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One-pot asymmetric cyclocarbohydroxylation sequence for the enantioselective synthesis of functionalised cyclopentanes†

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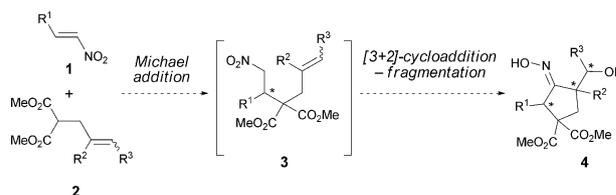
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A new method has been developed for the enantioselective synthesis of highly functionalised cyclopentanes bearing up to three stereogenic centres with very high stereoselectivity. This one-pot process combines an enantioselective organocatalytic Michael addition with a highly diastereoselective [3+2]-cycloaddition–fragmentation step.

The development of organocatalytic enantioselective methods to access enantiopure molecules has received much attention in the last ten years due to the many advantages in terms of efficiency, selectivity and environmental benefits offered by organocatalysis.¹ When the method involves simple starting materials and is associated with one-pot multiple bond-forming transformations (MBFTs),² the resulting tools are particularly useful for reaching a high level of structural complexity and functional diversity.

In this context, the asymmetric organocatalysed Michael addition of various nucleophiles to nitroolefins represents a very useful reaction.³ Although malonates have been used most often in Michael addition,⁴ synthetic developments in a sequential way, by further modification of the adducts, are limited by the lack of reactivity of 2-substituted malonates. An interesting recent example concerns the functional group pairing of modular nitro scaffolds obtained from enantioselective Michael addition catalysed by Cinchona alkaloids.⁵

Given our interest in the reactivity of nitroalkenes⁶ and domino processes,⁷ we envisioned a one-pot consecutive transformation consisting of an enantioselective organocatalytic Michael addition between nitroalkenes **1** and 2-allylmalonates **2** followed by an *in situ* [3+2] nitronate cycloaddition–fragmentation sequence leading to highly functionalised cyclopentanone oximes **4** (Scheme 1). The resulting intramolecular carbohydroxylation of the non-activated double bond with formation of the oxime function has been rarely exploited to date⁸ and this would constitute the first example of an enantioselective version. Herein, we disclose our results on this one-pot consecutive cyclopentannulation with a remote hydroxylation leading to highly functionalised five-membered rings with concomitant creation of two C–C bonds, one



Scheme 1 Strategy for the one-pot stereoselective construction of functionalised cyclopentanes.

C–O bond and the control of up to three stereogenic centres with very high diastereo- and enantioselectivities.^{9,10}

We first started to investigate the organocatalytic Michael addition and catalysts **I**,¹¹ **II**¹² and **III**^{4b} were screened under standard conditions (Table 1). Catalysts **I** and **III** bearing two different hydrogen bond donor sites respectively, in toluene or THF, were the most efficient (entries 1 and 4) although **I** showed a reduced activity in THF (entry 2). Catalyst **II** in toluene, showed a good selectivity but slightly lower yield (entry 3). Finally, when catalyst **III** was used in toluene instead of THF, we observed a significant decrease in the yield which could be due to its lower solubility (entry 5). We were also very pleased to find that both enantiomers of **3a** could be obtained using structurally different catalysts **I** and **III**.

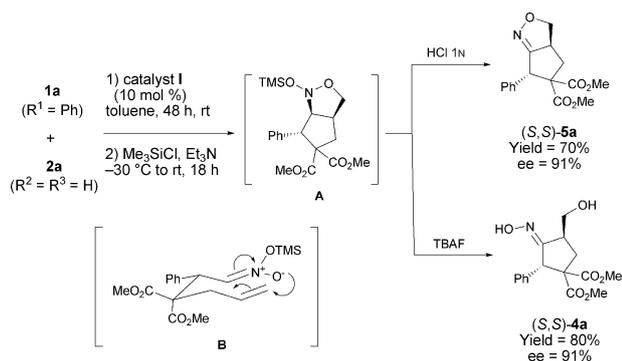
Table 1 Screening of reaction conditions for the enantioselective Michael addition of dimethyl 2-allylmalonate (**2a**) to β -nitrostyrene (**1a**)^d

Entry	Catalyst	Solvent	Yield (%) ^b	Ee (%) ^c
1	I	Toluene	95	92 (<i>S</i>)
2	I	THF	95 ^d	88 (<i>S</i>)
3	II	Toluene	78	90 (<i>R</i>)
4	III	THF	94	90 (<i>R</i>)
5	III	Toluene	67	87 (<i>R</i>)

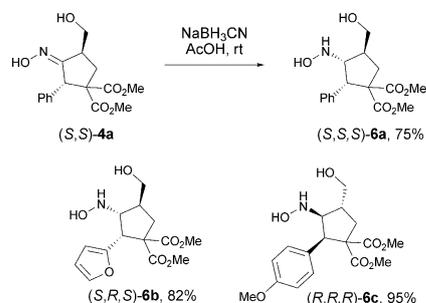
^a Reaction conditions: 1 mmol of **1a**, 2 mmol of **2a** and catalyst **I**, **II** or **III** (10 mol%) in 2 mL of solvent at room temperature for 48 h. ^b Isolated yield by flash chromatography. ^c Determined by HPLC on a chiral stationary phase. ^d 7 days of reaction time.

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Scheme 2 Cyclocarbohydroxylation sequence.

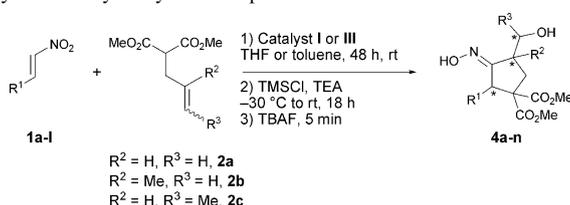


Scheme 3 Diastereoselective reduction of oximes.

We next turned our attention to the carbohydroxylation *via* an intramolecular [3+2]-silylnitronate olefin cyclisation (ISOC)-fragmentation sequence (Scheme 2).¹³ In the first attempt, generation of the silylnitronate resulted in a highly stereoselective process driven by a 1,3-allylic strain^{6,14} with a

total transfer of chirality to furnish the transient isoxazolidine **A** through the preferred nitronate conformation **B**. Treatment with aqueous HCl did not result in its fragmentation but led to the known isoxazoline **5a** with 70% yield in diastereomerically pure form.¹⁵ More interestingly, using tetrabutylammonium fluoride (TBAF) provoked the expected selective fragmentation affording the corresponding hydroxymethyl oxime **4a** also in a highly stereoselective manner¹⁶ probably through the tautomeric nitroso intermediate.^{13g} The absolute configuration was unambiguously determined to be (*E*)-(2*S*,4*S*) by X-ray crystallographic analysis of **4a**.†

The overall cyclocarbohydroxylation in a one-pot consecutive manner with organocatalysts **I** and **III** has been extended to various substrates (Table 2). Pleasingly, in all cases, this led to the formation of the desired cyclopentanone oximes **4a–n** in good to excellent yields and with high diastereo- and enantioselectivities.¹⁷ This allowed the one-pot creation of a five-membered ring and the control of two stereogenic centres starting from commercially available acyclic achiral substrates and operated a remote hydroxylation. The use of catalysts **I** and **III** allowed the formation of both enantiomers with comparable efficiencies (entries 1, 2 and 13, 14). Aromatic nitroalkenes bearing electron-withdrawing and electron-donating groups reacted well in the reaction and gave all excellent enantioselectivities (entries 3–8). However **4h** was obtained in moderate yield (entry 9, 57%) due to the lower electrophilic character of the corresponding electron rich nitroalkene **1h**. Heteroaromatic nitroolefins proved also to be very good substrates affording the desired products **4i–l** (entries 10–13) in good yields (72–95%) and excellent enantioselectivities (93–97%). The (*R,S*)-enantiomer of **4l** was also easily obtained using catalyst **I**, although with a somewhat

Table 2 Scope of the enantioselective cyclocarbohydroxylation sequence^a

Entry	R ¹	Malonate 2	Catalyst	Product	Yield (%) ^b	Ee (%) ^c
1	Ph (1a)	2a	III	(<i>R,R</i>)- 4a	92	91
2	Ph (1a)	2a	I	(<i>S,S</i>)- 4a	74	97
3	4-FC ₆ H ₄ (1b)	2a	III	(<i>R,R</i>)- 4b	81	93
4	4-MeOC ₆ H ₄ (1c)	2a	III	(<i>R,R</i>)- 4c	73	97
5	2-BrC ₆ H ₄ (1d)	2a	I	(<i>R,S</i>)- 4d	80	93
6	4-MeC ₆ H ₄ (1e)	2a	III	(<i>R,R</i>)- 4e	99	88
7	2-Cl-6-FC ₆ H ₄ (1f)	2a	III	(<i>S,R</i>)- 4f	97	92
8	2-NO ₂ C ₆ H ₄ (1g)	2a	III	(<i>R,R</i>)- 4g	82	98
9	3,4,5-(MeO) ₃ C ₆ H ₄ (1h)	2a	III	(<i>R,R</i>)- 4h	57	94
10	2-Furyl (1i)	2a	III	(<i>R,R</i>)- 4i	95	93
11	3-Furyl (1j)	2a	III	(<i>R,R</i>)- 4j	80	96
12	2-Thienyl (1k)	2a	III	(<i>R,R</i>)- 4k	77	97
13	2-Pyridinyl (1l)	2a	III	(<i>S,R</i>)- 4l	72	95
14	2-Pyridinyl (1l)	2a	I	(<i>R,S</i>)- 4l	71	89
15	Ph (1a)	2b	III	(<i>R,R</i>)- 4m	60	92
16	Ph (1a)	(<i>E</i>)- 2c	III	(<i>R,R,S</i>)- 4n	84	91
17	Ph (1a)	(<i>Z</i>)- 2c	III	(<i>R,R,R</i>)- 4n	74	94

^a Reaction conditions: 1 mmol of **1**, 2 mmol of **2** catalyst in 2 mL of solvent (toluene with **I**, THF with **III**). ^b Isolated yield by flash chromatography. ^c Determined by HPLC on a chiral stationary phase.

reduced efficiency (entry 14). When dimethyl 2-methylallylmalmate (**2b**) was employed, the consecutive process allowed the formation and control of an all-carbon quaternary stereogenic centre¹⁸ in the final product **4m** with 92% ee (entry 15). Finally, when (*E*)-**2c** was used as the starting malonate, the consecutive reaction sequence afforded the cyclopentanone oxime **4n** with the stereospecific control of a third stereogenic centre in high yield and selectivity (entry 16). Starting from (*Z*)-**2c** gave the single diastereomer of **4n** with opposite configuration of the carbon bearing the hydroxy function (entry 17).

Oximes are an important class of compounds with potential pharmaceutical properties¹⁹ and constitute versatile building blocks since they can be easily transformed into various functional groups.²⁰ As an illustration of their synthetic potential, oximes **4a**, **4c** and **4i** were reduced with NaBH₃CN affording the corresponding hydroxylamines **6a**, **6b** and **6c** as single diastereomers in good yields where a supplementary stereogenic centre was created (Scheme 3). Here again, depending on the catalyst used in the consecutive enantioselective reaction, both configurations of the new created stereogenic centre can be accessed.

In conclusion, we have identified two structurally different and complementary organocatalysts for the successful enantio-divergent cyclohydroxylation sequence allowing the construction of highly functionalised and optically pure functionalised cyclopentanes with the creation and control of up to three stereogenic centres. The high efficiency and the practical simplicity of the method make it an important platform for the stereoselective formation of complex molecules.

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