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Organocatalytic formal [2+2] cycloaddition initiated by vinylogous Friedel–Crafts alkylation: enantioselective synthesis of substituted cyclobutane derivatives†

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An organocatalytic vinylogous Friedel–Crafts alkylation-initiated formal [2+2] cycloaddition was successfully developed based on tandem iminium–enamine activation of enals. Transformable pyrrole-functionalized cyclobutanes with three contiguous stereocenters were readily obtained with excellent levels of regio-, diastereo- and enantiocontrol.

Cyclobutanes represent an intriguing strained molecular scaffold and constitute the backbone of a large number of natural products and biologically interesting molecules (Fig. 1).[1,2] Driven by the relief of the ring strain, the functionalized cyclobutanes can act as reactive intermediates for further ring-opening and ring expansion reactions enabling the development of new synthetic methods as well as complex molecule synthesis.[3] Therefore, many reports directed toward the synthesis of these privileged building blocks have appeared so far. Among them, the [2+2] cycloaddition reaction stands out as the most versatile and powerful strategy for the construction of such systems.[4] Surprisingly, however, the asymmetric catalytic [2+2] cycloaddition, especially organocatalytic variants to construct enantioenriched cyclobutanes are extremely rare and less explored.[5] In 2007, Ishihara and co-workers reported an elegant example of the enantioselective synthesis of substituted cyclobutanes by means of chiral organoammonium salt-promoted [2+2] cycloaddition of unactivated alkenes with α-acyloxyacroleins.[5c] More recently, Jørgensen and Vicario groups independently discovered two [2+2] cycloaddition reactions of enals and nitroalkenes on the basis of dienamine catalysis.[5d,e] Herein, we report a method for the organocatalytic synthesis of chiral cyclobutanes using organocatalytic [2+2] cycloaddition of enals and 2-vinylpyrroles, generating chiral cyclobutanes with high stereocontrol.

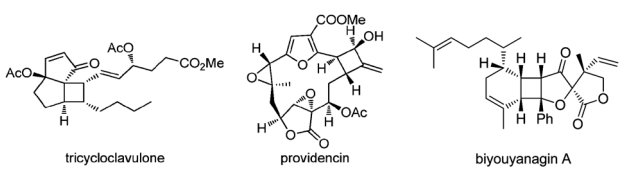

Fig. 1 Representative natural products containing a cyclobutane scaffold.

The vinylogy principle is a commonly encountered strategy to implement new reactivity and diversity in organic synthesis and catalysis.[6] Over the past decade, with the rapid development of organocatalysis, a wide array of organocatalytic transformations involving vinylogous nucleophiles or electrophiles were devised to furnish valuable enantiomerically enriched molecules.[7] Recently, vinylindole-involved vinylogous Friedel–Crafts alkylation has been successfully incorporated into organocatalytic [4+2] cycloaddition.[8] Chiral amine-mediated Friedel–Crafts alkylation of aromatic substrates to enals is a reliable strategy to generate synthetically versatile β-aryl carbonyls.[9] We envisioned that aminocatalyzed vinylogous Friedel–Crafts alkylation-initiated [2+2] cycloaddition of 2-vinylpyrroles[10] and enals would be feasible on the basis of tandem iminium–enamine activation of enals.[11] Importantly, this chemistry will allow for the enantioselective synthesis of challenging but significant pyrrole-functionalized cyclobutanes.

As a proof of concept study, 2-vinyl-1-allyl-pyrrole (**1a**) was reacted with *trans*-cinnamaldehyde (**2a**) as a model reaction under the influence of the commonly used α,α-diphenylprolinol trimethylsilyl ether (**4a**).[12] The preliminary results demonstrated a strong solvent effect on reactivity and selectivity. Under the specified time, no desired product could be found with toluene or CH_2Cl_2 as the solvent (Table 1, entries 1 and 2), while in Et_2O and THF, the desired product was readily obtained with high enantioselectivities albeit in low yields (Table 1, entries 3 and 4). Improved results were observed by means of alcoholic solvents (Table 1, entries 5–7) and EtOH gave a satisfactory yield and excellent enantioselectivity (76% yield, 93% ee). Apparently, these results showed that the protic solvent is helpful for the hydrolysis of the intermediate to

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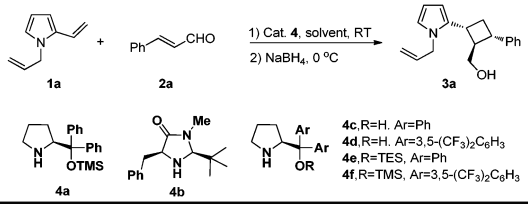
Table 1 Screening of the reaction parameters[a]



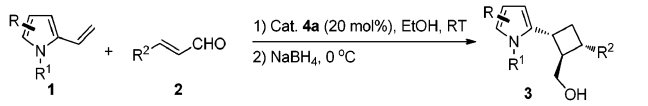
Entry	Catalyst	Solvent	t (h)	Yield[b] (%)	ee[c] (%)
1	**4a**	Toluene	48	—	—
2	**4a**	CH_2Cl_2	48	Trace	n.d.
3	**4a**	Et_2O	48	43	90
4	**4a**	THF	48	40	90
5	**4a**	MeOH	48	70	92
6	**4a**	EtOH	48	76	93
7	**4a**	iPrOH	48	50	88
8[d]	**4a**	EtOH	48	<10	n.d.
9[e]	**4a**	EtOH	48	<10	n.d.
10	**4b**	EtOH	72	Trace	n.d.
11	**4c**	EtOH	60	60	87
12	**4d**	EtOH	72	46	83
13	**4e**	EtOH	48	67	90
14	**4f**	EtOH	72	30	80

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.15 mmol), **2a** (0.10 mmol) and **4** (0.02 mmol) in the specified solvent (0.5 mL) at room temperature. [b] The isolated yield. [c] Determined using HPLC analysis. [d] $PhCO_2H$ (20 mol%) was added. [e] TsOH (20 mol%) was added.

release the catalyst and thus increase the catalytic turnover. Further screening revealed a dramatic negative effect of acidic additives possibly due to the acid-sensitive nature of the pyrrole ring (Table 1, entries 8 and 9). Next, the impact of various chiral secondary amine catalysts on the reaction was tested in ethanol at room temperature. Among them, MacMillan imidazolidinone catalyst **4b** proved to be ineffective under the tested conditions (Table 1, entry 10), while diphenylprolinol **4c** and **4d** gave the desired product in moderate yield and slightly decreased stereoinduction (Table 1, entries 11 and 12). Compared with **4a**, its analogues **4e** and **4f** exhibited relatively inferior results with respect to reactivity and selectivity (Table 1, entries 13 and 14). In all the tested cases described above, the diastereocontrol was perfect with only one of the four possible diastereomers found. We then decided to investigate the scope of the reaction under the optimal reaction conditions (Table 1, entry 6).

The results are summarized in Table 2. With regard to the α,β-unsaturated aldehydes, it was found that a wide range of cinnamaldehyde derivatives are well tolerated regardless of the nature and position of the substituent of the aromatic ring (Table 2, entries 1–11). However, a remarkable substituent effect on reactivity was observed (Table 2, entries 2 and 4 *vs.* 9–11). Reaction of the pyrrole component bearing a bromide atom at the C4-position proceeded smoothly under the standard conditions, giving rise to the desired products in comparable yields and enantioselectivities while the 5-methyl pyrroles exhibited diminished reactivity and ee possibly owing to steric hindrance (entries 12–14). Simple variation of the substituent at the nitrogen atom had little impact on reactivity and enantioselectivity (Table 2, entries 15–17).

Table 2 Scope of the asymmetric formal [2+2] cycloaddition of 2-vinyl pyrroles with α,β-unsaturated aldehydes[a]



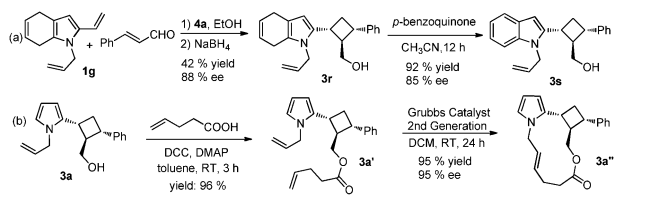
1a, R=H,R^1=allyl; **1b**, R=4-Br,R^1=ally
1c, R=5-Me,R^1=ally; **1d**, R=H, R^1=allenyl
1e, R=H, R^1=CH_2CO_2Et; **1f**, R=H, R^1=Bn

Entry	1	R^2	3	t (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	Ph	**3a**	60	76	93
2	**1a**	2-MeC_6H_4	**3b**	72	53	91
3	**1a**	2-ClC_6H_4	**3c**	60	78	95
4	**1a**	2-BrC_6H_4	**3d**	60	63	92
5	**1a**	3-ClC_6H_4	**3e**	60	68	91
6	**1a**	4-MeC_6H_4	**3f**	60	62	91
7	**1a**	4-ClC_6H_4	**3g**	60	70	89
8	**1a**	4-BrC_6H_4	**3h**	60	65	94
9	**1a**	4-FC_6H_4	**3i**	60	72	96
10	**1a**	4-CNC_6H_4	**3j**	60	79	95
11	**1a**	4-$CF_3C_6H_4$	**3k**	60	71	92
12	**1b**	4-CNC_6H_4	**3l**	72	70	98
13	**1b**	4-$CF_3C_6H_4$	**3m**	72	65	97
14	**1c**	Ph	**3n**	60	53	65
15	**1d**	Ph	**3o**	60	62	92
16	**1e**	Ph	**3p**	60	68	90
17	**1f**	Ph	**3q**	60	72	90
18[d]	**1a**	Ph	**3a**	72	70	90
19[e]	**1f**	Ph	**3q**	72	65	85

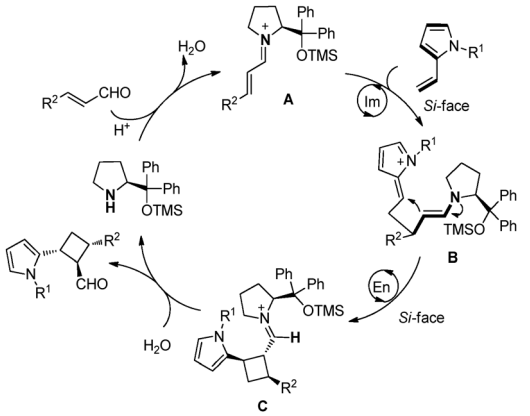
[a] Unless otherwise noted, the reaction was carried out with **1** (0.15 mmol), **2** (0.10 mol) and **4a** (0.02 mmol) in EtOH (0.5 mL) at room temperature. [b] The isolated yield. [c] Determined using HPLC analysis. [d] The reaction was carried out with **1** (9.0 mmol), **2** (6.0 mmol) and **4a** (1.2 mmol). [e] The reaction was carried out with **1** (6.0 mmol), **2** (4.0 mmol) and **4a** (0.8 mmol).

Notably, gram-scale synthesis of the product also could be achieved (Table 2, entries 18 and 19).

To further demonstrate the generality of this formal [2+2] cycloaddition reaction, 4,7-dihydroindole-derived substrate **1g** was explored under the established conditions.[13] Gratifyingly, the desired cycloadduct **3s** was readily achieved with high enantioselectivity. The dihydroindole tether could be oxidated under mild conditions to deliver the trisubstituted cyclobutane with an indole pendant in high yield with no loss of enantioselectivity (Scheme 1a). Subsequently, a representative example of the generation of a biologically interesting fused 12-membered macrolide was performed to demonstrate the synthetic potential of this reaction. As illustrated in Scheme 1b, the target molecule could be obtained efficiently in a simple esterification step and ring closing metathesis sequence in satisfactory yield and enantioselectivity.[14]



Scheme 1 (a) Synthesis of indole-functionalized cyclobutane; (b) transformation of cycloadduct **3a** to the fused 12-membered macrolide.



Scheme 2 The proposed reaction cycle.

Mechanistically, this chemistry represented a novel approach for the asymmetric synthesis of cyclobutanes directly from simple enals and 2-vinylpyrroles. Based on previous studies and our experimental observations, a proposed catalytic cycle is illustrated in Scheme 2. First, chiral iminium ion **A** was formed from the catalyst and enal, which was susceptible to attack by the electron-rich 2-vinylpyrroles from the unshielding *Si*-face to generate the chiral triiminium ion **B**. The intermediate **B** was immediately trapped by the tethered enamine from the *Si*-face of the reactive double bond to give rise to chiral iminium ion **C**, which underwent hydrolysis thus liberating the catalyst and product **3**. The absolute configuration of the product was determined as (1*R*,2*R*,4*S*) using X-ray crystallographic analysis.[15]

In summary, we have developed an efficient approach for the construction of functionalized chiral cyclobutanes *via* organocatalyzed formal [2+2] cycloaddition of 2-vinyl pyrroles with α,β-unsaturated aldehydes in moderate to high yields and with excellent enantioselectivities. For the first time, based on tandem iminium–enamine activation of α,β-unsaturated aldehydes, vinylogous Friedel–Crafts reaction was efficiently incorporated to produce the desired products. In principle, this chemistry holds great potential in novel reaction design and synthesis of intriguing chiral molecules with high molecular complexity.

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