-unsaturated aldehydes for the formation of iminiums. Catalysts proline **V**, pyrrolidine **VI**, and pyrrolidine diamine **VII** only catalyze Michael-alkylation reactions to give cyclopropanation product **3a** (which was observed earlier) but give poor enantioselectivities (Table 1, entries 5 and 6). Under the reaction conditions, no ring-opening product **4a** is formed. The above studies display that the both pyrrolidine and silyl ether moieties in catalyst **I** are essential for catalyst activities and reaction stereoselectivities.

Finally, we survey the solvent effect on the process as well (Table 5, entries 9 and 10). It is realized that although the reaction takes place in toluene and CH_3CN but with unsatisfied results. Therefore, the above investigation leads us to selecting **I** as catalyst and NaOAc (4.0 equiv) as base in CH_2Cl_2 to determine the scope of the process.

2.2.2. Scope of I-Catalyzed One-Pot Synthesis of α,β-Unsaturated Aldehydes 4. The optimized protocol has been demonstrated to be general to a variety of α,β-unsaturated aldehydes **1** and bromomalonates **2** (Table 6). The cascade processes between the various aldehydes **1** and bromomalonates **2** proceed smoothly to furnish the desired products **4** in overall good yields and high stereoselectivities. The investigation of the structural variation of the ester part in **2** reveals that increasing steric hindrance slows down the reaction and lessens the reaction yields (entries 1−4). This is consistent with the results of the cyclopropanations we have observed due to the steric effect. In addition, the stereoselectivity drops as well as the size increases. It seems that the stereochemical outcome and reaction yield are immune to the electronic properties of the substituents on α,β-unsaturated aromatic aldehydes **1**, which possess electron-withdrawing (entries 1, and 6−8) and -donating (entry 9) groups, a combination of electron-withdrawing and -donating (entry 11) groups, and neutral (entry 12) groups at the para positions. However, the substitution patterns have significant influence on the reaction yields and stereoselectivity. The substituents at meta and para positions have limited effects (entries 1, 6−8, 9, and 11). However, the ortho-positioned

Scheme 3. Proposed Reaction Mechanism for the Formation of Product **4**

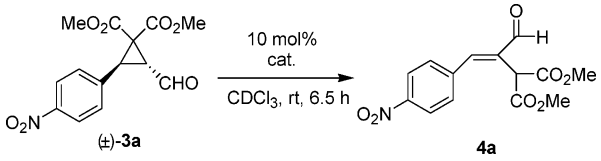


groups create significant steric effect, and they not only decrease the reaction rate, they also dramatically depreciate the *E:Z* selectivity (entries 5 and 10). We also find that the less reactive alkyl α,*β*-unsaturated aldehydes cannot undergo the ring-opening reactions (entries 13 and 14). Only cyclopropanation products are obtained.

2.2.3. Mechanistic Insights. How the products **4** are formed in the **I**-catalyzed cascade reactions between α,*β*-unsaturated aldehydes and bromomalonates prompts us to undertake a mechanistic study. A possible reaction mechanism has been proposed (Scheme 3). The pathway involves a Michael-alkylation−deprotonation (enamine)−retro-Michael reaction sequence. After the Michael-alkylation reaction, the cyclopropane intermediate **6** is deprotonated in the presence of a base to give an enamine **7**, which subsequently undergoes a retro-Michael reaction to afford product **4**. It understands that the major product **4** with (*E*) stereoconfiguration resulting from the stereoselective retro-Michael process is consistent with the geometry of the starting material, *trans*-α,*β*-unsaturated aldehyde.

To verify the proposed mechanism, we designed several experiments. We hypothesize that if the reaction undergoes a retro-Michael process from **6**, the treatment of pure product **3** in the presence of catalyst **I** should lead to product **4**. Therefore, an experiment is carried out by the reaction of pure (±)-**3a** with NaOAc (2.0 equiv) and 10 mol % racemic catalyst **I** in $CDCl_3$ at rt. After 6.5 h, ^{1}H NMR analysis reveals that product **4a** is formed in 100% conversion (Table 7, entry 1). It is expected that without the base NaOAc, the process should be slower because it can facilitate the formation of enamine **7**. This presumption is confirmed by the study. In the absence of NaOAc, indeed only 27% conversion is observed under the same reaction conditions (entry 2). Interestingly, no conversion is observed when TEA is used (entry 3). In contrast to NaOAc, TEA somehow hinders the ring-opening reaction. This result is in agreement with the observation that the predominant product is a cyclopropanation one (**3a**) (17:1 of **3a:4a**) with TEA (Table 3, entry 1), whereas a major product is ring-opening one (**4a**) (1:3 of **3a:4a**) obtained from NaOAc (Table 3, entry 6). Moreover, the catalyst **I** is key for the formation of **4** based on the proposed reaction mechanism (Scheme 3). It activates the aldehyde group in **3** to produce enamine **7**, which is subject to subsequent retro-Michael reaction to give rise to **4**. As expected, without catalyst **I**, no transformation from (±)-**3a** to **4a** occurs (entry 4). Additional evidence further proves the observation. The addition of α,*β*-unsaturated aldehyde **1a**, which competes with cyclopropyl aldehyde **3a** for the catalyst **I**, results in slower conversion (entry 5). Therefore, the above experiments demonstrate that the proposed Michael-alkylation−retro-Michael mechanism is a plausible pathway for the formation of products **4**. It is noteworthy that this is the first example of an organocatalyst-promoted ring-opening of the cyclopropanes, whereas such reactions have been intensively explored by Lewis acid-based catalysis.[2,5]

Table 7. Design of Experiments for the Verification of Proposed Michael-Alkylation−Retro-Michael Mechanism



entry	catalyst	additive	base (equiv)	% conversion[a]
1	racemic **I**	none	NaOAc (2)	100
2	racemic **I**	none	none	27
3	racemic **I**	none	TEA (2)	0
4	none	none	NaOAc (2)	0
5	racemic **I**	**1a** (0.5 equiv)	NaOAc (2)	87

[a] Determined by ^{1}H NMR.

3. Conclusion

In conclusion, a new organocatalytic, highly enantio- and diastereoselective cascade Michael-alkylation process, catalyzed by readily available (*S*)-diphenylprolinol TMS ether, has been achieved. The simplicity and practical nature of the asymmetric protocols presented here is underscored by the use of simple starting materials and the generation of synthetically useful, highly optically active, and heavily functionalized cyclopropanes. The merit of the cascade process in one single operation is highlighted by its high efficiency of the production of two new C−C bonds, two new stereogenic centers, and one quaternary carbon center, which otherwise are difficult to access by traditional strategies. Moreover, the power of the cascade process is further fueled by the nature of the product formation, depending on the reaction conditions. When the switch of base from 2,6-lutidine (1.1 equiv), which is effective for cyclopropanations, to NaOAc (4.0 equiv), the subsequent ring-opening of cyclopropanes takes place to lead to stereose-

lective (*E*) α-substituted malonate α,*β*-unsaturated aldehydes. The mechanistic study proves the cascade Michael-alkylation−retro-Michael process.

4. Experimental Section

4.1. General Procedure for Michael-Alkylation Reactions (Table 4). To the mixture of bromomalonate ester **2** (0.12 mmol), 2,6-lutidine (0.13 mmol), and catalyst **I** (0.012 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C is added α,*β*-unsaturated cinnamaldehyde **1** (0.14 mmol). The resulting mixture is then stirred at the same temperature for a specified period of time. The pure product is obtained after purification by column chromatography on silica gel, and ee and dr are determined by chiral HPLC analysis and ^{1}H NMR respectively (see Supporting Information for details).

4.2. General Procedure for One-Pot Synthesis of Compounds 4 (Table 6). To the mixture of bromomalonate ester **2** (0.13 mmol), sodium acetate (0.52 mmol), and catalyst **I** (0.013 mmol) in CH_2Cl_2 (0.5 mL) at rt is added aldehyde **1** (0.14 mmol). The resulting mixture is then kept stirring at rt until the reaction is complete. The pure product is obtained after purification by column chromatography on silica gel, *E*/*Z* ratio is determined by ^{1}H NMR.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectra, chiral HPLC analysis data for products **3** and **4**, and X-ray data (CIF files) of **4a** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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