Addition Reactions

Highly Enantio- and Diastereoselective Organocatalytic Asymmetric Domino Michael–Aldol Reaction of β-Ketoesters and α,β-Unsaturated Ketones**

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The catalytic asymmetric formation of chiral building blocks represents an increasingly important field in organic chemistry owing to the usefulness of these products in further synthetic transformations. The catalytic enantioselective for-

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mation of C–C bonds is a widely developed method for achieving this goal and a number of reactions and methodologies have been developed.[1] Among the various asymmetric C–C bond-forming reactions, the direct catalytic domino[2] and cycloaddition[3] reactions are of particular interest as multiple stereogenic centers can be formed in a single reaction.

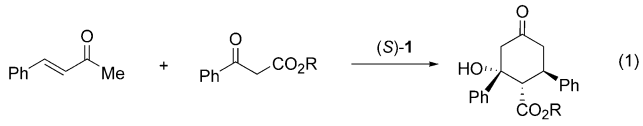
Recently we reported the environmentally benign imidazolidine-catalyzed Michael reaction of malonates,[4] cyclic β-ketoesters,[5] and nitroalkanes.[6] Herein we present the first organocatalytic asymmetric domino Michael–aldol reaction of acyclic β-ketoesters and unsaturated ketones to afford optically active cyclohexanones with up to four stereogenic centers with excellent enantio- and diastereoselectivity. The domino Michael–aldol reaction reported herein is related to the proline-catalyzed Robinson annulation pioneered by Wiechert and co-workers and by Hajos and Parrish 30 years ago,[7] but was originally discovered by Fischer and Dieckmann almost a century ago and more recently reinvestigated by Christoffers.[8] The potential of this novel catalytic enantioselective domino Michael–aldol reaction is demonstrated by the easy formation of optically active cyclohexanone and cyclohexanediol, as well as γ- and ε-lactone building blocks in high yields and enantioselectivities.

The phenylalanine-derived imidazolidine catalyst **1** has proved to be a powerful catalyst for the catalytic asymmetric Michael reaction of unsaturated ketones **2** with various Michael donors. Herein we present its application to the catalytic asymmetric domino Michael–aldol reaction with acyclic β-ketoesters **3** (Scheme 1).

An initial screening of reaction conditions was carried out to optimize the reaction of benzylideneacetone (**2a**) with several β-ketoesters **3** [Eq. (1)] and some representative results obtained during the screening are presented in Table 1.[9] The results of the initial screening experiments revealed that catalyst **1** is an excellent catalyst for the domino Michael–aldol reaction and that higher enantioselectivities were obtained when using benzyl benzoylacetate (**3b**) than when using ethyl benzoylacetate (**3a**). Furthermore, it was observed that the reaction proceeded readily in various solvents, as well as under solvent-free conditions; excellent enantioselectivities were obtained in all solvents, although yields varied somewhat. Protic solvents such as MeOH and EtOH gave the highest reaction rates and up to 80% yield with 95% *ee* could be obtained (Table 1, entries 9–11) and therefore EtOH was chosen for further reactions. We also tested other chiral amines as catalysts: for example, L-proline gave a fast reaction, but the product was formed as a racemate. Notably, to obtain analytically pure domino Michael–aldol adducts no chromatography was required as the optically active cyclohexanones precipitated from the reaction mixture and were recovered by simple filtration, washing with Et_2O (to remove unconverted starting materials), and drying under vacuum. This very simple work-up procedure suggests that a continuous recrystallization takes place during the reaction, but reactions purified by flash chromatography afforded domino Michael–aldol adducts with the same optical purity as those recovered by filtration.

After optimization of the reaction conditions, various α,β-unsaturated ketones were treated with benzyl benzoylacetate (**3b**) to determine the scope of the reaction ([Eq. (2)], Table 2). The various α,β-unsaturated ketones **2** carrying aromatic and heteroaromatic β-substituents (Ar^1) all reacted well with β-ketoester **3b**, affording cyclohexanones in moderate to good yields and with excellent enantioselectivities (Table 2, entries 1–10). Furthermore, several other aromatic β-ketoesters **3c**,**d** could be employed in the reaction and led

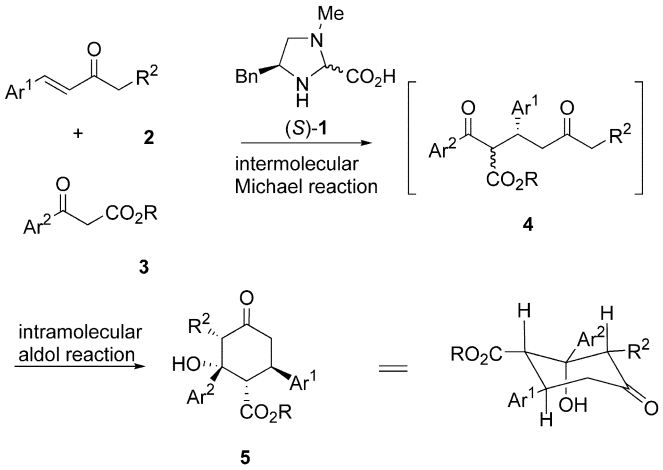
Table 1: Optimization of the diastereo- and enantioselective domino Michael–aldol reaction catalyzed by (*S*)-**1**.



2a **3** **5**

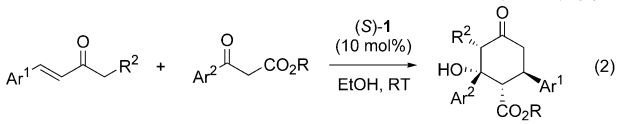
Entry	R	**3**	**1** [mol%]	Solvent	**5**	*t* [h]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	Et	**a**	20	neat	**a**	110	89	>97:3	70
2	Et	**a**	10	CH_2Cl_2	**a**	144	60	>97:3	88
3	Et	**a**	10	H_2O	**a**	93	<5	–	–
4	Et	**a**	10	$EtOH/H_2O$[d]	**a**	93	57	>97:3	87
5	Bn	**b**	10	neat	**b**	96	20	>97:3	94
6	Bn	**b**	10	neat	**b**	120	60	>97:3	95
7	Bn	**b**	10	THF	**b**	96	10	>97:3	99
8	Bn	**b**	10	CH_2Cl_2	**b**	80	42	>97:3	94
9	Bn	**b**	10	EtOH	**b**	44	89	>97:3	89
10	Bn	**b**	10	EtOH	**b**	190	80	>97:3	95[e]
11	Bn	**b**	10	MeOH	**b**	44	52	>97:3	90
12	Bn	**b**	10	CH_3CN	**b**	68	70	>97:3	90
13	Bn	**b**	10	CH_3CN	**b**	42	30	>97:3	91[e]

Experimental conditions: β-Ketoester **3** (1.0 mmol, 2 equiv) and catalyst (*S*)-**1** were added to a solution of benzylideneacetone **2a** (0.5 mmol) in solvent (1.0 mL), and the reaction mixture was stirred at ambient temperature for the time indicated in the table. [a] Yields of isolated products. [b] Determined by ^1H NMR spectroscopic analysis. [c] Determined by CSP-HPLC. [d] Performed in $EtOH/H_2O$ 4:1. [e] Reaction performed at 10°C.



Scheme 1. Domino Michael–aldol reaction of acyclic β-ketoesters **2** with α,β-unsaturated ketones **3** catalyzed by (*S*)-**1**.

Table 2: Domino Michael–aldol reaction of α,β-unsaturated ketones **2** with β-ketoesters **3** catalyzed by (*S*)-**1**.



(2)

2 **3** **5**

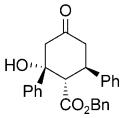
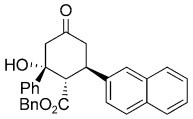
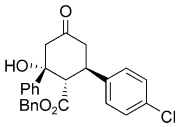
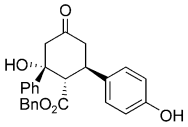
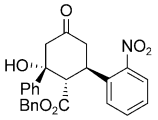
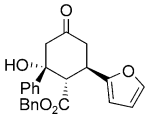
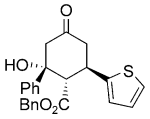
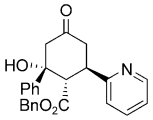
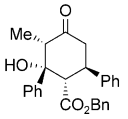
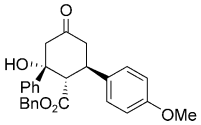
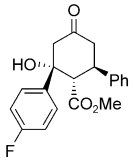
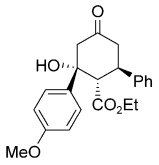
Entry	**2**	Ar^1	R^2	**3**	Ar^2	R	*t* [h]	Product	**5**	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	**a**	Ph	H	**b**	Ph	Bn	192		**b**	80	>97:3	95[d]
2	**b**	2-Np	H	**b**	Ph	Bn	95		**c**	85	>97:3	91
3	**c**	4-Cl-Ph	H	**b**	Ph	Bn	95		**d**	60	>97:3	97
	c	4-Cl-Ph	H	**b**	Ph	Bn	240		**d**	80	>97:3	93[c]
4	**d**	4-HO-Ph	H	**b**	Ph	Bn	95		**e**	20	>97:3	99
5	**e**	2-NO_2-Ph	H	**b**	Ph	Bn	125		**f**	56	>97:3	96
6	**f**	2-furyl	H	**b**	Ph	Bn	140		**g**	40	>97:3	85
7	**g**	2-thienyl	H	**b**	Ph	Bn	165		**h**	52	>97:3	83
8	**h**	2-pyrimidyl	H	**b**	Ph	Bn	240		**i**	84	>97:3	89[d]
9	**i**	Ph	Me	**b**	Ph	Bn	95		**j**	50	>97:3	95
	i	Ph	Me	**b**	Ph	Bn	165		**j**	61	>97:3	96
10	**j**	Ph	H	**b**	Ph	Bn	140		**k**	70	>97:3	86

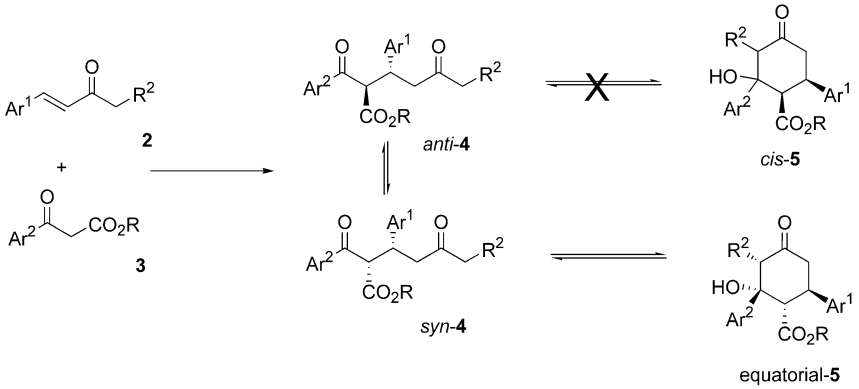
Table 2: (Continued)

Entry	2	Ar^1	R^2	3	Ar^2	R	*t* [h]	Product	5	Yield [%][a]	d.r.[b]	*ee* [%][c]
11	**a**	Ph	H	**c**	4-F-Ph	Me	160		**l**	44	>97:3	92
12	**a**	Ph	H	**d**	4-MeO-Ph	Et	165		**m**	22	>97:3	90

Experimental conditions: β-Ketoester **3** (1.0 mmol, 2.0 equiv) and catalyst (*S*)-**1** (10 mol%) were added to α,β-unsaturated ketone **2** (0.5 mmol) in EtOH[14] (1.0 mL), and the reaction mixture was stirred for the time indicated in the table. [a] Yields of isolated products. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Determined by CSP-HPLC. [d] Reaction performed at 10°C.

to the formation of cyclohexanones with excellent enantioselectivities, although the yields were moderate (Table 2, entries 11 and 12). The low yield of **5e** (Table 2, entry 4) is due to low conversion because of the electron-donating substituent at the *para* position of Ar^1 in **2d**.

In all cases only a single diastereomer of the domino Michael–aldol adduct was formed, something that is easily rationalized. The reaction proceeds through initial formation of the Michael adduct **4**, which bears two stereogenic centers, but only the Ar^1-substituted stereogenic carbon center is stable, whereas the stereogenic carbon center with both the ketone and ester substituents epimerizes in the reaction mixture as the proton is highly acidic and therefore the Michael adduct **4** exists as a mixture of *syn* and *anti* isomers (Scheme 2).

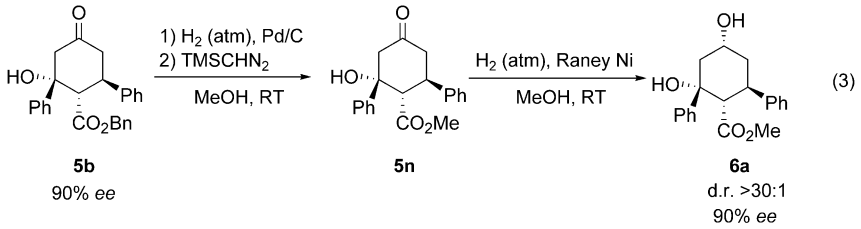


Scheme 2. Diastereoselectivity in the domino Michael–aldol reaction.

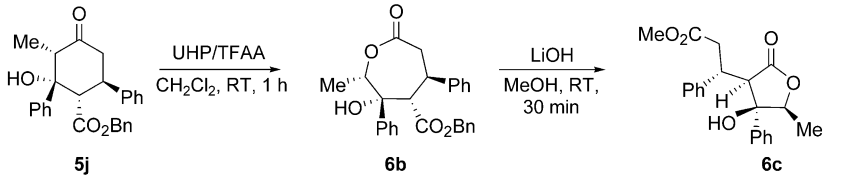
Fortunately, the intramolecular aldol reaction proceeds in a highly diastereoselective fashion to form the six-membered ring so that all large substituents are equatorial and thus are controlled by the stable stereogenic center formed in the initial Michael reaction. It should be noted that the high-energy diastereomers *cis*-**5** are not observed in the course of the reaction. Furthermore, in contrast to the intermolecular Michael reaction, which is catalyzed by the chiral imidazolidine catalyst, the intramolecular aldol reaction is believed to be base-catalyzed, as shown by Dieckmann and Fischer and by Christoffers,[8] with the imidazolidine catalyst acting as the base. The catalyst plays three roles in the reaction: a) it activates the Michael acceptor by iminium-ion formation, b) it generates the active Michael donor by deprotonation of the β-ketoester, and c) it acts as a base in the intramolecular aldol reaction. However, it cannot be completely excluded that the intramolecular aldol reaction is catalyzed by the imidazolidine compound and proceeds through an enamine mechanism.

The assignment of the relative stereochemistry of the cyclohexanones is based on X-ray crystallographic studies (see Supporting Information) of cyclohexanol **6a** formed by a diastereoselective reduction of cyclohexanone **5n** as outlined below [Eq. (3)].[10]

As we were unable to obtain X-ray-quality crystals of the domino Michael–aldol adduct **5j** with four stereogenic centers, we subjected **5j** to Baeyer–Villiger oxidation followed by a translactonization as outlined below [Eq. (4)].[11]



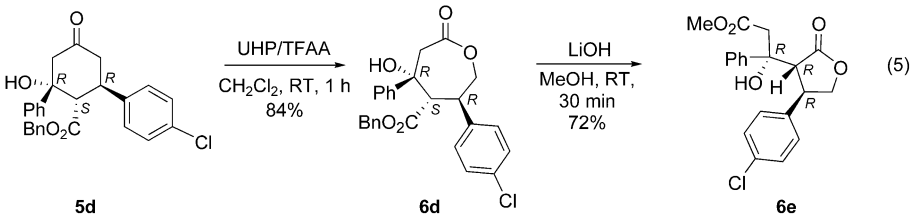
(3)



(4)

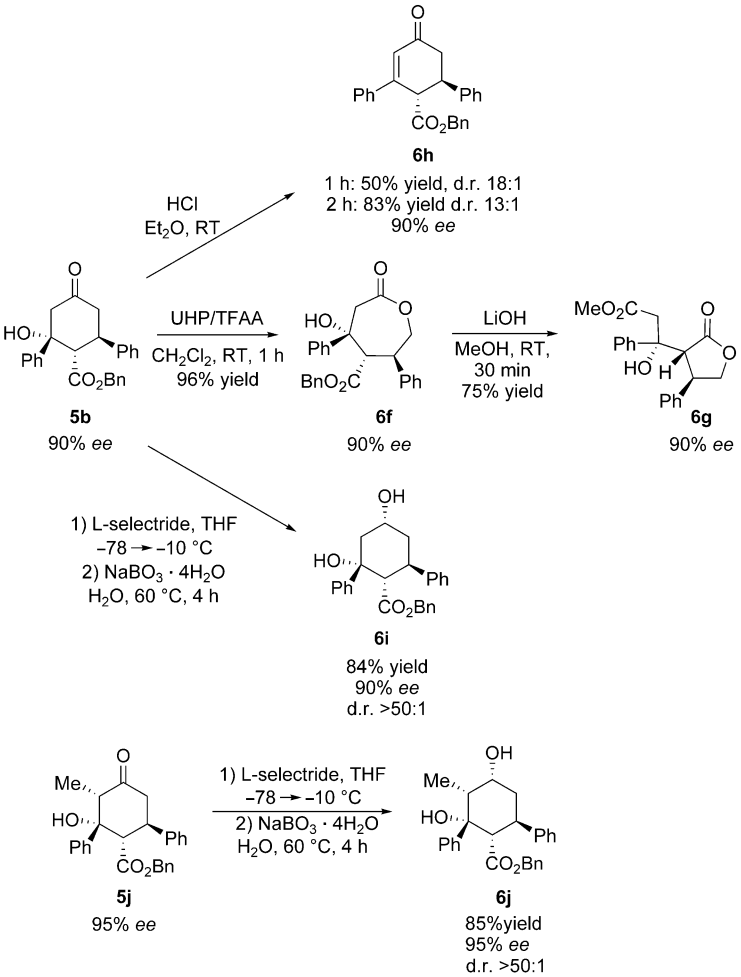
This afforded the γ-lactone **6c**, which readily afforded X-ray-quality crystals upon recrystallization from MeOH, and the relative stereochemistry of **6c** was determined by X-ray crystallography, thus providing information on the relative stereochemistry of the α-keto compound (see Supporting Information).[12]

The absolute stereochemistry of the domino Michael–aldol adducts was similarly determined from the γ-lactone **6e** derived from domino Michael–aldol adduct **5d** [Eq. (5)].



(5)

The absolute stereochemistry of γ-lactone **6e** was determined to be *R*,*R*,*R* by X-ray crystallography, and the absolute configuration of the domino Michael–aldol adduct **5d** was therefore determined to be 3*R*,4*S*,5*R*, as indicated in Equation (5).[12]



Scheme 3. Transformations of cyclohexanones **5**.

To demonstrate the potential of the domino Michael–aldol reaction, several product modifications were performed on the domino Michael–aldol adducts to determine the versatility of the cyclohexanone derivatives **5** (Scheme 3). Baeyer–Villiger oxidation of **5b** proceeded smoothly, with complete regioselectivity, in the presence of urea–hydrogen peroxide (UHP) and trifluoroacetic anhydride (TFAA) as a very convenient way of generating trifluoro peroxyacetic acid, giving the optically active ε-lactone **6f** in 96% yield.[13] The ε-lactone **6f** was easily translactonized to γ-lactone **6g** in good yield by brief exposure to LiOH/MeOH, maintaining the high enantiopurity. Furthermore, the cyclohexenone **6h** could be formed by acid-catalyzed dehydration of **5b**, although some epimerization occurred at C4 under the reaction conditions. However, diastereoselectivities of up to 18:1 were obtained. Lastly, the cyclohexanediols **6i**,**j** were prepared in good yields as single diastereomers by reduction of the corresponding cyclohexanones **5b**,**j** with L-selectride.

These optically active building blocks with up to five contiguous stereogenic centers are all formed in one or two simple high-yielding transformations, without racemization, from the domino Michael–aldol adducts.

In summary, we have developed the first highly enantio- and diastereoselective organocatalytic domino Michael–aldol reaction of acyclic β-ketoesters and α,β-unsaturated ketones in the presence of an imidazolidine catalyst, which is easily prepared from phenylalanine. The reaction proceeds for a number aromatic and heteroaromatic β-ketoesters and α,β-unsaturated ketones, forming adducts with 3–4 contiguous stereogenic centers. Furthermore, the synthetic scope of the reaction was demonstrated by the easy formation of various optically active building blocks.

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Keywords: aldol reaction · domino reaction · esters · ketones · Michael addition

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[9] The 4,5-diphenyl-imidazolidine-2-carboxylic acid catalyst recently reported for the catalytic enantioselective formation of warfarin,[5] also promoted the domino Michael–aldol reaction in up to 90% *ee* in moderate yield.

[10] CCDC-224447 (**6a**), CCDC-224448 (**6c**), and CCDC-224449 (**6e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[11] Baeyer-Villiger oxidations generally occur with retention of stereochemistry at the migrating center; see, for example: *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon, Berlin, **1991**.

[12] Inversion of the α-carbonyl stereogenic center was observed during the translactonization procedure.

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[14] The reaction rate is strongly concentration-dependent (see Supporting Information).

