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A Simple Organocatalytic Enantioselective Cyclopropanation of α,β-Unsaturated Aldehydes

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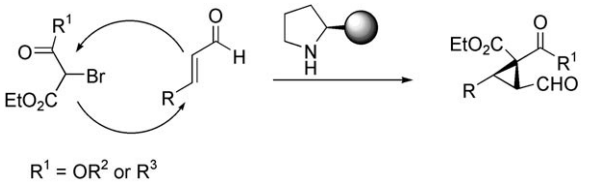
Abstract: A highly chemo- and enantioselective organocatalytic cyclopropanation of α,β-unsaturated aldehydes with bromomalonate and 2-bromoacetoacetate esters is presented. The reaction is catalyzed by chiral amines and gives access to 2-formylcyclopropanes in high yields and up to 99% *ee*.

Keywords: asymmetric catalysis; cyclopropanes; domino reactions; halomalonates; organocatalysis; α,β-unsaturated aldehydes

The cyclopropane motif has long been an interesting target for organic chemists. The cyclopropane ring is a constituent in more than 4000 natural isolated[1] and 100 biologically active agents. In addition, cyclopropyl derivatives are attractive as intermediates in complex molecule synthesis,[2] as synthetic building blocks,[3] and as templates for the construction of conformationally restricted amino acids and peptides.[4] Hence, the importance of cyclopropyl derivatives has inspired chemists to develop asymmetric methods for their synthesis.[5] For example, in the last few years high levels of asymmetric induction have been achieved involving metal-catalyzed intermolecular cyclopropanations of electron-rich olefins.[6] In the realm of organocatalysis, there are a few examples of enantioselective cyclopropanations.[7–11] For instance, Aggarwal and Gaunt pioneered the use of catalyst-bound ylides in enantioselective intermolecular cyclopropanation reactions.[7b] Moreover, Gaunt developed a very elegant catalytic intramolecular cyclopropanation using modified *Cinchona* alkaloids as organocatalysts.[10] *Cinchona* alkaloid derivatives have also been used by Connon and co-workers as catalysts for the asymmetric cyclopropanation of nitroalkenes.[8] Most recently, MacMillan and co-workers disclosed a novel enantioselective cyclopropanation rection between stabilized ylides and α,β-unsaturated aldehydes using a 2-carboxylic acid dihydroindole as the catalyst.[11] Encouraged by these studies and our previous experience on the combination of enamine and iminium catalysis,[12] we envisioned a chiral amine-catalyzed domino reaction between halomalonates or 2-halo-β-keto esters and enals would be a simple asymmetric entry to 2-formylcyclopropanes [Eq. (1)].[13]



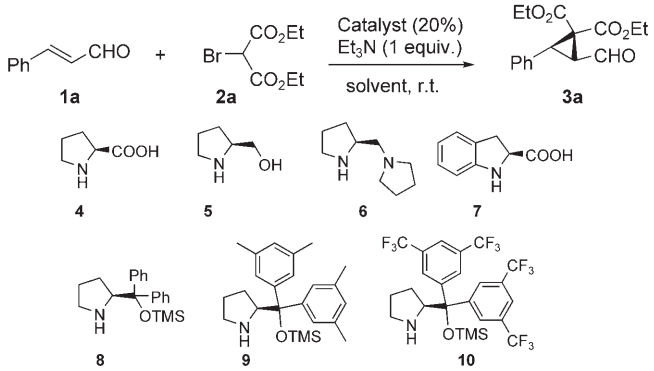
(1)

Herein, we report the highly enantioselective catalytic asymmetric reaction between bromomalonates or 2-bromoacetoacetate esters and α,β-unsaturated aldehydes that gives the corresponding 2-formylcyclopropanes in high yields and diasteromeric ratios and excellent asymmetric induction (93–99% *ee*).

After an extensive screening of catalysts and different solvents for the asymmetric cyclopropanation of cinnamic aldehyde **1a**, we found that that the addition of 1 equivalent of Et_3N was crucial in order to obtain high yields. In Table 1, selected results from the screening of reaction conditions for the enantioselective transformation between enal **1a** and diethyl bromomalonate **2a** are shown.

We found that chiral amines **4**–**9** catalyzed the asymmetric formation of the corresponding 2-formylcyclopropanes **3a** with up to >25:1 *dr* (*trans*/*cis*) and *ee* values ranging from 9–99%. Chiral amines **8**[14] and **9** were the most efficient catalysts under our reaction conditions and catalyzed the formation of **3a** with high chemo-, diastereo- and enantioselectivity (en-

Table 1. Selected reactions for the **4a**-catalyzed enantioselective domino reactions between **1a** and **2a**.[a]

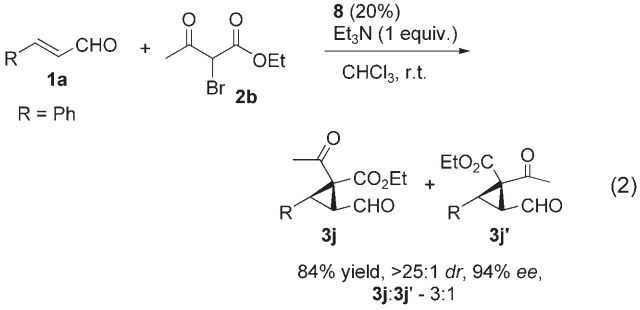


Entry	Catalyst	Solvent	Time	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**4**	$CHCl_3$	14 h	80	>25:1	30
2	**5**	$CHCl_3$	14 h	62	>25:1	9
3	**6**	$CHCl_3$	14 h	55	>25:1	71
4	**7**	$CHCl_3$	14 h	72	>25:1	-63
5	**8**	$CHCl_3$	3 h	91	>25:1	96
6	**9**	$CHCl_3$	14 h	87	>25:1	99
7	**10**	$CHCl_3$	14 h	traces	n.d.	n.d.
8	**8**	MeOH	3 h	23	>25:1	89
9	**8**	DMF	3 h	traces	n.d.	n.d.
10	**8**	Toluene	3 h	76	>25:1	92

[a] *Experimental conditions:* A mixture of **2a** (0.25 mmol), aldehyde **1a** (0.3 mmol) and catalyst (20 mol%) in 1.0 mL solvent was stirred at the temperature and conditions displayed in the table.
[b] Isolated yield.
[c] Determined by NMR analyses.
[d] Determined by chiral-phase HPLC analyses.

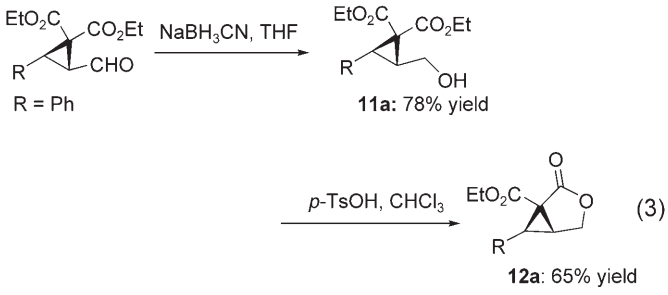
tries 5 and 6). Moreover, chiral amine **8** catalyzed the asymmetric formation of **3a** in other solvents such as MeOH and toluene. Based on our initial results, we decided to investigate the enantioselective cyclopropanation of enals **1** with diethyl bromomalonate **2a** using amines **8** and **9** as the catalysts (Table 2).

The organocatalytic enantioselective cyclopropanations were highly chemo- and enantioselective and the corresponding 2-formylcyclopropanes **3** were isolated in high yields with *ee* values of 93–99% *ee*. The diastereoselectivity of the reaction was excellent (>25:1 *dr*) when 3-aryl-substituted enals **1** were used as the substrates. In addition, the organocatalytic cyclopropanation of aliphatic enals **1** were highly diastereoselective (up to 25:1 *dr*). To our delight, the reaction was regiospecific when 2,4-hexadienal was used as the substrate (entry 10). Notably, the *E*/*Z* ratio of the starting dienal **1h** was 3:1, while the diastereomeric ratio of the corresponding *trans* product **3h** was 14:1. Reducing the catalyst loading to 10 mol% did not significantly affect the yield and the enantioselectivity of the reaction (Table 2, entry 2; Table 1, entry 5). We also investigated the enantioselective organocatalytic cyclopropanation reaction between 2-bromoketo esters and enals [Eq. (2)].



(2)

For example, the reaction between enal **1a** and ethyl-2-bromo-3-oxobutanoate **2b** was highly diastereo- and enantioselective (>25:1 *dr*, 94% *ee*) and gave the corresponding cyclopropane products **3j** and **3j′** in a 3:1 ratio. The 2-formylcyclopropanes **3** from the catalytic reaction are valuable chiral precursors to 3–5 bicyclic frameworks with a quaternary carbon stereocenter. Accordingly, cyclopropane **3a** was treated with $NaBH_3CN$ in THF, to afford the corresponding alcohol **11a**, which upon intramolecular cyclization gave the corresponding lactone **12a** by treatment with *p*-TsOH in $CHCl_3$ [Eq. (3)].

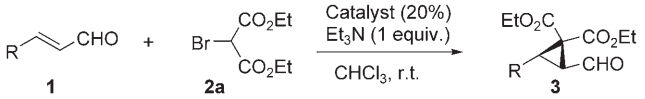


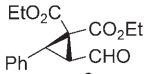
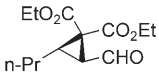
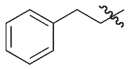
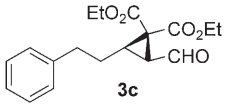
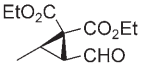
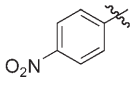
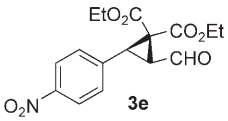
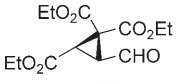
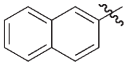
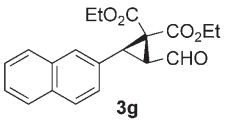
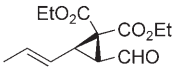
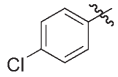
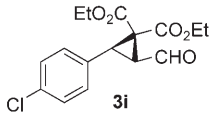
(3)

The absolute configuration of the cyclopropanes **3** was determined by synthesis. Thus, thiazolium-catalyzed C–C bond cleavage of **3a** gave the corresponding β-malonate acid ester **13a** in 72% yield and 97% *ee* [Eq. (4)].[14]

Comparison with the literature revealed that the absolute configuration of compound **13a** at C-3 was *R*

Table 2. Scope of the organocatalytic cyclopropanation.[a]



Entry	R	Catalyst	Product	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	Ph	**9**	 **3a**	14	87	>25:1	99
2		**8**		3	83	>25:1	94[e]
3	n-Pr	**8**	 **3b**	3	80	15:1	99
4		**8**	 **3c**	3	74	25:1	94
5	Me	**8**	 **3d**	5	88	9:1	94
6		**9**	 **3e**	14	81	>25:1	98
7	CO_2Et	**8**	 **3f**	14	50	>25:1	93[f]
8		**8**	 **3g**	14	83	>25:1	96[g]
9		**9**		14	80	>25:1	93
10	 E/Z = 3:1	**8**	 **3h** E/Z = 14:1	3	76	14:1	99
11		**8**	 **3i**	4	60	>25:1	96

[a] *Experimental conditions:* A mixture of **1** (0.25 mmol), aldehyde **2** (0.30 mmol), triethylamine (0.25 mmol) and catalyst **8** or **9** (20 mol%) in $CHCl_3$ (1.0 mL) was stirred at room temperature. The crude product **3** was purified by column chromatography.

[b] Isolated yield of pure product **3** after silica gel column chromatography.

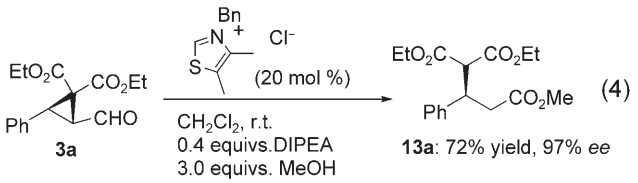
[c] Determined by NMR analysis.

[d] Determined by chiral-phase HPLC or GC analyses.

[e] 10 mol% catalyst.

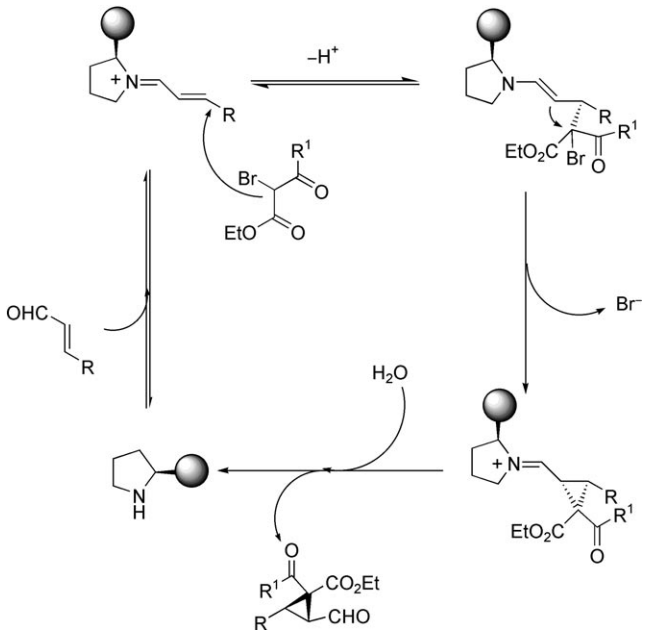
[f] Reaction performed at −20 °C.

[g] Reaction performed at 4 °C.



{$[\alpha]_D^{25}$: −33.2 (*c* 1.0, $CHCl_3$), Lit. (*R*-**13a**, $[\alpha]_D^{25}$: −29 (*c* 1.0, $CHCl_3$)[16]}. Hence, the reactions with catalysts (*S*)-**8** and (*S*)-**9** give access to (2*R*,3*R*)-2-formylcyclopropanes **3**. Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups of chiral pyrrrolidines **8** and **9** leads to stereoselective *Re*-facial nucleophilic conjugate addition by the 2-bromo-substituted malonates and β-keto esters **1** (Scheme 1). Next, the generated chiral enamine intermediate performs an intramolecular 3-*exo-tet* nucleophilic attack to form the cyclopropane ring. The intramolecular ring-closure pushes the equilibrium forward and makes this step irreversible. The same type of reaction mechanism has also been observed in the organocatalytic asymmetric epoxidation of enals[12l,o] and asymmetric aziridination of enals.[17]

In summary, we report a new example of a highly chemo- and enantioselective organocatalytic cyclopropanation of α,β-unsaturated aldehydes. The reaction was efficiently catalyzed by simple chiral pyrrolidine derivatives and gives the corresponding 2-formylcyclopropanes in high yields with 9:1 to >25:1 *dr* and 93–99% *ee*. Moreover, the cyclopropanation of 2,4-hexadienal was regiospecific affording the corresponding vinylcyclopropane in high yield and high enantiopurity. Mechanistic studies, synthetic applications of this transformation as well as the development of other enantioselective cyclopropanations based on this concept are ongoing in our laboratory.



Scheme 1. A plausible reaction pathway for a chiral amine-catalyzed enantioselective cyclopropanation.

Experimental Section

Typical Procedure for the Organocatalytic Cyclopropanation Reactions

To a stirred solution of catalyst (20 mol%) in $CHCl_3$ 1.0 mL, was added α,β-unsaturated aldehyde (1.2 equivs.), triethylamine (1.0 equiv.) and diethyl bromomalonate (1.0 equiv.). The reaction mixture was vigorously stirred for the time given in Table 2. Next, the crude product was purified by silica gel chromatography [pentane (toluene): EtOAc-mixtures] to give the corresponding cyclopropane derivatives.

Acknowledgements

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