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PAPER

Very high stereoselectivity in organocatalyzed desymmetrizing aldol reactions of 3-substituted cyclobutanones†

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N-Phenylsulfonyl (*S*)-proline catalyzes the direct aldol reaction of 3-substituted cyclobutanones and aryl aldehydes in good yield and with excellent diastereoselectivity and enantioselectivity. This desymmetrization process provides highly functionalized cyclobutanones with control over three contiguous stereogenic centers.

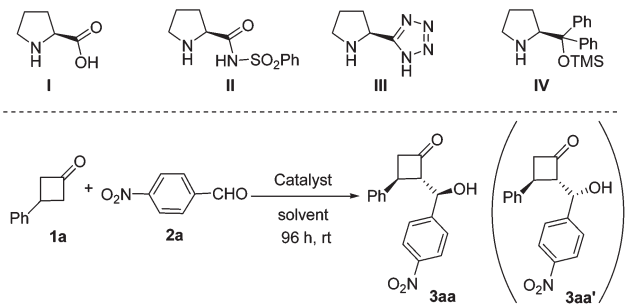
Introduction

The development of easily applicable synthetic strategies for the construction of carbon–carbon bonds with complete stereochemical control remains an important challenge in organic synthesis. Synthetic methods which rely on the use of cyclobutane-based molecular building blocks are intrinsically appealing, since these compounds are readily accessible and can undergo a variety of ring fission or ring enlargement reactions as a result of their inherent ring strain.[1]

Cyclobutanones[1] are particularly useful intermediates in the synthesis of natural products and various complex organic molecules.[2] Despite significant recent advances in asymmetric organocatalysis,[3] only a few applications have been made to cyclobutanones, providing 2-substituted[4] or 2,2-disubstituted[5] derivatives. Organocatalyzed desymmetrization[6,7] of prochiral 3-substituted cyclobutanones has been strictly limited to a Baeyer–Villiger oxidation[8] and a lactam-forming ring expansion reaction.[9] Organocatalyzed asymmetric aldol reactions of 3-substituted cyclobutanones, implying stereochemical control of three contiguous stereocenters, represent an attractive but hitherto unprecedented endeavour.

Results and discussion

The condensation of 3-phenylcyclobutanone **1a** (in excess) and 4-nitrobenzaldehyde **2a** was chosen as a model reaction for catalyst screening and the results are summarized in Table 1. (*S*)-Proline (**I**) was tested first in DMSO. The requisite aldol product was obtained in modest yield (Table 1, entry 1) but with high diastereoselectivity: only two of the four possible diastereomers, designated **3aa** and **3aa′**, were observed, with the former predominating. Furthermore, chiral HPLC analysis showed the major diastereomer **3aa** to be highly enantiomerically enriched. When **I** was employed in dichloromethane (Table 1, entry 2), the reaction yield decreased, but the stereoselectivity was even higher: only one diastereomer **3aa** was formed, with at least 99% enantiomeric purity.



These results prompted the study of the model reaction using other (*S*)-proline-derived catalysts, **II–IV** (Table 1).

Gratifyingly, the use of catalyst **II** (Table 1, entry 3) in dichloromethane was entirely satisfactory: a good chemical yield was combined with an excellent diastereomeric and enantiomeric control in the formation of the major **3aa** diastereomer. The same reaction conducted with a lower molar excess of **1a** (Table 1, entry 4) diminished the yield and enantioselectivity somewhat. Catalyst **III** (Table 1, entry 5) gave a slightly improved chemical yield of the aldol adduct, but with a

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diminished diastereoselectivity. Catalyst **IV**, used in conjunction with a Brønsted acid, also provided an excellent yield of aldol, but the stereoselectivity of the reaction was greatly reduced – indeed, the second diastereomer **3aa′** became the major component (Table 1, entry 6), with a poor enantiomeric excess (ee).

With the encouraging lead result using catalyst **II** in hand, we retained the conditions used in entry 3 of Table 1 for a study of the scope of the reaction. Organocatalyzed aldolisations of a series of 3-substituted cyclobutanones **1** with a selection of aldehydes **2** were examined, and the results are shown in Table 2.

Firstly, the aldehyde scope was considered using **1a** as the representative cyclobutanone. Similarly to the reaction of **2a** in standard conditions (Table 2, entry 1), other aryl aldehydes bearing an electron-withdrawing group in the *para*-position, **2b–2e**, reacted with **1a** to give good yields of the corresponding aldols **3ab–3ae**, with good-to-excellent diastereo- and enantioselectivities (Table 2, entries 2–5). At most, only very small amounts of one other diastereomer (**3ab′–3ae′**) were detected. An aldehyde with an electron-withdrawing group in the *meta*-position also gave excellent selectivity (Table 2, entry 6), but reactions involving aldehydes with substituents in the *ortho*-position failed to proceed (Table 2, entries 7–8), presumably due to steric hindrance. Less reactive aryl aldehydes (Table 2, entries 9–10) and an aliphatic aldehyde (Table 2, entry 11) also failed to provide any aldol adduct.

Next, the substituent tolerance of cyclobutanone **1** was investigated in a series of aldolisation experiments (Table 2, entries 12–16) using **2a** as the aryl aldehyde. The reactions of **1b–1f** proceeded with uniform chemical yields to give the corresponding aldol adducts **3ba–3fa**. Once again, one diastereomer always predominated, with *dr* values going up to 99 : 1, and in each case, this diastereomer was obtained with high *ee* in the range 84% to >99%. The cyclobutanone substrate tolerance included both aromatic and aliphatic chains at the 3-position. Some other combinations of diversely substituted cyclobutanones and aryl aldehydes completed the survey (Table 2, entries 17–19) and confirmed the scope and high stereoselectivity of the reaction.

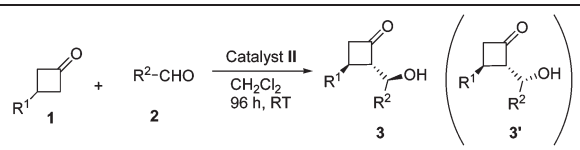
These organocatalyzed aldolisation reactions invariably provided one stereoisomer of the product **3** with excellent selectivity. In order to establish the absolute configuration at the three newly-formed stereocenters, the aldol product **3ba** was transformed by a Baeyer–Villiger oxidation (81% yield) into the crystalline lactone **4** (Scheme 1). Single crystal X-ray diffraction analysis established the absolute configuration of compound **4** as

Table 1 Optimization of reaction conditions and catalyst screening[a]

Entry	Cat.	Solvent	Yield **3aa**[b] (%)	dr[c] **3aa**:**3aa′**	ee **3aa**[d] (%)
1	**I**	DMSO	31	82 : 18	96
2	**I**	CH_2Cl_2	10	99 : 1	99
3	**II**	CH_2Cl_2	71	98 : 2	99
4[e]	**II**	CH_2Cl_2	61	98 : 2	93
5	**III**	CH_2Cl_2	80	78 : 22	99
6[f]	**IV**	CH_2Cl_2	92	37 : 63	26

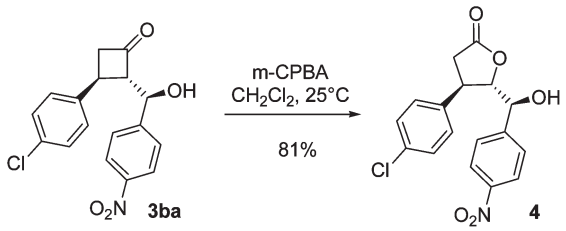
[a] Cyclobutanone **1a** (10 mmol), aldehyde **2a** (0.5 mmol), catalysts **I–IV** (20 mol%), solvent (2 mL), 96 h, room temperature. [b] Total yield of all isomers of **3aa**. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] The excess of **1a** was halved (5 mmol instead of 10 mmol). [f] Benzoic acid (20 mol%) was included in the reaction mixture.

Table 2 Asymmetric aldol reactions between 3-substituted cyclobutanones **1** and aldehydes **2**[a]



Entry	R^1	R^2	Product	Yield **3**[b] (%)	dr[c] **3** : **3′**	ee[d] (%) **3** (major)
1	Ph–	4-NO_2–C_6H_4–	**3aa**	71	98 : 2	99
2	Ph–	4-CN–C_6H_4–	**3ab**	76	97 : 3	98
3	Ph–	4-Cl C_6H_4–	**3ac**	64	98 : 2	84
4	Ph–	4-F C_6H_4–	**3ad**	66	96 : 4	81
5	Ph–	4-CF_3 C_6H_4–	**3ae**	51	98 : 2	91
6	Ph–	3-NO_2–C_6H_4–	**3af**	51	99 : 1	95
7	Ph–	2-NO_2 C_6H_4–	—	0	—	—
8	Ph–	2,4-Cl_2–C_6H_3–	—	0	—	—
9	Ph–	Ph–	—	0	—	—
10	Ph–	4-CH_3–C_6H_4–	—	0	—	—
11	Ph–	i-Pr–	—	0	—	—
12	4-Cl–C_6H_4–	4-NO_2–C_6H_4–	**3ba**	77	89 : 11	97
13	4-Br–C_6H_4–	4-NO_2–C_6H_4–	**3ca**	63	96 : 4	89
14	4-CH_3–C_6H_4–	4-NO_2–C_6H_4–	**3da**	74	93 : 7	83
15	*n*-C_6H_{13}–	4-NO_2–C_6H_4–	**3ea**	70	98 : 2	>99
16	$PhCH_2CH_2$–	4-NO_2–C_6H_4–	**3fa**	60	99 : 1	98
17	4-Cl–C_6H_4–	4-CF_3–C_6H_4–	**3be**	70	90 : 10	92
18	*n*-C_6H_{13}–	4-CN–C_6H_4–	**3eb**	60	98 : 2	83
19	4-Br–C_6H_4–	4-CN–C_6H_4–	**3cb**	64	96 : 4	89

[a] Cyclobutanone **1** (10 mmol), aldehyde **2** (0.5 mmol), catalyst **II** (20 mol%), CH_2Cl_2 (2 mL), 96 h, room temperature. [b] Total yield of all isomers of **3**. [c] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis.



Scheme 1 Synthesis of the lactone **4**.

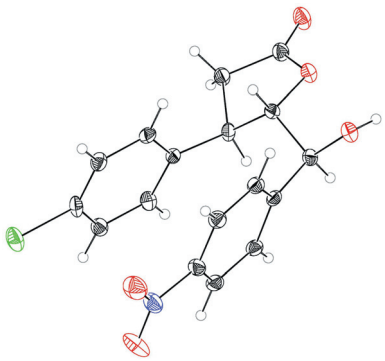


Fig. 1 X-Ray crystal structure of the lactone **4**.

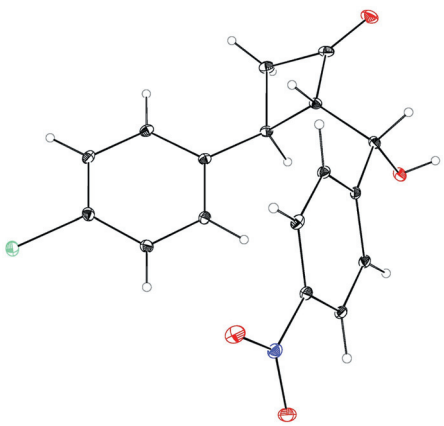


Fig. 2 X-Ray crystal structure of compound **3ba′**.

R,*S*,*S* (Fig. 1).[10] It was thus deduced that compound **3ba** had the same configuration and, by analogy, the *R*,*S*,*S* configuration was attributed to each major stereoisomer of the suite of aldols **3**. Single crystal X-ray diffraction analysis of the minor diastereomer from the same aldol reaction, **3ba′**, was also carried out. The crystal contained racemic material. The relative configuration was established as that of a *trans* 2,3-cyclobutanone ring substitution and a *syn* aldol geometry (Fig. 2).[11]

On the basis of previous models for (*S*)-proline catalyzed aldol reactions, supported by both experiments and DFT calculations,[12] the stereochemical course of the reactions described here can be rationalized in terms of the favoured transition state model shown in Fig. 3. The lowest energy transition state for a proline-type Brønsted acid mediated intermolecular aldol reaction implicates Re attack on an *anti* enamine, with the aryl

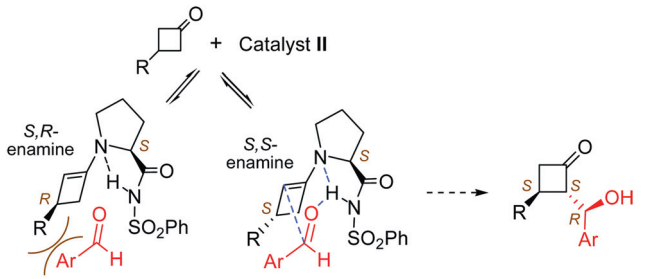


Fig. 3 Proposed transition-state model leading to the predominant aldol stereoisomer.

moiety of the aldehyde oriented away from the steric bulk (in the equatorial position of the Zimmerman–Traxler six-membered ring model).[12] Two diastereomeric enamines are likely to coexist; however, only one—designated the *S*,*S*-enamine, assuming for the sake of argument that the 3-substituent has nomenclature priority—allows hydrogen bond-assisted approach of the aldehyde to the unhindered face of the *anti* enamine. This model leads to the preferred *R*,*S*,*S* configuration in the aldol product.

Conclusions

In conclusion, the **II**-catalyzed aldol reaction allows the desymmetrization of 3-substituted cyclobutanones **1** to give aldol products **3** with unprecedented control of all three contiguous stereocenters. The aldol adducts with *trans* ring substitution and an *anti* aldol geometry are obtained with high enantioselectivity. Given the value of functionalized cyclobutanones as building blocks in organic synthesis, further studies of asymmetric organocatalyzed transformations of these substrates are an appealing area for further developments.

Experimental

General procedure for the enantioselective organocatalyzed aldol reactions

To a solution of aldehyde **2** (0.5 mmol) and 3-substituted cyclobutanone **1** (10 mmol) in anhydrous CH_2Cl_2 (2 mL) was added (2*S*)-*N*-(2-pyrrolidine-2-carbonyl)-benzenesulfonamide **II** (0.05 mmol). The resulting mixture was stirred at room temperature for 96 h. The reaction was quenched with saturated aqueous ammonium chloride (10 mL). The reaction mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography to give the corresponding aldol product **3**.

(See ESI† for details.)

Acknowledgements

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