Controlling the formation of 1 out of 64 stereoisomers using organocatalysis†

Søren Bertelsen, Rasmus L. Johansen and Karl Anker Jørgensen*

Received (in Cambridge, UK) 15th April 2008, Accepted 12th May 2008
First published as an Advance Article on the web 9th June 2008
DOI: 10.1039/b806418k

The formation of 1 out of 64 stereoisomers, *i.e.* controlling the creation of 6 stereocenters, of important optically active bicyclo[3.3.1]non-2-ene compounds, has been achieved using organocatalysis; the reaction proceeds with excellent stereocontrol and can be carried out with the generation of enantiopure products using chromatography-free procedures.

Recently, organocatalysis has proven to be a powerful strategy for the stereoselective synthesis of highly valuable building blocks, being complementary to the established methods using metals or enzymes.[1] The organocatalysts are readily available small organic molecules, which are easily synthesized or purchased and are tolerant of a great variety of benign reaction conditions.[1]

In the field of synthesis of complex molecules with one or multiple stereocenters, the asymmetric catalytic strategy, using *e.g.* organocatalysis, has shown promising results towards the simultaneous synthesis of several stereocenters in easy multicomponent, domino or cascade procedures,[2] a task that was traditionally considered elusive. Examples are now available for the formation of six-membered ring systems having several stereocenters as in *e.g.* the substituted cyclohexenes developed by Enders *et al.* using a three-component domino reaction,[2d] or Hayashi *et al.*'s Michael–Henry reaction sequence for the formation of optically active cyclohexane derivatives.[2f] Recently, we have shown the development of a one-pot asymmetric reaction with the formation of five stereocenters by an intermolecular two-component reaction of α,β-unsaturated aldehydes with a dinitroalkane, leading in this particular case to the formation of highly substituted optically active cyclohexanols.[3,9]

In the present work we will show the development of a new organocatalytic asymmetric cascade reaction by demonstrating that two simple molecules, an α,β-unsaturated aldehyde and a tricarbonyl compound, react in a one-pot reaction to selectively form 4 new carbon–carbon bonds, providing 6 new stereocenters, and thereby 1 out of 64 possible (2^6) stereoisomers with excellent diastereo- and enantioselectivity (Scheme 1). The optically active products formed, bicyclo[3.3.1]non-2-enes, have a number of important applications and properties. The carbon skeleton in these compounds is a recurrent target in total synthesis of highly important biomolecules,[4] while the racemic analogues[5] have shown antitumor activity.[6]

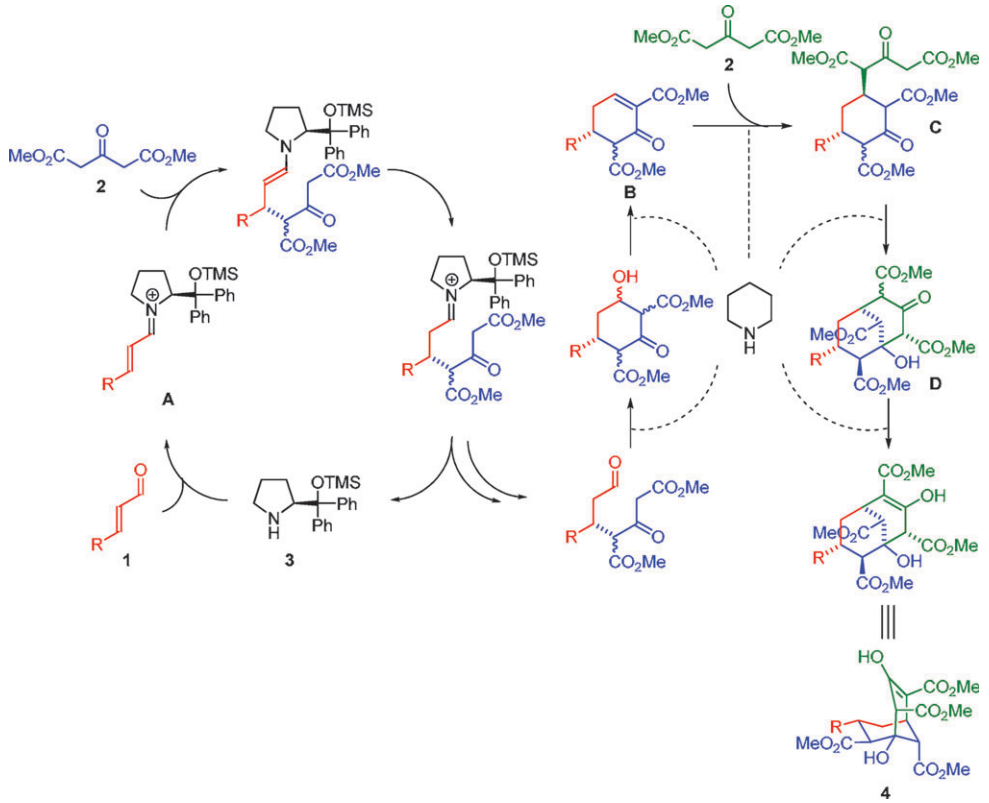
Scheme 1 Organocatalytic asymmetric two-component reaction leading to bicyclo[3.3.1]non-2-enes.

The proposed mechanism for the formation of the 6 stereocenters in the optically active bicyclo[3.3.1]non-2-ene products **4** is outlined in Scheme 2. The chiral organocatalyst **3** acts by first activating the α,β-unsaturated aldehyde **1** *via* an iminium ion intermediate **A** shown to the left in the scheme. This allows for a nucleophilic attack by one of the methylene carbon atoms of the tricarbonyl compound **2** at the β-carbon atom in **A**, generating the first 2 stereocenters. A cyclization initiated by the second activated methylene of the tricarbonyl compound leads to intermediate **B**. It is likely, yet unclear, that the cyclization is preceded by hydrolysis of the catalyst. Intermediate **B** can undergo a stereoselective conjugate addition by another molecule of tricarbonyl compound **2** leading to the formation of **C**. The diastereocontrol of this second addition is probably governed by the stereocenter bearing R in the second catalytic cycle to the right in Scheme 2. A final ring closure reaction, between the last free activated methylene and the central ketone leads to the highly functionalized product **D** (with 7 stereocenters), which is in tautomeric equilibrium with the more stable enol form **4**, by reason of strong intramolecular hydrogen bonding. The piperidine might act as a catalyst for several of the reaction steps in the second part of the reaction course.

A series of experiments were performed to develop the optimal reaction conditions for the formation of the optically active bicyclo[3.3.1]non-2-ene products. The optimization investigations gave the following standard reaction conditions: dimethyl 3-oxapentanedioate **2** (0.50 mmol) was added at room temperature to a stirred solution of (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether[7] **3** (0.025 mmol), benzoic acid (0.025 mmol) and the α,β-unsaturated aldehyde **1** (0.25 mmol) in toluene (125 μL). After complete consumption of the α,β-unsaturated aldehyde, as monitored by ^{1}H NMR spectroscopy, MeOH (1.0 mL) and piperidine (0.05 mmol) were added and the reaction was stirred at 40 °C until full consumption of **2** (as indicated by TLC). Table 1

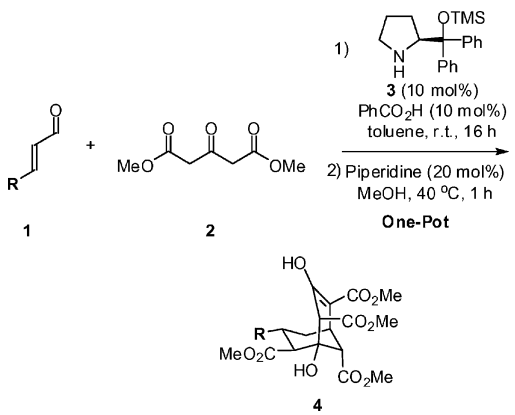
Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark. E-mail: kaj@chem.au.dk; Fax: +45 8619 6199; Tel: +45 8942 3910

† Electronic supplementary information (ESI) available: Full experimental details. CCDC 682910 and 687505. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b806418k



Scheme 2 Proposed organocatalytic cycles for the formation of 1 out of 64 stereoisomers by one-pot organocatalytic cascade reaction of an α,β-unsaturated aldehyde with a tricarbonyl compound.

shows the results obtained for the reaction of a number of different α,β-unsaturated aldehydes **1** with dimethyl 3-oxapentanedioate **2** in the presence of **3** (10 mol%) and piperidine (20 mol%) as the catalysts (Scheme 3).



Scheme 3 Reaction of different α,β-unsaturated aldehydes **1** with dimethyl 3-oxapentanedioate **2** in the presence of **3** (10 mol%) and piperidine (20 mol%) as the catalysts.

As it appears from Table 1, various α,β-unsaturated aldehydes have successfully been subjected to the reaction conditions giving a broad range of optically active bicyclo[3.3.1]non-2-enes **4**. Aliphatics (linear and branched, including heteroatoms and olefins), aromatics, heteroaromatics and esters are all well tolerated as substituents in the reaction. For the simple aliphatic α,β-unsaturated aldehydes (entries 1–3), the optically active products **4a**–**4c** are formed in good yields, after the multiple reaction steps, and for the two former products, only one diastereoisomer could be detected and both with more than 94% ee. For the optically active bicyclo[3.3.1]non-2-enes having an ester or olefin as R, **4d** and **4e**, respectively, excellent results are also obtained (entries 4, 5). The product diversity can be expanded to also include aromatic and heteroaromatic substituents as shown for **4f**–**4i**. The aromatic compounds, both unsubstituted, and *para*- and *ortho*-substituted phenyls (entries 6–9), gave excellent yields with up to 93% isolated yield, one diastereoisomer and up to 96% ee. The presence of a heteroaromatic substituent, such as furyl, **4h**, led to an 86% yield, 94 : 6 dr and 90% ee.

Table 1 Organocatalytic asymmetric cascade reaction of different α,β-unsaturated aldehydes with dimethyl 3-oxapentanedioate

Entry	R		Yield (%)	Dr[a]	Ee[b] (%)
1	Et	**4a**	48	>99 : 1	94
2	*i*-Pr	**4b**	65	>99 : 1	96
3	n-C_7H_{15}	**4c**	69	88 : 12	95
4	EtO_2C	**4d**	38	>99 : 1	89
5	(*Z*)-3-Hexenyl	**4e**	51	94 : 6	94
6	Ph	**4f**	70	>99 : 1	93
7	*p*-MeOPh	**4g**	93	92 : 8	91
8	2-Furyl	**4h**	86	94 : 6	90
9	*o*-BrPh	**4i**	86	>99 : 1	96

[a] Dr measured by ^{1}H NMR spectroscopy. [b] Ee measured by HPLC using a Daicel Chiralpak AD column.

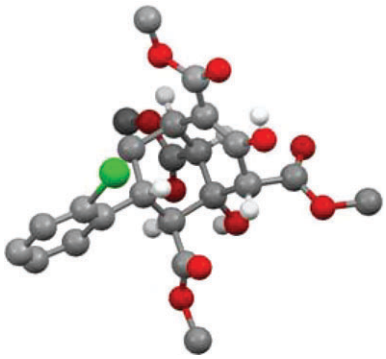


Fig. 1 X-Ray structure of (1*R*,4*R*,5*S*,6*S*,7*R*,9*S*)-tetramethyl 7-(2-bromophenyl)-3,5-dihydroxybicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate **4i**. Colour coding: white: hydrogen; grey: carbon; red: oxygen; green: bromine. Some hydrogen atoms are omitted for clarity.

This new organocatalytic reaction can easily be scaled up to gram scale and isolation of the optically active bicyclo[3.3.1]-non-2-enes **4** was performed using chromatography-free procedures by crystallizing the product after finishing the reaction. Using this procedure, product **4a** was isolated in 3 g quantity (44% yield, compared to 48% on the mg scale) and as an enantiopure compound; *i.e.* dr >99 : 1 and >99% ee. The other products could also be isolated as enantiopure compounds after recrystallization.

The optically active bicyclo[3.3.1]non-2-enes having 6 stereocenters are set up for the introduction of 2 additional stereocenters in the ring systems and *e.g.* initial hydrogenation studies of the enol in **4a** shows promising results and is currently under investigation.

The absolute configuration of tetramethyl 7-(2-bromophenyl)-3,5-dihydroxybicyclo[3.3.1]non-2-ene-2,4,6,9-tetracarboxylate **4i**, was unambiguously established as (1*R*,4*R*,5*S*,6*S*,7*R*,9*S*) by X-ray crystallographic analysis (Fig. 1).[8]

Organocatalysis has been taken to a new level, allowing the selective formation of 4 new carbon–carbon bonds, providing 6 new stereocenters, one of which is quaternary, leading to the controlled synthesis of 1 out of 64 possible stereoisomers by mixing two simple molecules, an α,β-unsaturated aldehyde and a tricarbonyl compound. The products generated, optically active bicyclo[3.3.1]non-2-enes, are formed in high yield, and with excellent diastereo- and enantiocontrol and performing the reaction on the gram scale leads to optically pure products. The optically active bicyclo[3.3.1]non-2-enes are bicyclic carbon skeletons which are precursors for important biomolecules with antitumor activity.

This work was made possible by a grant from The Danish National Research Foundation and OChemSchool. Thanks are expressed to Dr Jacob Overgaard for the X-ray analysis.

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