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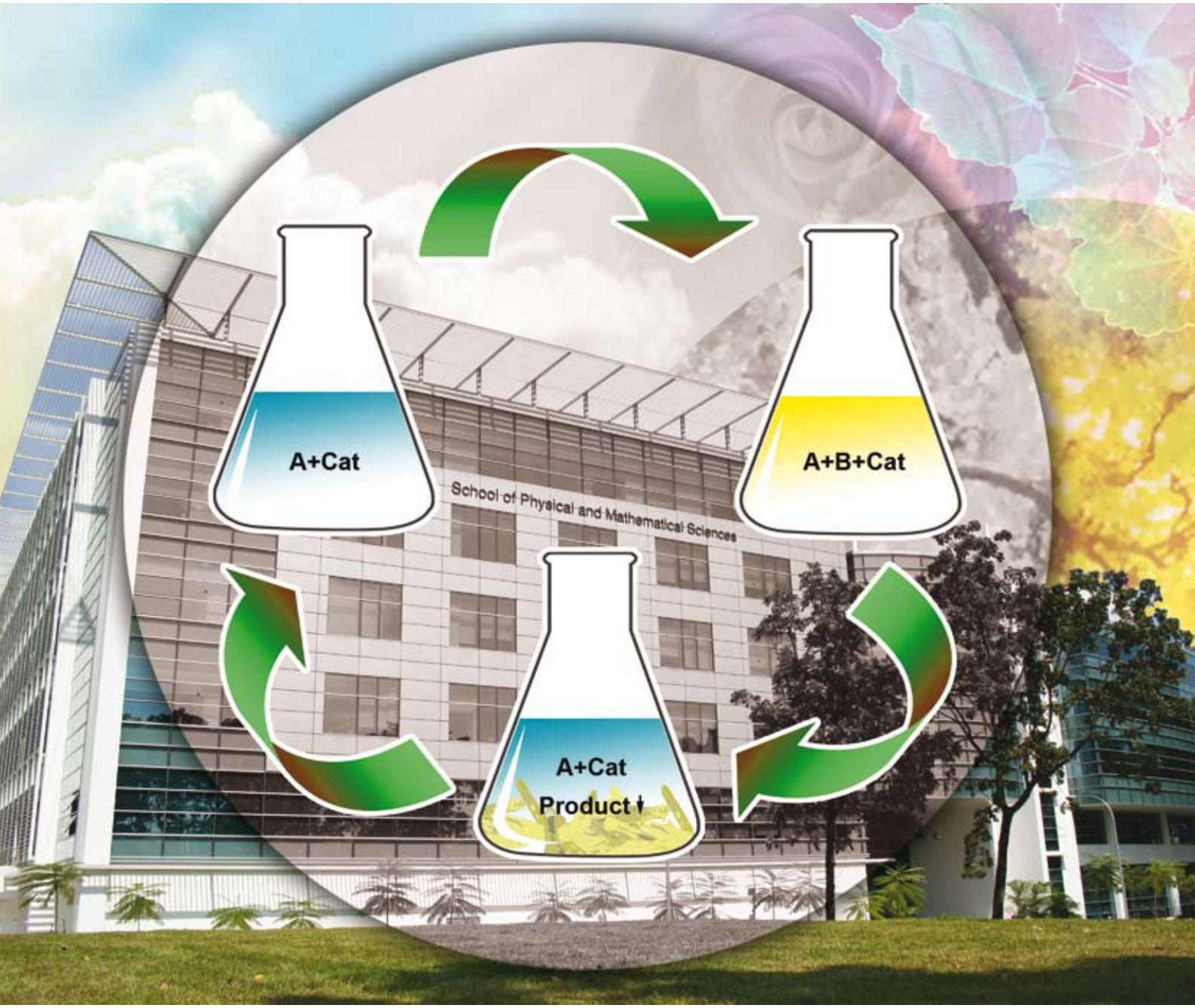

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Recyclable organocatalysis

FEATURE ARTICLE
Takashi Kato *et al.*
Self-assembly of functional columnar liquid crystals

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Recyclable organocatalysis: highly enantioselective Michael addition of 1,3-diaryl-1,3-propanedione to nitroolefins†

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The first Michael addition of 1,3-diaryl-1,3-propanedione to nitroolefins was demonstrated using a simple organocatalyst, which afforded excellent yields (81–97%) and enantioselectivities (90 to >99% ee); the catalyst and excess reactant can be reused seven times through a simple filtration operation.

Recent years have witnessed a dramatic upsurge in awareness among chemists of the potential utility of asymmetric organocatalysis as a tool for the synthesis of enantiopure molecules under mild and environmentally benign conditions.[1] The Michael addition of 1,3-dicarbonyl nucleophiles to nitroolefins[2] provides a particularly attractive target for organocatalyst design, largely due to the ready availability and high reactivity of nitroalkenes and the ability of the nitro functionality to accept hydrogen bonds from suitably designed catalyst systems, especially for the synthesis of important nitrogen containing bioactive agrochemical and pharmaceutical compounds.[3] Thus, reactions of this nature have been reported to proceed in high yield and with good enantioselectivity by the use of various asymmetric catalysts.[4] In contrast, organocatalytic conjugated additions using aromatic ketones as the Michael donor are rarely studied. 1,3-Diphenyl-1,3-propanedione (**1a**) is normally not considered as a good Michael donor due to the steric hindrance of the two aryl groups and usually requires harsh reaction conditions and long reaction times.

Bifunctional catalysts containing a thiourea group and a tertiary amine in the molecule usually lead to high yields and enantioselectivities.[5] Takemoto *et al.* assumed that a thiourea moiety and a tertiary amino group in the catalyst activated a nitro group and a 1,3-dicarbonyl compound respectively to afford the Michael adduct with high enantio- and diastereoselectivity.[6] Recently, 9-*epi*-amino *Cinchona* alkaloid derivatives and diaminocyclohexane derivatives have proved to be efficient organocatalysts to catalyze Michael reactions,[7] aldol reactions[8] and aminations.[9] Based on our recent research[10] and comprehension of this type of reaction, we reasoned that more readily available primary amines of *Cinchona* alkaloid derivatives can activate **1a** through H-bond activation and thus promote the Michael addition reaction to nitroolefins.

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The development of a highly enantioselective recyclable strategy[11] for organocatalysis remains a challenging task. To the best of our knowledge, only a few recyclable processes have been designed by attaching the catalyst to polymers,[12] using recyclable fluorous catalysts[13] and ionic liquids.[14] However, only moderate results have been achieved so far. Herein, we present the first asymmetric Michael addition reaction of 1,3-diaryl-1,3-propanedione to nitroolefins using a more readily accessible organocatalyst involving a recyclable homogenous organocatalysis strategy.

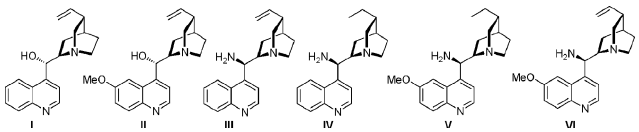


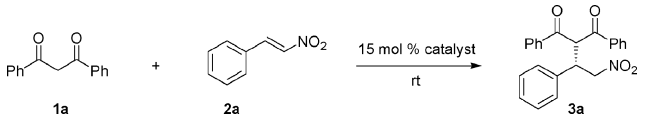
Fig. 1 Structures of the *Cinchona* alkaloid catalysts.

In the initial studies, six *Cinchona* alkaloid catalysts (Fig. 1) were screened for their catalytic ability to promote the Michael addition reaction of **1a** and *trans*-β-nitrostyrene (**2a**) (Table 1). A survey of solvents revealed that all the reactions proceeded smoothly and completed within 17 h at room temperature. Reactions conducted in THF, toluene and diethyl ether all offered good yields and enantioselectivities (up to 98% ee). Remarkably, the Michael adduct precipitated in solid form in diethyl ether gave the highest ee value. This suggested a route to develop a recyclable and practical methodology to reuse the catalyst and excess reactant.

As shown in Table 1, reaction promoted by catalyst **VI** gave the highest enantioselectivity and catalyst **V** (with the double bond reduced) gave a slightly lower ee value. Lowering the reaction temperature to 4 °C or reducing the catalyst loading to 10 mol% prolonged the reaction time and decreased the yield, though the ee value remained the same. Examination of the structures of catalysts **I–IV** revealed that both the primary amine and the methoxy groups played significant roles in controlling enantioselectivity. The reactions promoted by quinine and cinchonidine which do not contain the primary amine group resulted in very low ee values. Almost racemic adducts were observed for the processes catalyzed by cinchonidine derivatives **III** and **IV**, both of which do not contain a methoxy group.

Having established the optimum reaction conditions for the enantioselective Michael addition of **1a** to nitroolefins, we next screened a series of analogues bearing various substituents on the aromatic ring (Table 2). All the reactions proceeded smoothly at room temperature (23 °C) in the presence of 15 mol% of catalyst **VI** and completed within 8–30 h regardless of the electronic properties. The desired adducts were obtained

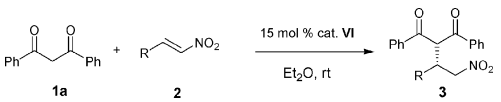
Table 1 Organocatalytic asymmetric Michael addition of **1a** and *trans*-β-nitrostyrene[a]



Entry	Catalyst	Solvent	*t*/h	Yield (%)[b]	Ee (%)[c]
1	**I**	Et_2O	8	95	−21
2	**II**	Et_2O	8	95	−2
3	**III**	Et_2O	8	97	3
4	**IV**	Et_2O	8	98	7
5	**V**	Et_2O	8	94	93
6	**VI**	Et_2O	8	96	98
7	**VI**	MeOH	8	93	65
8	**VI**	THF	15	82	98
9	**VI**	Toluene	8	97	95
10[d]	**VI**	Et_2O	17	94	98
11[e]	**VI**	Et_2O	12	85	98

[a] Unless otherwise specified, the reaction was carried out with dione **1a** (3 eq.) and nitrostyrene **2a** (0.1 mmol, 1 eq.) dissolved in solvent (0.3 mL) in the presence of 15 mol% of catalyst at room temperature. [b] Isolated yields. [c] Enantiomeric excess (ee) determined by chiral HPLC analysis (Chiralpak AS-H). [d] Reaction at 4 °C. [e] 10 mol% catalyst used.

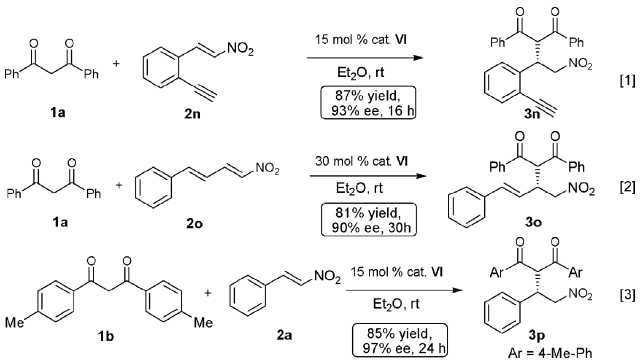
Table 2 Michael addition of **1a** and *trans*-nitroolefins catalyzed by catalyst **VI**[a]



Entry	R	Product	*t*/h	Yield (%)[b]	Ee (%)[c]
1	Ph	**3a**	8	96	98
2	4-OMe-Ph	**3b**	12	92	97
3	3-OMe-Ph	**3c**	16	91	93
4	2-OMe-Ph	**3d**	16	94	99
5	4-Me-Ph	**3e**	12	93	98
6	4-Br-Ph	**3f**	8	96	>99
7	4-Cl-Ph	**3g**	8	97	>99
8	2-Thienyl	**3h**	12	92	97
9	2-Furyl	**3i**	16	91	98
10	3-Furyl	**3j**	12	91	97
11	1-Naphthyl	**3k**	16	88	96
12	2-NO_2-Ph	**3l**	12	92	94
13	4-NO_2-Ph	**3m**	24	86	94

[a] Unless otherwise specified, the reaction was carried out with dione **1a** (3 eq.) and nitrostyrene **2** (0.1 mmol, 1 eq.) dissolved in solvent (0.3 mL) in the presence of 15 mol% of catalyst at room temperature. [b] Isolated yields. [c] Enantiomeric excess (ee) determined by chiral HPLC analysis.

exclusively in yields of 86–97% and excellent enantioselectivity (up to >99%). The nitroolefins bearing either neutral (Entries 1, 11), electron-donating (Entries 2–5), electron-withdrawing (Entries 6–7, 12–13) or heterocyclics (Entries 8–10) and containing a variety of substitution (*para*, *meta* and *ortho*) patterns all participated in this reaction efficiently. It is noteworthy that different functional groups on the benzene ring did not affect the results (eqn (1), Scheme 1), and substrate **2o** displayed the great regioselectivity and enantioselectivity of this method (eqn (2), Scheme 1). Further investigation of the diversity of the Michael donor revealed that different substituents in the 1,3-dione have limited influence on the reactivities and enantioselectivities (eqn (3), Scheme 1).



Scheme 1 Diversities of Michael donors and acceptors.

According to the dual activation model,[6] the two substrates involved in the reaction are activated simultaneously by the catalyst as shown in Fig. 2 (left). In this model, we predicted the configuration of **3g** to be *S*. The absolute configuration of **3g**, which was determined by X-ray analysis, (Fig. 2, right, the X-ray crystallographic data deposition number: CCDC 658642†) is in accordance with our prediction and the relative structure anticipated from the catalytic mechanism.

To examine the validity of recyclable homogenous organocatalysis, the reactions of **1a** and nitroolefins (**2a** and **2g**) in diethyl ether were further studied as typical examples using 15 mol% catalyst **VI** (Fig. S4, in ESI†). Interestingly, the Michael adducts' very poor solubility in diethyl ether could be used to separate organocatalyst **VI** from the product **3a** or **3g** by simple filtration since it was precipitated from the reaction solution. The recyclability of the catalyst was tested seven times and amazingly, the catalyst kept its high efficiency, giving almost quantitative yields (average 96%) and excellent enantioselectivities in each cycle (Table 3) (also, see ESI†). Based on this operationally simple ***product*** (***precipitate***)–***catalyst*** (***soluble***) ***separation***, the pure product is isolated by filtration from the reaction mixture when the reaction is complete and the catalyst, which is kept in the filtrate, could be reused directly for the next cycle. Hence, the strategy for recyclable homogeneous organocatalysis was developed (Fig. S4†).

In summary, we have demonstrated the first example of a highly enantioselective Michael addition reaction with a simple organocatalyst **VI**. 9-Amino-9-deoxyepiquinine (**VI**) has been successfully employed as a catalyst in the Michael additions of 1,3-diaryl-1,3-propanedione to various nitroolefins, where the diketone is usually not a good donor. The

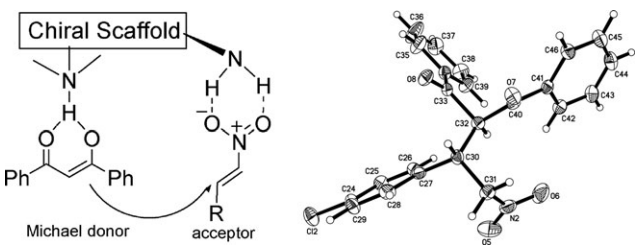
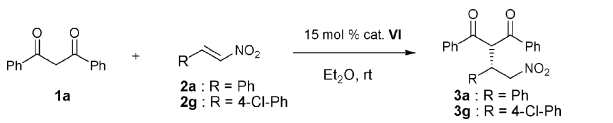


Fig. 2 Left: proposed action of catalyst; right: X-ray structure of **3g**.

Table 3 Recycling in the organocatalytic Michael addition of 1,3-diphenyl-1,3-propanedione and *trans*-β-nitrostyrene with catalyst **VI**[a]



	R = Ph (**3a**)			R = 4-Cl-Ph (**3g**)		
Cycle	*t*/h	Yield (%)[b]	Ee (%)[c]	*t*/h	Yield (%)[b]	ee (%)[c]
1	8	74	98	8	76	>99
2	9	83	97	10	82	99
3	10	110	97	11	108	98
4	12	95	96	13	96	97
5	15	109	96	16	114	96
6	19	94	95	19	97	96
7	30	101	94	23	97	95

[a] The reaction was carried out using **2a** or **2g** (0.1 mmol, 1 eq.) and dione **1a** (0.3 mmol, 3 eq.) with 15 mol % of **VI** in cycle 1 and in cycles 2–7 only **2a** or **2g** (0.1 mmol) and **1** (0.1 mmol) were added. [b] Average yield 96%. [c] Determined by chiral HPLC analysis.

reactions proceeded smoothly at room temperature, giving high to excellent yields (81–97%) and excellent enantioselectivities (90 to >99% ee). Exploiting the use of the insolubility of the adduct, ***product* (*precipitate*)–*catalyst* (*soluble*) *separation*** significantly simplified the separation and purification process, and allowed the reaction to be recyclable. Such reactions may be applicable to large scale industrial production and thus greatly reduce the cost of catalyst preparation.

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