Stereoselective desymmetrisation of prochiral α,α-dicyanoalkenes *via* domino Michael–Michael addition reactions†

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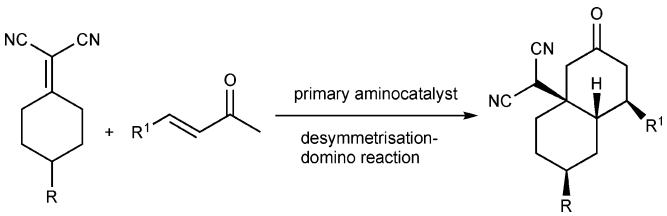
The desymmetrisation of prochiral α,α-dicyanoalkenes *via* tandem Michael–Michael addition reactions with α,β-unsaturated ketones catalysed by 9-amino-9-deoxyepicinchona alkaloids was investigated, from which bicyclic products bearing four stereogenic centers were afforded in a single operation with high stereoselectivities (>99% de, up to >99.5% ee).

The desymmetrisation of *meso*-configured or prochiral substrates is a versatile protocol to yield enantiomerically pure products in organic synthesis. A number of enzyme, metal or organic molecule-based catalysis has been successfully applied to various desymmetrisation reactions.[1] In comparison with the termini differentiation of C_2-symmetric compounds by mono-functionalisation,[2] it would be more desirable if the new carbon–carbon bond forming reaction was accompanied by a desymmetrisation process, because the chiral products bearing two or more stereogenic centers could be constructed simultaneously.[3]

The domino reaction is a powerful strategy for generating complex chiral molecules from simple substrates in an atom-economical way.[4] It permits the stereoselective formation of several bonds with a single catalyst in a single operation, without the need for isolation of the intermediates. Abundant organocatalytic domino reactions have been well presented over the past years.[5] Recently, we have reported a novel vinylogous Michael addition reaction of α,α-dicyanoalkenes[6] and α,β-unsaturated ketones by employing primary aminocatalysts derived from cinchona alkaloids. A domino Michael–Michael addition reaction was realised in the reaction of some α,α-dicyanoalkenes and α,β-unsaturated ketones through tandem iminium-enamine catalysis.[7,8] We wondered whether the desymmetrisation of prochiral α,α-dicyanoalkenes from 4-substituted cyclohexanones and malononitrile could be well furnished in such a domino process, from which chiral bicyclic compounds bearing up to four stereocenters could be efficiently constructed (eqn (1)).



(1)

Inspired by these considerations, we investigated the reaction of prochiral α,α-dicyanoalkene **2a** and benzylideneacetone **3a** in THF by employing a previously reported 9-amino-9-deoxyepiquinine **1a**–TFA–DIPEA catalytic system (Fig. 1).[7] As illustrated in Table 1, the expected cascade Michael–Michael adduct **4a** was cleanly isolated in excellent stereoselectivity (>99% de, 99% ee) at 0 °C after 110 h, but the reaction rate was too sluggish (Table 1, entry 1). To our gratification, a much better isolated yield could be obtained when the reaction was conducted at 25 °C without affecting the high stereoselectivity, and a few unidentified byproducts were detected only in trace amounts (entry 2). Subsequently, other acid additives were explored, and inferior results were generally attained (entries 3–5). Nevertheless, almost no reaction occurred when strong triflic acid was used (entry 6). Less satisfying data were also observed in other solvents (entries 7 and 8). On the other hand, primary amines **1b** and **1c**, derived from cinchonine and quinidine, respectively, were tested. The desired adduct **4a** possessing the opposite configuration to that of **1a** was obtained in high stereoselectivity (entries 9 and 10). Thus both enantiomers could be readily available catalysed by different primary amines derived from natural cinchona alkaloids.

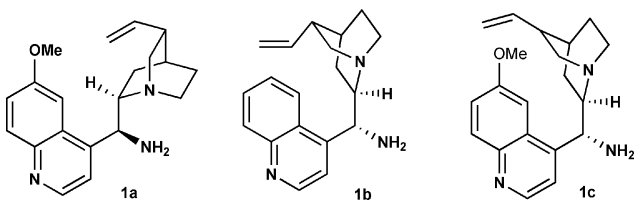


Fig. 1 The structures of chiral primary aminocatalysts.

With the optimised reaction conditions in hand, the scope and limitation of the desymmetrisation–domino reaction were investigated. As revealed in Table 2, the tandem process generally served as a versatile approach to the preparation of highly functionalised chiral bicyclic compounds. The electronic and steric nature of the substituents of a,β-unsaturated ketones **3** had limited influences on the stereo outcome. Excellent stereoselectivities were obtained in the reactions of prochiral α,α-dicyanoalkene **2a** and α,β-unsaturated ketones with a diverse array of aryl or heteroaryl substitutions (Table 2, entries 1–8). β-Alkyl substituted

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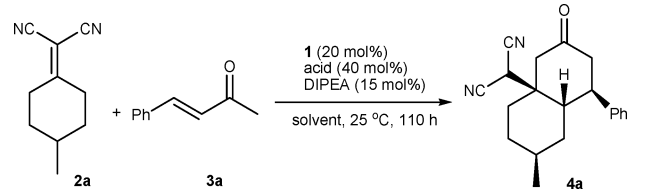
† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, NMR and HPLC spectra of the products, CIF file of enantiopure **4c**. CCDC reference number 690120. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b809308c

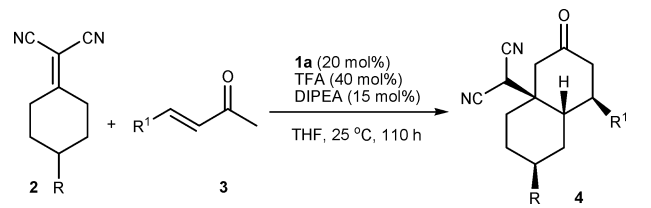
Table 1 Screening studies on the asymmetric domino reaction of prochiral α,α-dicyanoalkene **2a** and benzylideneacetone **3a**[a]



Entry	Cat. **1**	Solvent	Acid	Yield[b] (%)	ee[c] (%)
1[d]	**1a**	THF	TFA	16	99
2	**1a**	THF	TFA	81	99
3	**1a**	THF	*p*-TSA	64	93
4	**1a**	THF	PhCOOH	70	95
5	**1a**	THF	AcOH	60	95
6	**1a**	THF	CF_3SO_3H	Trace	/
7	**1a**	DCM	TFA	76	87
8	**1a**	Toluene	TFA	78	66
9	**1b**	THF	TFA	75	−87
10	**1c**	THF	TFA	81	−90

[a] Unless noted otherwise, reactions were conducted with **2a** (0.1 mmol), **3a** (0.12 mmol), catalyst **1** (0.02 mmol) and acid (0.04 mmol) in solvent (0.3 mL) at 25 °C for 110 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis, >99% de. [d] At 0 °C.

Table 2 Asymmetric desymmetrisation–domino reaction of prochiral α,α-dicyanoalkenes **2** and α,β-unsaturated ketones **3**[a]



Entry	R	R^1	Product	Yield[b] (%)	ee[c] (%)
1	Me	Ph	**4a**	81	99
2	Me	*p*-CH_3O-Ph	**4b**	71	>99.5
3[d]	Me	*p*-Cl-Ph	**4c**	64	>99.5
4	Me	*m*-Cl-Ph	**4d**	72	95
5	Me	*o*-Cl-Ph	**4e**	68	92
6	Me	1-Np	**4f**	45	98
7	Me	2-Furyl	**4g**	64	97
8	Me	2-Thienyl	**4h**	60	97
9[e]	Me	*n*-Pr	**4i**	54	98
10	Ph	Ph	**4j**	61	95
11	Ph	*p*-CH_3O-Ph	**4k**	66	97
12	Ph	*p*-Cl-Ph	**4l**	67	97
13	Ph	2-Furyl	**4m**	62	90
14	*n*-Pr	Ph	**4n**	61	94
15	*t*-Bu	Ph	**4o**	71	99.5
16	BzO	Ph	**4p**	60	98
17[f]	Me	*p*-CH_3O-Ph	**4b**	69	−90
18[f]	Me	*p*-Cl-Ph	**4c**	61	−87

[a] Unless noted otherwise, reactions were performed with **2** (0.1 mmol), **3** (0.12 mmol), catalyst **1a** (0.02 mmol) and TFA (0.04 mmol) in THF (0.3 mL) at 25 °C for 110 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis, >99% de was observed. [d] The absolute configuration of enantiopure **4c** was determined by X-ray analysis (see Fig. 2).‡ The other products were assigned by analogy. [e] For 160 h. [f] With catalyst **1c**.

α,β-unsaturated ketone could also be successfully applied, while a longer reaction time was required (entry 9). On the other hand, the structural effects of prochiral α,α-dicyanoalkenes **2** in the

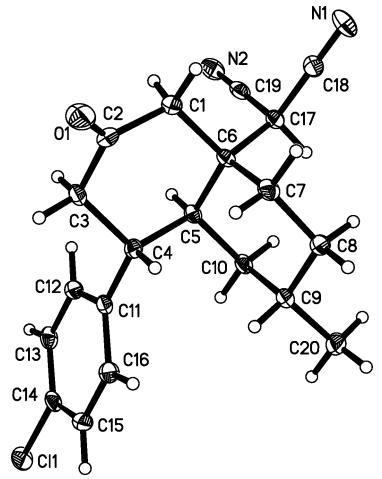
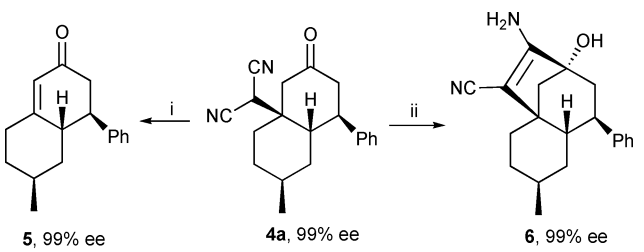


Fig. 2 X-Ray structure of enantiopure **4c**. Thermal ellipsoids are shown at 30% probability.

domino reaction were probed, and good reactivity and remarkable stereoselectivities were afforded (entries 10–15). It should be noted that the functionalised α,α-dicyanoalkene also gave rise to good results under the same conditions (entry 16). Moreover, further application of catalyst **1c** derived from quinidine was conducted, and products **4b** and **4c** with the opposite configuration to that of **1a** were delivered in high stereoselectivities (entries 17 and 18). On the other hand, a very sluggish reaction was observed when enone, having an ethyl group as the α-substituent, was applied.

The domino reaction products could be converted to some interesting compounds without any racemisation. As outlined in Scheme 1, the elimination of malononitrile readily proceeded in the presence of Cs_2CO_3 to give cyclic enone **5**, which might serve as a useful building block for further transformations. With the aid of *in situ* formed low-valent titanium reagent ($TiCl_4$–Zn), an intramolecular reductive coupling reaction could be conducted to provide multifunctional tricyclic compound **6**.[9]



Scheme 1 Transformations of the domino reaction product **4a**.

In conclusion, we have developed the highly stereoselective desymmetrisation–domino Michael–Michael addition reactions of prochiral α,α-dicyanoalkenes condensed from 4-substituted cyclohexanones and malononitrile with α,β-unsaturated ketones, employing chiral primary amines derived from natural cinchona alkaloids. These reactions exhibited high synthetic efficacy, and two new C–C bonds, four stereogenic centers, including one quaternary carbon center, were assembled in a single operation with a high level of stereoselectivity. Currently, the study of the potential applications of these multifunctional adducts in the

synthesis of some biologically important molecules is under way in this laboratory.

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Notes and references

‡ Crystal data for enantiopure **4c** $C_{20}H_{21}ClN_2O$ (340.84), monoclinic, space group $P2_1$, $a = 6.0880(12)$, $b = 14.543(3)$, $c = 9.779(2)$ Å, $U = 865.8(3)$ Å^3, $Z = 2$, specimen $0.24 \times 0.20 \times 0.08$ mm^3, $T = 113(2)$ K, Mac Science M18XHF22-SRA diffractometer, absorption coefficient 0.229 mm^{-1}, reflections collected/unique 5433/3325 [R(int) = 0.0249], refinement by full-matrix least-squares on F^2, data/restraints/parameters 3325/1/218, goodness-of-fit on $F^2 = 1.061$, final R indices [$I > 2\sigma(I)$] $R1 = 0.0294$, $wR2 = 0.0737$, R indices (all data) $R1 = 0.0332$, $wR2 = 0.0753$, absolute structure parameter 0.01(4), largest diff. peak and hole 0.237 and -0.274 e Å^{-3}.

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