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Quaternary Stereogenic Carbon Atoms in Complex Molecules by an Asymmetric, Organocatalytic, Triple-Cascade Reaction

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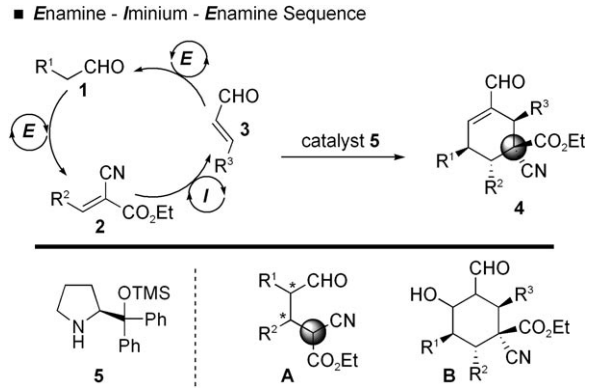
The stereoselective construction of all-carbon quaternary sterogenic centers in complex organic molecules is an ongoing synthetic challenge.[1] This is due to the growing number of biologically active natural products and pharmaceutical agents that possess quaternary stereogenic carbons. However, creating these complex fragments rapidly and selectively is a difficult task, because of the inherent steric bias encountered in the C–C bond-forming event. In this field, enantioselective cascade catalysis has been recognized as a new synthetic solution to the stereoselective construction of molecular complexity.[2] This bio-inspired strategy is based upon the combination of multiple asymmetric transformations in a cascade sequence, providing rapid access to complex molecules containing multiple stereocenters from simple precursors and in a single operation.

Here we report the development of an organocatalytic,[3] triple-cascade reaction that allows the direct, one-pot synthesis of tri- and tetra-substituted cyclohexene carbaldehydes **4** with three or four stereogenic carbon atoms, one of which is quaternary by all-carbon substitution (Scheme 1). This three-component domino strategy is based on an operationally trivial procedure that employs unmodified, cheap, and commercially available starting materials and catalyst, while achieving excellent levels of stereocontrol (up to 20:1 diastereomeric ratio (dr) and complete enantioselectivity). Notably, the development of the first asymmetric conjugate addition of aldehydes **1** to cyanoacrylates **2**, a new class of suitable Michael acceptors for enantioselective aminocatalysis, is at the heart of the presented triple organocascade.



Scheme 1. Quaternary stereocenters through a triple organocascade.

Recently, the use of simple chiral organic molecules to catalyze asymmetric domino reactions has represented an additional step forward to the identification of a powerful and reliable strategy for the stereoselective synthesis of complex molecules.[4] In this approach, the synthetic benefits inherent to cascade sequences—which avoids time consuming and costly protection/deprotection as well as isolation procedures of intermediates—is combined with the use of environmentally friendly, robust, and nontoxic organocatalysts. In particular, chiral secondary amines have been successfully used in cascade catalysis, because of the possibility to integrate orthogonal activation modes of carbonyl compounds (enamine and iminium ion catalysis)[5] into more elaborate reaction sequences.[6,7]

Despite the impressive recent achievements in the field, a general and efficient organocatalytic cascade reaction that allows the direct preparation of complex fragments, containing all-carbon quaternary stereocenters, is still lacking.[8] Toward this ambitious goal, we were inspired by the spectacular example of an enantioselective, organocatalytic, triple-cascade reaction recently reported by Enders and collea-

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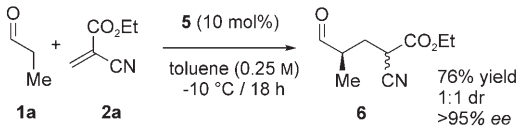
gues.[6] Exploiting the catalytic behavior of the chiral secondary amine **5**,[9] they realized an outstanding enamine–iminium–enamine sequential activation of aldehydes **1**, nitroalkenes, and α,β-unsaturated aldehydes **3**, affording cyclohexene aldehydes with four stereocenters in essentially enantiopure form.[6a] We speculated that an adequate combination of the reaction components, still including the aldehydic partners **1** and **3** to preserve the catalytic machinery of this efficient triple cascade sequence, might provide a rapid and highly selective creation of quaternary stereocenters in complex molecules.

Central to the implementation of this strategy was the individuation of a suitable Michael acceptor **2** that must address some specific issues. Initially, such reagent must intercept the enamine intermediate, generated by catalyst condensation with aldehyde **1**, much faster than the unsaturated carbonyl compounds do (aldehyde **3** or the corresponding activated iminium intermediate). The resulting conjugate adduct **A** (Scheme 1) should constitute a prochiral carbon nucleophile that can selectively engage in the iminium-catalyzed conjugate addition to **3**. The last step is an enamine-promoted aldol reaction, in which the less hindered aldehyde acts as a nucleophile affording the intermediate **B** and, after dehydration, the desired cyclohexene carbaldehydes **4**. Along these lines, we envisaged cyanoacrylate derivatives **2** as a potential candidate to address these concerns.

To assess the feasibility of such an asymmetric, organocatalytic, triple-cascade strategy, we focused on the use of ethyl 2-cyanoacrylate (**2a**),[10] probing its ability to act as a suitable Michael acceptor for enamine-catalyzed, enantioselective, direct conjugate addition of aldehydes. Exposure of propanal (**1a**) to **2a** in the presence of diphenylprolinol silyl ether **5** (10 mol%) in toluene (0.25 M) resulted in a fast, clean and highly selective (>95% enantiomeric excess (*ee*), determined by ^{1}H NMR analysis in chiral medium, see Supporting Information) conjugate addition [Eq. (1)].

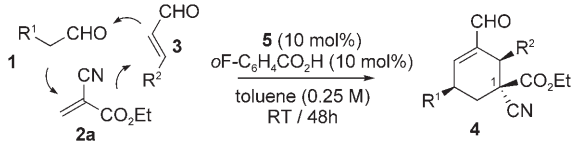


(1)

These results, besides broadening the scope of enamine catalysis, set conditions for the realization of the cascade sequence. Extensive optimization experiments revealed that the presence of an acidic additive and the relative ratios of the reagents were the crucial parameters to obtain high levels of stereocontrol and reaction efficiency:[11] mixing aldehyde **1** (2 equiv), cyanoacrylate **2a** (1.2 equiv), and unsaturated aldehyde **3** at room temperature in the presence of the catalytic salt **5**·*o*F-$C_6H_4CO_2H$ (10 mol%) in toluene, the desired cyclohexene carbaldehyde **4** was obtained in good diastereoselectivity and complete enantiocontrol after 48 h. Importantly, the main diastereomer can be easily isolated (diastereomeic excess (*de*) and *ee* up to 99%) by column chromatography.

As summarized in Table 1, the triple organocascade proved successful for a range of aldehyde substituents, providing a facile and flexible access to highly functionalized tri-substituted cyclohexenals **4a–e**, with a quaternary stereocenter, in almost enantiomerically pure form.

Table 1. Organocatalytic triple-cascade: a route toward quaternary stereocenters.[a]

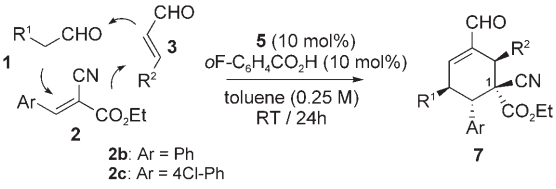


Entry	R^1	R^2	**4**	Yield [%][b]	dr[c]	*ee* [%][d]
1	Me	Ph	**a**	42	5.5:1	>99
2[e]	Me	Ph	**a**	40	5.4:1	>99
3	Et	Ph	**b**	35	3.5:1	>99
4	allyl	Ph	**c**	40	3:1	>99
5	Me	*p*NO_2-C_6H_4	**d**	34	3.8:1	98
6	Me	Me	**e**	42	2.5:1	>99

[a] Reactions performed on a 0.4 mmol scale by using 2 equivalents of aldehyde **1**, 1.2 equivalents of **2a**, and 1 equivalent of enal **3**. [b] Yield of the isolated main diastereomer. The diastereomeric purity of the isolated products **4** (*de*>99%) was determined by HPLC and ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis of the crude mixture. The minor diastereomer was identified as the 1-epimer of **4**. [d] The enantiomeric excesses were determined by HPLC analysis of the isolated products **4**. [e] (*R*)-**5** was used as the catalyst, affording the opposite enantiomer of compound *ent*-**4a**.

This three-component domino strategy can also be successfully extended to the highly chemo-, diastereo-, and enantioselective synthesis of tetra-substituted cyclohexene carbaldehydes **7** (Table 2). The use of *trans*-α-cyanocinna-

Table 2. Control of four stereocenters through an organocatalytic triple-cascade reaction.[a]

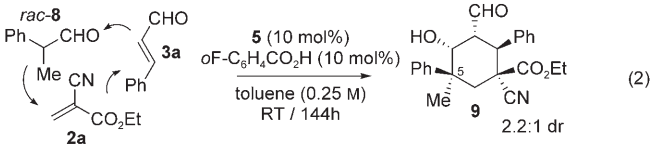


Entry	**2**	R^1	R^2	**7**	Yield [%][b]	dr[c]	*ee* [%][d]
1	**b**	Me	Ph	**a**	52	2.6:1	>99
2[e]	**b**	Me	Ph	**a**	45	2.2:1	>99
3	**b**	Et	Ph	**b**	40	2.3:1	>99
4	**c**	Me	Ph	**c**	32	2:1	>99
5	**b**	Me	Me	**d**	48	>20:1	98
6	**b**	Et	Me	**e**	39	>20:1	98
7	**b**	allyl	Me	**f**	40	>20:1	99
8	**c**	Me	Me	**g**	38	7.6:1	99

[a] Reactions performed on a 0.4 mmol scale using 2 equivalents of aldehyde **1**, 1.2 equivalents of **2** and 1 equivalent of enal **3**. [b] Yield of the isolated main diastereomer. The diastereomeric purity of the isolated products **7** (*de*>99%) was determined by HPLC and ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis of the crude mixture. The minor diastereomer was identified as the 1-epimer of **7**. [d] The enantiomeric excess was determined by HPLC analysis of the isolated products **7**. [e] Reaction carried out with 5 mol% of the catalyst **5.**

mates **2b**,**c**[12] determines a fast and efficient triple organocascade, leading to the desired products after 24 h reaction time. Interestingly, aliphatic β-substituted enals induce an higher stereocontrol, with diastereomeric ratio of up to 20:1.

The efficiency of the presented organocatalytic strategy prompted us toward a more ambitious goal, the formation of a complex structure with *two* all-carbon quaternary stereocenters. Employing an α,α-disubstituted aldehyde, such as 2-phenyl propanal (**8**), as a component of the triple organocascade led to the unexpected formation of cyclohexane **9**, a highly functionalized molecule with five stereocenters [Eq. (2)]. It is worth noting that this reaction allows the highly enantioselective synthesis of just two diastereomers, out of the 16 possible ones—compound **9** and its 5-epimer (epi-**9**)—that can be separated by chromatography.[13]



(2)

9: 36% isolated yield, 96% *ee*
epi-**9**: 19% isolated yield, 91% *ee*

The relative configuration of the tri- and tetra-substituted cyclohexene carbaldehydes **4a** and **7a** and the cyclohexanes **9** and epi-**9** was determined by NMR NOE analysis and X-ray crystallography (see Supporting Information). Interestingly, **4a** and **7a** have an opposite configuration at the C(1) quaternary center, while the other stereogenic carbon atoms, directly forged by the catalyst stereo-induction, have the same configuration. The absolute configuration was assigned by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra.[14] As shown in Figure 1, the experimental ECD spectra match with the theoretical data. The relative and absolute configurations are in agreement with related aminocatalytic conjugate additions promoted by catalyst **5**.[6,9]

In summary, we have disclosed a novel organocatalytic triple cascade that allows the stereoselective construction of all-carbon quaternary sterogenic centers in complex organic molecules. The method provides a flexible and direct access to cyclohexene carbaldehydes with three or four stereogenic carbon atoms with high diastereomeric and complete enantiomeric control, and can be extended to the preparation of enantiopure cyclohexanes with five chiral centers and two quaternary carbons.[13] A full account of this new organocascade strategy will be forthcoming.

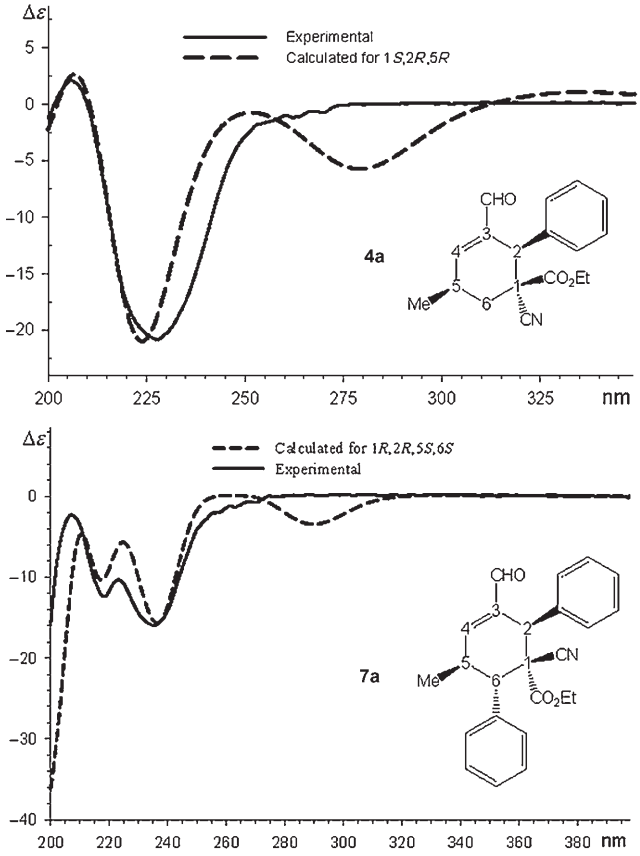


Figure 1. Experimental (full trace) and calculated ECD spectra (dotted trace) of the tri- and tetra-substituted cyclohexene carbaldehydes **4a** (top) and **7a** (bottom).

Experimental Section

All the reactions were carried out in undistilled toluene without any precautions to exclude air. In an ordinary vial equipped with a Teflon-coated stir bar, catalyst **5** (0.04 mmol, 13.0 mg, 10 mol%) and 2-fluorobenzoic acid (0.04 mmol, 5.6 mg, 10 mol%) were dissolved in toluene (1.12 mL). After addition of the aldehyde **1** (0.8 mmol, 2 equiv), the solution was stirred for 10 min at room temperature. Then the cyanoacrylate derivatives **2** (0.48 mmol, 1.2 equiv) and α,β-unsaturated aldehyde **3** (0.4 mmol, 1 equiv) were sequentially added. After 24–48 h stirring, the crude reaction mixture was diluted with DCM (2 mL) and flushed through a short plug of silica, using DCM/Et_2O 2:1 as the eluent. Solvent was removed in vacuo, and the residue was purified by flash chromatography (FC) to yield the desired products **4** or **7** as a single diastereomer in almost enantiomerically pure form.

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Keywords: asymmetric synthesis · domino reactions · multicomponent reactions · organocatalysis · quaternary stereocenters

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[10] It is impressive how, despite being the main component of one of the most used superglue solution (Loctite® Super Attak, Henkel), ethyl 2-cyanoacrylate **2a** is compatible with organocatalytic reaction conditions. This underscores, once again, the reliability and the synthetic potential of asymmetric aminocatalysis.

[11] The use of different acidic (e.g., pNO$_2$-C$_6$H$_4$CO$_2$H) and basic additives (e.g., DABCO) resulted in considerably lower reaction rate and worse diastereoselectivity.

[12] Efforts to use aliphatic cyanoacrylate derivatives in the triple organocascade resulted in very poor conversion.

[13] Further studies toward the asymmetric preparation of enantiopure cyclohexanes having six stereocenters are underway.

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