Asymmetric Catalysis

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Asymmetric Organocatalytic Relay Cascades: Catalyst-Controlled Stereoisomer Selection in the Synthesis of Functionalized Cyclohexanes**

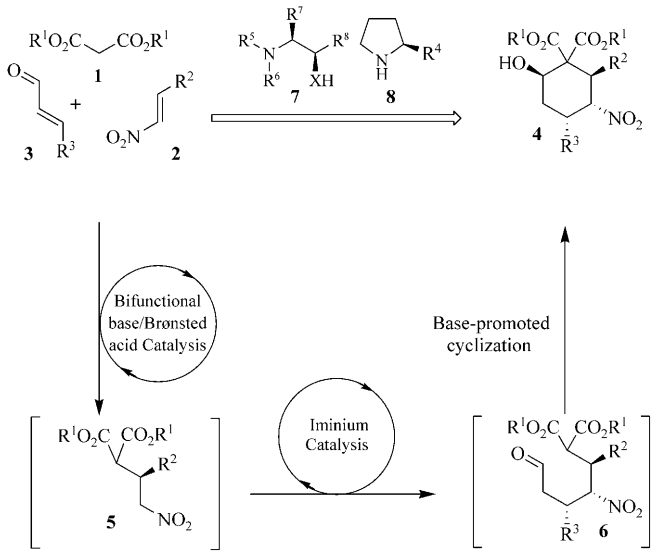
Yao Wang, Rong-Gang Han, Yong-Long Zhao, Shu Yang, Peng-Fei Xu, and Darren J. Dixon**

Amongst the challenges currently facing synthetic chemists is the development of efficient and elegant chemical processes that allow the rapid creation of stereochemically defined molecular complexity and diversity.[1] One of the most effective ways of achieving this goal is to implement reaction cascades; these allow multiple bond-forming events to occur in a single vessel and, as a consequence, significantly increase resource efficiency for the overall process.[1] To this end, the field of asymmetric organocatalytic cascade/domino reaction development—arguably one of the most stimulating, dynamic, and synthetically powerful areas in contemporary organic synthesis—is beginning to provide genuine solutions.[2,3] Recently, organocatalytic cascade approaches to polysubstituted chiral cyclohexanes have attracted a great deal of attention, owing to the prevalence of such motifs in pharmaceutical compounds and complex natural products.[4,5] However, despite the progress that has been achieved in this field, further advances are needed, particularly with regard to the controlled preparation of different stereoisomers by routine changes to the reaction conditions and/or catalysts employed.

Recently, the combination of two organocatalysts has been elegantly employed in one-pot reactions with the controlled, sequential addition of reagents and/or catalysts throughout the course of the reaction.[6] That the vessel is not necessarily charged with all reactants and catalysts from the outset of the reaction belies incompatibilities between combinations of reactants, intermediates, or catalyst-activated species with respect to the desired product outcome. Instead of controlling the outcome of the cascade through the order or rate of addition of reactants/catalysts, our aim was to employ catalysts with orthogonal, but mutually compatible, reactant activation modes. By judicious choice of catalysts and reactants, cycle specificity can be engineered into the reaction cascade such that the product of the first catalytic cycle becomes the sole substrate which then reacts with the third "spectator" reagent.

Relay catalysis has been used as an efficient strategy in non-asymmetric transformations,[7] and some examples of asymmetric metal/organocatalyst relay catalysis have also been reported.[8] Covalent-bond and bifunctional base/Brønsted acid catalysis are two fundamental activation modes in organocatalysis.[9] We envisaged that the merging of these two fields would allow desirable levels of stereocontrol and resource efficiency in an asymmetric organocatalytic relay cascade (AORC) to polysubstituted cyclohexanes.

Our proposed three-step asymmetric organocatalytic relay cascade to polysubstituted cyclohexanes is shown in Scheme 1. Initially, a bifunctional base/Brønsted acid catalyst of type **7** would preferentially activate the malonate ester **1** and the nitroalkene **2**, thus promoting a chemoselective and stereoselective Michael addition.[10] The Michael adduct **5** would then be poised to participate directly in the second catalytic cycle by serving as the donor in a regioselective nitro-Michael reaction to α,β-unsaturated aldehydes under iminium ion activation with a cyclic secondary amine catalyst of type **8**. The new Michael adduct **6**, with its suitably



Scheme 1. AORC approach to polysubstituted cyclohexanes.

[*] Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, Prof. Dr. P.-F. Xu
State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University
Lanzhou 730000 (China)
Fax: (+86) 931-891-5557
E-mail: xupf@lzu.edu.cn
Prof. Dr. D. J. Dixon
Department of Chemistry, Chemistry Research Laboratory
University of Oxford
Mansfield Road, Oxford, OX1 3TA (UK)
Fax: (+44) 1865-285-002
E-mail: darren.dixon@chem.ox.ac.uk

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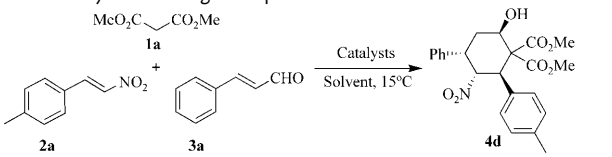
positioned aldehyde and malonate functionalities, would then undergo a base-promoted aldol cyclization to generate the desired cyclohexane **4**. Not only could the cascade have perfect atom economy,[11] high levels of chemo-, regio-, and stereoselectivity were also anticipated;[12] importantly, we expected that different stereoisomeric products could be prepared by changing the stereochemical configurations of the organocatalysts employed. Consequently, three new bonds, four new stereogenic centers, and one quaternary carbon center could be assembled, incorporating multiple functional groups in a simple-to-perform, single-operation cascade sequence. Herein, we present our findings on this new organocatalytic cascade reaction.

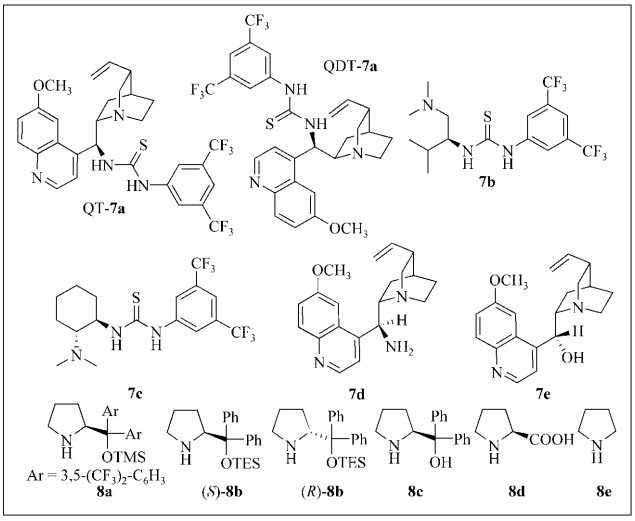
An initial study revealed that dimethylmalonate **1a**, *p*-methylnitrostyrene **2a**, and *trans*-cinnamaldehyde **3a** reacted smoothly in the presence of two organocatalysts, QT-**7a** (15 mol%), and **8a** (15 mol%), in toluene at 15°C to furnish the desired product in 38% yield and greater than 99% *ee* (Table 1, entry 1). Following a screen of various catalyst combinations, QT-**7a** and (*S*)-**8b** was found to be the most promising catalyst pair for the reaction (Table 1, entry 2). Optimization of the reaction conditions established toluene as the solvent of choice, we found that addition of 2.0 equivalents of NaOAc could promote the reaction rate, and lead to higher yield and diastereoselectivity, without a drop in *ee* (Table 1, entry 10).

A range of reactant combinations were then considered (Table 2). The cascade process was found to be broad in scope, with very good to excellent enantioselectivities obtained for all addition products (**4**; 88–99% *ee*), where measurable. The nitro olefin **2** allowed incorporation of a wide range of functionalization in the cyclohexane products; aromatic groups bearing electron-withdrawing or electron-donating groups were tolerated, as were *ortho*-, *meta*-, and *para*-substituted aromatic rings. Heteroaromatic groups, such as furan, could also be successfully employed to afford cyclohexane derivatives with excellent enantioselectivity (Table 2, entries 1–7, 9, 16). Alkyl substrates did not perform as well in the reaction; the use of the catalyst pair of QT-**7a** and (*S*)-**8b** gave very low conversion into the reaction products. Modification of the optimized conditions, by using the catalyst pair **7c** (20 mol%) and (*S*)-**8b** (15 mol%), provided the desired product **4h**, albeit in 26% yield. Unfortunately, the enantiomeric excesses of compounds **4e**, **4h** and **4j** could not be determined by HPLC analysis (Table 2, entries 5, 8 and 10). The α,β-unsaturated aldehyde **3** could also be varied, thus allowing another point of diversity in the cascade products. For substituted cinnamaldehyde derivatives, excellent enantioselectivities (>99% *ee*) were obtained regardless of the substituents on the aryl moiety (Table 2, entries 11–14). Importantly, through judicious choice of the organocatalysts employed, this relay cascade could be readily adapted to predominantly afford an alternative major diastereomer of the polysubstituted cyclohexane product (Table 2, entries 5, 6, 9, 15). For example, replacing (*S*)-**8b** with (*R*)-**8b** in the cascade reaction between dimethyl malonate, *p*-methylnitrostyrene, and cinnamaldehyde resulted in the formation of **4e**, not **4d**, as the major diastereomer (Table 2, entry 5 versus entry 4). Using the same combination of catalysts, the reaction of crotonaldehyde with dimethyl malonate and the 2-furanaldehyde-derived nitro olefin afforded product **4o** in 88% *ee* and 69% yield (Table 2, entry 15).

To further illustrate the synthetic potential of this methodology, the use of QDT-**7a** (15 mol%) and (*R*)-**8b** (15 mol%) gave the enantiomer of **4d** as the major diastereomer (4.4:1.8:1 d.r., >99% *ee*) in 54% yield. However, the combination of QDT-**7a** (15 mol%) and (*S*)-**8b** (15 mol%) gave the enantiomer of **4e** as the major product, albeit in low conversion (for details, see the Supporting Information). The absolute and relative configuration of the major diastereomeric product of the cascade with catalysts QT-**7a** and (*S*)-**8b** was established by single-crystal X-ray diffraction of **4p**.[13]

Table 1: Catalyst screening and optimization of the reaction conditions.[a]

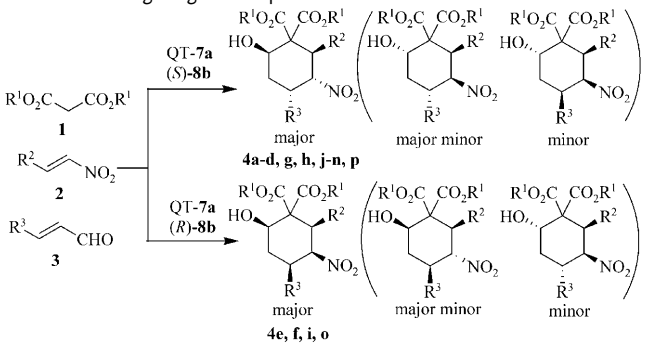




Entry	Catalysts	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	QT-**7a**+**8a**	toluene	38	4.5:2.5:1	>99
2	QT-**7a**+(*S*)-**8b**	toluene	54	3.1:1:1	>99
3	QT-**7a**+**8c**	toluene	<10	n.d.	n.d.
4[e]	QT-**7a**+**8d**	toluene	<10	n.d.	n.d.
5	QT-**7a**+**8e**	toluene	19	1.7:1:1	92
6	**7b**+(*S*)-**8b**	toluene	46	3.5:1.3:1	>99
7	**7c**+(*S*)-**8b**	toluene	39	2.2:1.6:1	>99
8	**7d**+(*S*)-**8b**	toluene	<10	n.d.	n.d.
9	**7e**+(*S*)-**8b**	toluene	42	3.3:2:1	>99
10[f]	QT-**7a**+(*S*)-**8b**	toluene	61	4.2:1:1	>99
11	QT-**7a**+(*S*)-**8b**	CH_2Cl_2	49	3.8:1.3:1	>99
12	QT-**7a**+(*S*)-**8b**	THF	54	2.5:2:1	>99

[a] Unless otherwise noted, all the reactions were performed with malonate **1a** (0.2 mmol), nitroalkene **2a** (0.4 mmol), *trans*-cinnamaldehyde **3a** (0.3 mmol), and a pair of organocatalysts (0.03 mmol of each) in solvent (1.0 mL) at 15°C. [b] Combined yield of the three isolated stereoisomers. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase (Chiralpak AD-H). [e] 20 mol% of QT-**7a**, and 10 mol% of **8d** were employed. [f] 2.0 equivalents of NaOAc was used as an additive.

Table 2: Investigating the scope of the cascade reaction. [a]

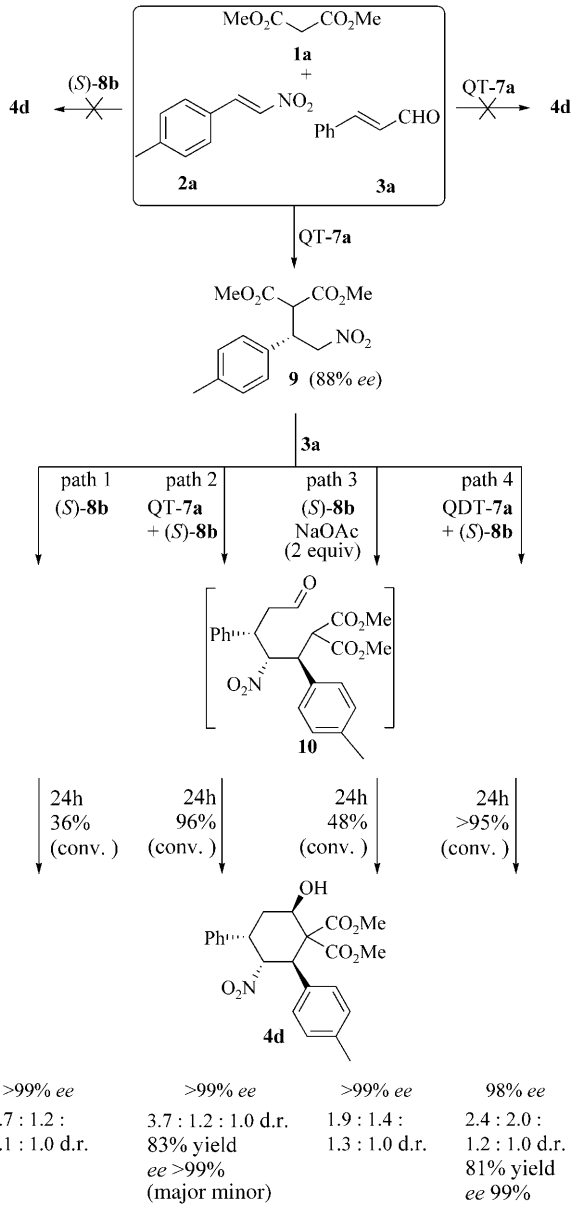


Entry	R^1	R^2	R^3	4	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me	2-Br C_6H_4	Ph	**4a**	63	4.1:1.3:1	98
2	Me	2-furyl	Ph	**4b**	87	3.1:2.9:1	>99 (>99)
3	Me	3-NO_2 C_6H_4	Ph	**4c**	58	2.1:1.5:1	96
4	Me	4-CH_3 C_6H_4	Ph	**4d**	61	4.2:1:1	>99
5[e]	Me	4-CH_3 C_6H_4	Ph	**4e**	52	6.7:2.5:1	n.d.[g]
6[e]	Me	4-CN C_6H_4	Ph	**4f**	47	3.4:1.7:1	>99
7	Me	4-Cl C_6H_4	Ph	**4g**	52	5.1:1.9:1	>99
8[f]	Me	*n*-C_6H_{13}	Ph	**4h**	26	6.7:1:0	n.d.[g]
9[e]	Me	Ph	Ph	**4i**	52	7.1:1.8:1	96
10	Me	Ph	Ph	**4j**	63	3.7:1.4:1	n.d.[g]
11	Me	Ph	2-CH_3 C_6H_4	**4k**	45	3.9:1.3:1	>99
12	Me	Ph	4-CH_3 C_6H_4	**4l**	54	4:1.3:1	>99
13	Me	Ph	4-CN C_6H_4	**4m**	67	2.8:2:1	>99 (>99)
14	Me	2-furyl	4-CN C_6H_4	**4n**	74	9.3:1.8:1	>99
15[e]	Me	2-furyl	CH_3	**4o**	69	3.2:1:0	88
16	Et	2-Br C_6H_4	Ph	**4p**	56	3.1:1:1	>99

[a] Unless otherwise noted, the reactions were performed with malonate **1** (0.2 mmol), nitroalkene **2** (0.4 mmol), α,β-unsaturated aldehyde **3** (0.3 mmol), QT-**7a** (0.03 mmol, 15 mol%), (*S*)-**8b** (0.03 mmol, 15 mol%) and NaOAc (0.4 mmol) in toluene (1.0 mL) at 15°C. [b] Combined yield of the three isolated stereoisomers. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis (Chiralpak AD-H and OD-H); where measurable, the *ee* value of the most abundant minor diastereomer is given in parentheses (for details, see Supporting Information). [e] QT-**7a** (0.03 mmol) and (*R*)-**8b** (0.03 mmol) were used as the catalyst pair. [f] **7c** (20 mol%) and (*S*)-**8b** (15 mol%) were used as the catalyst pair. [g] Products could not be separated by chiral HPLC.

Once the absolute configuration of the stereocenter that had been formed in the first catalytic cycle had been determined, the stereochemistry of compounds **4e**, **4f**, **4i**, and **4o** (from the cascade using catalyst pair QT-**7a** and (*R*)-**8b**) was established through ^{1}H NMR spectroscopy nuclear Overhauser effect (nOe) experiments and 2D NMR data. The two minor diastereomers were separated by flash chromatography or preparative thin layer chromatography; the relative configurations were also determined using the same method (for details, see Supporting Information).

Mechanistic studies on the reaction cascade were performed by carrying out a series of control experiments (Scheme 2). Initially, reactions were performed using **1a**, **2a**, and **3a** in the presence of either QT-**7a** or (*S*)-**8b** as catalyst.



Scheme 2. Probing the mechanism.

In the absence of either catalyst, the cyclohexane product **4d** was not observed in the reaction mixture. For example, omission of (*S*)-**8b** gave the major product **9**[10a] in 88% *ee*, whereas omission of QT-**7a** slowly afforded the conjugate addition product of **1a** to **3a**.[14] With an authentic sample of **9** in hand, the second stage of the cascade was then investigated. Four reactions of **9** in the presence of **3a** and one or more catalysts or reagents, were performed. In the presence of (*S*)-**8b** (15 mol%; Scheme 2, path 1), **4d** was formed in excellent

enantiomeric excess (> 99%, 24 h), but with only moderate diastereoselectivity at 36% conversion with respect to Michael adduct **9**. In the presence of (*S*)-**8b** (15 mol%) and QT-**7a** (15 mol%), **4d** was formed in good diastereoselectivity (3.7:1.2:1.0 d.r., 24 h), in over 99% *ee* (the *ee* of the most abundant minor diastereomer was also determined as > 99%; for details see Supporting Information), and at 96% conversion (Scheme 2, path 2). The fact that no intermediate aldehyde **10** could be detected in either pathway points to a rate-limiting iminium-catalyzed nitro-Michael addition followed by a rapid base-promoted aldol reaction. Furthermore, the significantly improved conversion in path 2 suggests that the iminium-catalyzed Michael addition is also base promoted, and thus that both organocatalysts are working cooperatively. In the presence of (*S*)-**8b** (15 mol%) and NaOAc (2 equiv), **4d** was formed in excellent enantiomeric excess (> 99%, 24 h) and in 48% conversion with respect to Michael adduct **9** (Scheme 2, path 3). The improved conversion of path 3 relative to path 1 again suggests that base promotion is beneficial to the iminium-catalyzed Michael addition. In contrast with path 2, a lower diastereoselectivity was obtained when (*S*)-**8b** (15 mol%) and QDT-**7a** (15 mol%; the pseudo enantiomer of QT-**7a**) were employed as the catalyst pair (Scheme 2, path 4). These results indicate that there are putative matched and mismatched combinations of reaction intermediates and catalyst pairs. The significantly higher diastereoselectivity observed in path 2 with respect to other paths reveals that the d.r. could be improved by judicious choice of chiral catalysts; the diastereoselectivity of the second catalytic cycle and the final step was effectively controlled by both QT-**7a** and (*S*)-**8b**. As the enantiomeric purity of intermediate **9** was 88%, the excellent *ee* values of the final products were clearly a result of amplification by the generation of diastereomeric products.[15]

In conclusion, we have presented a highly enantioselective route to polysubstituted cyclohexanes. The triple cascade reaction is efficient, affords high selectivities, and has a broad scope. Importantly, different stereoisomers are readily accessed in high enantiomeric excesses by changing the combination of catalysts used in the cascade reaction. In principle, the strategy we have described can be extended to other relay catalysis cascades. Future work within the group is aimed at expanding the AORC concept for the asymmetric synthesis of natural products, biologically significant therapeutics, and diversity-oriented library synthesis.

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