Merging chiral organocatalysts: enantio- and diastereoselective direct vinylogous Mannich reaction of alkylimines†

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An enantio- and diastereoselective direct vinylogous Mannich reaction of α,α-dicyanoolefins and *N*-sulfonyl alkylimines has been developed by the catalysis of a new family of bifunctional organocatalysts merging chiral BINOL and 9-amino-9-deoxyepicinchona alkaloid skeletons, from which chiral β-, δ- or γ-amino compounds could be efficiently derived.

The development of reliable protocols to access both enantiomers of a target chiral compound is still a challenging endeavour in asymmetric synthesis, especially for the chiral ligands or organocatalysts are derived from the naturally available sources in only one enantiomeric form.[1] Although many successful examples of the reversal of enantioselectivity have been reported through careful manipulation of the reaction components, such as Lewis acid, ligand, solvent, or temperature, *etc*.,[2] they are not always effective and are usually unpredictable and time-consuming tasks. Moreover, the problem would be further aggravated when the diastereoselectivity is involved and the synthesis of all the stereo isomers must be considered.[3] The design of catalysts which can be available with resourceful chiral properties may be applicable to stereo diversity synthesis. Herein we would like to present an enantio- and diastereoselective asymmetric reaction by means of merging chiral organocatalysts.

Recently we have presented the first direct asymmetric vinylogous Mannich (AVM) reaction[4] of α,α-dicyanoolefins and *N*-Boc arylimines catalysed by bifunctional thiourea-tertiary amines.[5] However, a mixture of α- and γ-adducts was afforded when *N*-Boc alkylimines[6] were used and this important problem remains unsolved to date.[7,8] Nevertheless, the γ-selective product could be exclusively obtained by utilising *N*-Tos alkylimines. Although disappointing results were obtained in the extensive screenings with a variety of organocatalysts,[9] it was pleasing that a chiral compound *S*BADQ[10] **1a** (Fig. 1, 10 mol%), merging (*S*)-BINOL (*S*B) and 9-amino-9-deoxyepiquinine (ADQ) scaffolds,[11] exhibited promising stereocontrol in the reaction of α,α-dicyanoolefin **2a** and *N*-Tos alkylimine **3a** in toluene. The *syn*-adduct **4a** was obtained as the major isomer in a high ee value, while the

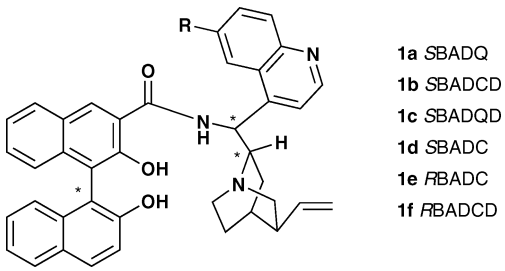
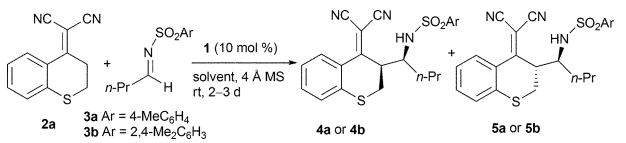


Fig. 1 The structures of bifunctional organocatalysts merging chiral BINOL and 9-amino-9-deoxyepicinchona alkaloids.

Table 1 Screening studies of organocatalytic AVM reaction[a]



Entry	Cat.	3	Yield[b] (%)	dr[c] (4 : 5)	ee[c] (4/5, %)
1	**1a**	**3a**	70	69 : 31	90/—
2	**1b**	**3a**	50	60 : 40	90/—
3	**1c**	**3a**	75	16 : 84	—/−45
4	**1d**	**3a**	50	20 : 80	—/−61
5	**1e**	**3a**	64	66 : 34	−90/—
6	**1f**	**3a**	42	17 : 83	—/53
7	**1a**	**3a**	88	79 : 21	93/—
8[d]	**1a**	**3a**	32	60 : 40	89/—
9	**1a**	**3b**	86	86 : 14	96/—
10[e,f]	**1a**	**3b**	98	81 : 19	97/—
11[e,f,g]	**1a**	**3b**	99	82 : 18	97/—

[a] Reactions were performed with 0.1 mmol of **2a**, 0.12 mmol of imine **3**, 0.01 mmol of catalyst **1**, 15 mg 4 Å MS in 0.4 mL of toluene (entries 1–6) or mesitylene (entries 7–11) for 2–3 d. [b] Combined isolated yield of **4** and **5**. [c] By chiral HPLC analysis. For major isomer (ee). [d] Without 4 Å MS. [e] Adding 30 mg 4 Å MS. [f] For 1 d. [g] With 15 mol % of **1a**.

diastereoselectivity was modest (Table 1, entry 1). The similar results were attained in the presence of *S*BADCD **1b** from *S*B and 9-amino-9-deoxyepicinchonidine (ADCD) (entry 2). Interestingly, the *anti*-product **5a** was dominantly attained in moderate enantioselectivity catalysed by *S*BADQD **1c** (ADQD, 9-amino-9-deoxyepiquinidine) or *S*BADC **1d** (ADC, 9-amino-9-deoxyepicinchonine) (entries 3 and 4). Subsequently, the catalytic efficacy of bifunctional *R*BADC **1e** and *R*BADCD **1f** derived from (*R*)-BINOL (*R*B) was tested. As expected, the *syn*- or *anti*-Mannich adducts **4a** or **5a** with the opposite configuration were delivered, respectively (entries 5 and 6). Then we screened more conditions with

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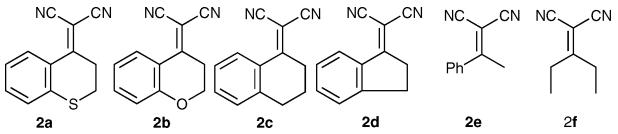
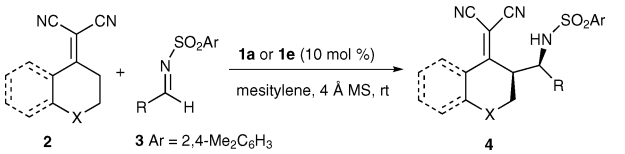


Fig. 2 The structures of α,α-dicyanoolefins.

1a to improve the stereoselectivity. Solvent had important effects, and much better results were obtained in mesitylene (entry 7).[9] It should be noted that the reaction was quite sluggish in the absence of 4 Å molecular sieves, indicating that the hydrogen bonding activation of hydroxyl groups of the catalysts was crucial for the reaction (entry 8). Moreover, better results were obtained for adduct **4b** by using imine **3b** with a 2,4-dimethylbenzenesulfonyl group (entry 9).[9] In addition, the reaction could be greatly accelerated when more 4 Å MS was added (entry 10). Nevertheless, the similar data were afforded when more catalyst **1a** was added (entry 11).

With the optimal conditions in hand, we then explored a variety of α,α-dicyanoolefins (Fig. 2) and *N*-sulfonyl alkylimines to establish the reaction generality. The reaction was firstly conducted with catalyst **1a** to deliver the *syn*-Mannich adducts **4**. As summarised in Table 2, excellent enantioselectivities were obtained for a few α,α-dicyanoolefins derived from cyclic aryl ketones (entries 1–4), and the diastereoselectivities were also acceptable except that of **2b** (entry 2).[12] A modest ee value was attained for a simple α,α-dicyanoolefin **2e** (entry 5). It was noteworthy that α,α-dicyanoolefin **2f** from aliphatic ketone could be applied, and excellent enantioselectivity was gained (entry 6). Subsequently, an array of aliphatic imines were tested, and remarkable ee values with

Table 2 *syn*-Stereoselective AVM reaction[a]



Entry	2	R	*t*/d	4	Yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**	*n*Pr	1	**4b**	98	81 : 19	97
2	**2b**	*n*Pr	6	**4c**	92	51 : 49	89
3	**2c**	*n*Pr	3	**4d**	89	86 : 14	95
4	**2d**	*n*Pr	4	**4e**	87	87 : 13	90
5	**2e**	*n*Pr	4	**4f**	83	—	63
6	**2f**	*n*Pr	4	**4g**	58[e]	85 : 15	96
7	**2a**	Et	1	**4h**	95	82 : 18	97
8	**2a**	*n*Hex	1	**4i**	92	91 : 9	86
9	**2a**	*i*Bu	1	**4j**	97	84 : 16	97
10	**2a**	$Ph(CH_2)_2$	1.5	**4k**	84	82 : 18	96
11	**2a**	$BnO(CH_2)_2$	1	**4l**	89	90 : 10	97
12	**2a**	$PhS(CH_2)_2$	2	**4m**	86	88 : 12	94[f]
13	**2a**	*n*Pr	2	**4b**	86	75 : 25	−91
14	**2a**	Et	2	**4h**	95	80 : 20	−94
15[g]	**2a**	$PhS(CH_2)_2$	3	**4m**	77	70 : 30	−92
16[g]	**2c**	*n*Pr	3	**4d**	71	86 : 14	−94

[a] At 0.1 mmol scale, in 0.4 mL solvent. Entries 1–12: with **1a**; entries 13–16: with **1e**. [b] Yields of diastereomers. [c] By HPLC or crude ^{1}H NMR analysis. [d] By chiral HPLC analysis, for major isomer. [e] Yield of pure **4g**. [f] The absolute configuration of enantiopure **4m** was determined by X-ray analysis, see Fig. 3.[14] The other products were assigned by analogy. [g] In 0.2 mL solvent.

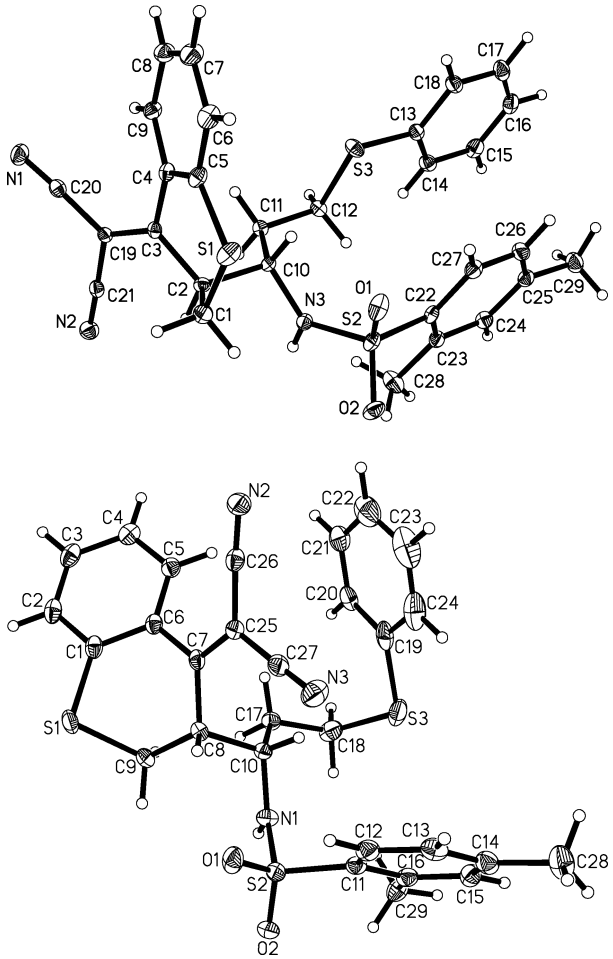


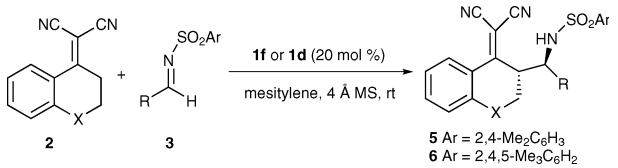
Fig. 3 X-Ray structures of enantiopure **4m** and **5m**. Thermal ellipsoids are shown at 30% probability.

good dr ratios were generally obtained (entries 7–12), even for two imines with side functional groups (entries 11 and 12).[13] On the other hand, we also studied some reactions with catalyst **1e** for the synthesis of *syn*-**4** with the opposite configuration. Excellent ee values were fortunately afforded, and the dr ratios were fair to good (entries 13–16).

We have also optimised the reaction conditions to prepare the chiral *anti*-Mannich adducts catalysed by *R*BADCD **1f** (20 mol%). Better enantiocontrol could be delivered for imines bearing a 2,4,5-trimethylbenzenesulfonyl group (Table 3, entry 1 *vs.* 2). Although only moderate stereoselectivities were obtained, the enantiomerically pure *anti*-adducts **6a**–**6c** could be provided in fair yields after a single recrystallisation (entries 2–4). In addition, the *anti*-adducts **6a**–**6c** with the opposite configuration were also similarly afforded catalysed by *S*BADC **1d** (entries 5–7).

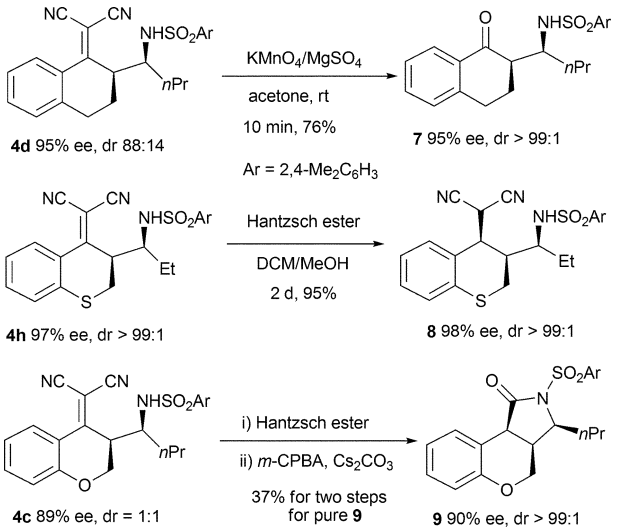
Apart from the conversion of the AVM adducts to β- or δ-amino compounds **7** or **8**, respectively, *via* known procedures,[7] a diastereomerically pure γ-lactam **9** could be smoothly prepared *via* a tandem reduction–oxidative degradation process (Scheme 1).[15] Thus the malononitrile motif could be regarded as a transient group for multiple functionalities and would be quite useful for diversity oriented synthesis (DOS).[16]

Table 3 *anti*-Stereoselective AVM reaction[a]



Entry	2	R	*t*/d	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**	$PhS(CH_2)_2$	2	**5m**	67 (27)	87 : 13	52 (97)[e]
2	**2a**	$PhS(CH_2)_2$	3	**6a**	70 (44)	84 : 16	83 (99)
3	**2a**	Et	3	**6b**	73 (39)	84 : 16	73 (97)
4	**2c**	*n*Pr	5	**6c**	60 (36)	85 : 15	77 (97)
5	**2a**	$PhS(CH_2)_2$	3	**6a**	74 (46)	85 : 15	−81 (−93)
6	**2a**	Et	3	**6b**	82 (45)	85 : 15	−70 (−99)
7	**2c**	*n*Pr	5	**6c**	62 (37)	84 : 16	−74 (−97)

[a] At 0.1 mmol scale, in 0.2 mL solvent. Entries 1–4: with **1f**; entries 5–7: with **1d**. Data in parentheses were related to the pure **5** or **6** after one recrystallisation. [b] Yields of two diastereomers. [c] By crude ^{1}H NMR analysis. [d] By chiral HPLC analysis. [e] The absolute configuration of enantiopure **5m** was determined by X-ray analysis, see Fig. 3.[14] The other products were assigned by analogy.



Scheme 1 Synthetic transformations of AVM adducts.

In conclusion, we have designed a new family of bifunctional organocatalysts merging chiral BINOL and 9-amino-9-deoxyepi-cinchona alkaloid skeletons. They have been successfully applied in an enantio- and diastereoselective direct vinylogous Mannich reaction of α,α-dicyanoolefins and *N*-sulfonyl alkylimines, from which four stereo isomers could be attainable in a highly enantioenriched form catalysed by a proper combination. Moreover, the chiral β-, γ- or δ-amino compounds could be efficiently derived from the AVM adducts. Currently, further applications of these bifunctional organocatalysts in other stereoselective reactions are underway in our laboratory.

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