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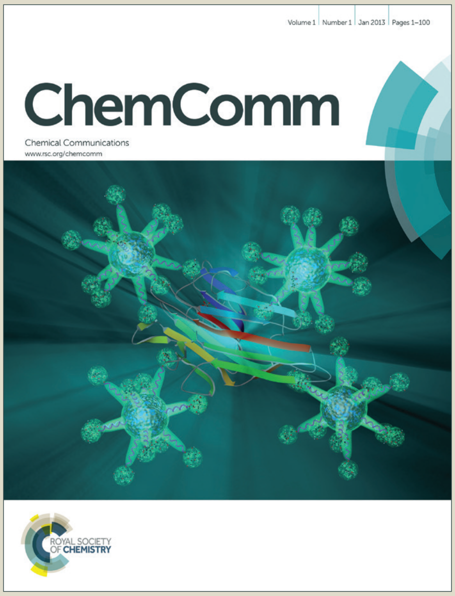

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Asymmetric synthesis of functionalized cyclohexanes bearing five stereocenters *via* a one-pot organocatalytic Michael/Michael/1,2-addition sequence

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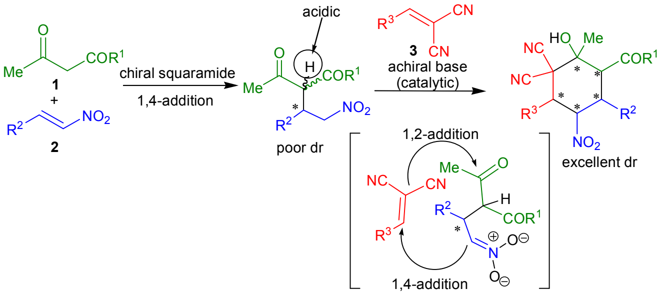
A highly stereoselective one-pot procedure involving an enantioselective Michael addition promoted by low loading of an amino-squaramide catalyst followed by an achiral base catalyzed domino Michael/Knoevenagel-type 1,2-addition sequence provides an efficient access to fully substituted cyclohexanes bearing five contiguous stereogenic centers in good yields (68-86%) and excellent stereoselectivities (>30:1 dr and 96-99% ee).

The asymmetric synthesis of complex molecular structures bearing several different functionalities is one of the major goals of modern synthetic organic chemistry as these structures exist in numerous pharmaceutical and natural products.[1] The stereocontrolled formation of such complex molecules with several adjacent stereogenic centers is regarded as a great challenge, because with an increase of the stereocenters the number of possible stereoisomers also increases exponentially. Recently, organocatalytic domino/cascade reactions have emerged as a powerful strategy for providing these complex molecular frameworks by employing simple and readily available precursors in a simple operational procedure.[2] The six-membered carobcyles, *i.e* cyclohexane derivatives bearing several adjacent stereogenic centers, are common structural features of many valuable natural products and synthetic bioactive compounds, thus leading to the rapid development of the synthetic strategies for obtaining these structures.[3]

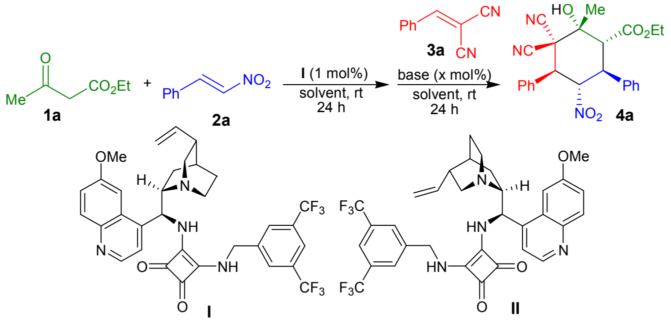
Most of the organocatalytic strategies for the stereoselective synthesis of functionalized cyclohexanes employ aliphatic aldehydes or α,β-unsaturated analogues as one of the substrates, which are activated by chiral amine catalysts *via* enamine or iminium ion formation.[4] The major problem associated with these transformations is the subsequent dehydration after the aldol reaction leading to the loss of two chiral centers. There are only a few reports on the asymmetric synthesis of fully functionalized cyclohexane derivatives. In 2010 Rodriguez et al.[5] observed that two molecules of a nitroalkene react in an organocascade asymmetric Michael/Michael/Henry sequence with 1,2-ketoamides to afford fully functionalized cyclohexane derivatives. This process was later on extended by Huang and co-workers[6] by using 1,2-ketoesters instead of 1,2-ketoamides in the presence of a copper complex of a chiral diamine. Chen and co-workers also succeeded to create as many as six stereogenic centers on spirocyclic oxindoles in one-pot tandem reactions promoted by a chiral secondary amine and achiral amines.[7] Recently, our group has found that one-pot reactions of β-ketoesters with two different electrophiles, *i.e.* nitroalkenes and enals, were facilitated by an amino-thiourea catalyst and a stoichiometric amount of an achiral base to afford fully functionalized cyclohexane derivatives in high stereoselectivities.[8]

It is highly desirable to extend the scope of these one-pot reactions beyond enals and nitroalkenes. Owing to the synthetic challenge of the controlled formation of many stereogenic centers and knowing the advantages associated with organocatalytic one-pot cascade reactions as well as the importance of the synthesis of cyclohexane derivatives, we herein disclose unprecedented one-pot organocatalytic Michael/Michael/Knoevenagel-type 1,2-addition reactions involving β-dicarbonyl compounds, nitroalkenes and α,α-dicyanoolefins. Employing sequential organocatalysis by using a low loading of a bifunctional amino-squaramide[9] and a catalytic amount of an achiral base virtually enantiopure cyclohexane derivatives bearing five stereogenic centers with two vicinal tetrasubstituted carbons could be obtained (Scheme 1). To achieve this we have used a chiral amino-squaramide (1 mol%) derived from quinine as catalyst to promote the Michael addition of the β-



Scheme 1. One-pot Michael/Michael/1,2-addition reaction for the asymmetric synthesis of functionalized cyclohexanes bearing five contiguous stereocenters.

Table 1. Optimizations of reaction conditions.[a]



entry	base (x mol%)	solvent	yield (%)[b]	ee (%)[c]
1	DBU (10)	CH_2Cl_2	53	98
2	DBN (10)	CH_2Cl_2	31	99
3	DABCO (10)	CH_2Cl_2	-	-
4	TEA (10)	CH_2Cl_2	35	89
5	TBD (10)	CH_2Cl_2	58	99
6	**TBD (20)**	**CH_2Cl_2**	**71**	**99**
7	TBD (30)	CH_2Cl_2	69	99
8	TBD (20)	$CHCl_3$	62	99
9	TBD (20)	Toluene	63	99
10	TBD (20)	THF	56	99
11	TBD (20)	CH_2Cl_2	70	96[d]

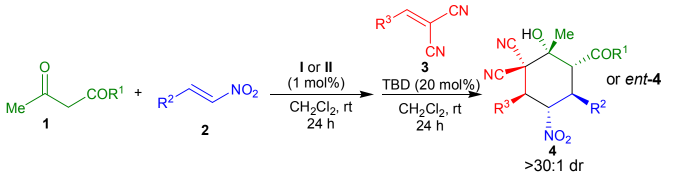
[a] Reaction conditions: 0.2 mmol of **1a**, 0.2 mmol of **2a**, 1 mol% of **I**, 0.24 mmol of **3a** and x mol% of base (0.1 M in solvent). [b] Yield of isolated **4a** after column chromatography. [c] Enantiomeric excess of the major diastereomer (>30:1 dr) determined by HPLC analysis on a chiral stationary phase. [d] ee value of *ent*-**4a**.

ketoester **1a** to β-nitrostyrene (**2a**) in dichloromethane and after 24 hours the α,α-dicyanoolefin **3a** was added followed by the addition of DBU (10 mol%) in dichloromethane.[10] Further stirring the reaction for 24 hours afforded the desired cyclohexane **4a** in 53% yield with 98% ee and >30:1 dr (Table 1, entry 1). The excellent diastereoselectivity of **4a** may be due to a dynamic kinetic resolution of the Michael adduct *via* base mediated deprotonation of the acidic proton followed by selective protonation (Scheme 1).[11] Further optimization of the reaction conditions by screening different bases and solvents showed that with 20 mol% of the guanidine base triazabicyclodecene (TBD) in dichloromethane provides good yields of 71% and excellent stereoselectivity (entry 6). The use of pseudo-enantiomeric catalyst **II** leads to the opposite enantiomer of the product in 70% yield and 96% ee with excellent diastereoselectivity (entry 11).

Under optimized reaction conditions, the substrate scope was evaluated at 0.5 mmol scale, which revealed that the use of various α,α-dicyanoolefins bearing electron withdrawing and electron-donating substituents provides a direct access to the corresponding cyclohexanes **4b-g** in very good yields (70-84%) and virtually complete enantioselectivity of 99% ee (Table 2, entry 2-7). A α,α-dicyanoolefin with a heteroaromatic group could be employed under the standard reaction conditions, which afforded the desired product **4h** in 80% yield and 99% ee (entry 8). However, a α,α-dicyanoolefin bearing a cyclohexyl group did not provide the desired cyclohexane under the optimized reaction conditions. Further screening of different nitroalkenes showed that various electron rich and electron deficient aromatic nitroalkenes as well as heteroaromatic nitroalkenes also worked well under this one-pot procedure to afford fully functionalized cyclohexanes **4i-n** in 68-75% and high stereoselectivities (>30:1 dr and 99% ee) (entry 9-14). An aliphatic nitroalkene was also tolerated to afford the corresponding adduct **4o** in 69% yield and excellent stereoselectivity (entry 15). Other β-ketoester and a β-diketone were also found to react efficiently to give good yields and excellent stereoselectivities of the corresponding products **4p** and **4q** (entry 16 and 17).

The synthesis of the enantiomers of the products is also possible by employing the pseudo-enantiomeric amino-squaramide catalyst **II**, which afforded the enantiomers of **4a, 4b, 4d, 4e, 4f, 4h, 4i**, and **4k** in very good yields (70-86%) and excellent stereoselectivities (>30:1 dr and 96-99% ee, entry 18-25).

Table 2. Substrate scope .[a]

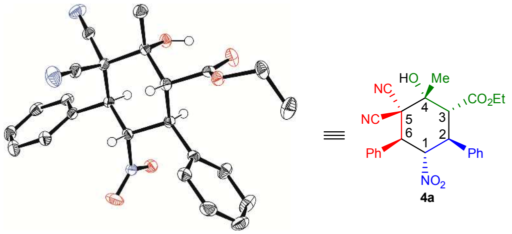


entry	R1	R2	R3	4/ *ent*-4	yield (%)[b]	ee (%)[c]
1	OEt	Ph	Ph	**4a**	72	99
2	OEt	Ph	4-FC_6H_4	**4b**	76	99
3	OEt	Ph	4-ClC_6H_4	**4c**	72	99
4	OEt	Ph	3-ClC_6H_4	**4d**	74	99
5	OEt	Ph	2-ClC_6H_4	**4e**	70	99
6	OEt	Ph	4-MeC_6H_4	**4f**	84	99
7	OEt	Ph	4-$MeOC_6H_4$	**4g**	80	99
8	OEt	Ph	2-Thienyl	**4h**	80	99
9	OEt	4-FC_6H_4	Ph	**4i**	74	99
10	OEt	4-ClC_6H_4	Ph	**4j**	73	99
11	OEt	4-MeC_6H_4	Ph	**4k**	68	99
12	OEt	3-$MeOC_6H_4$	Ph	**4l**	70	98
13	OEt	2-Furanyl	Ph	**4m**	75	99
14	OEt	2-Thienyl	Ph	**4n**	68	99
15	OEt	Cyclohexyl	Ph	**4o**	69	99
16	OMe	Ph	Ph	**4p**	69	99
17	Me	Ph	Ph	**4q**	71	99
18	OEt	Ph	Ph	***ent*-4a**	70	96
19	OEt	Ph	4-FC_6H_4	***ent*-4b**	77	97
20	OEt	Ph	3-ClC_6H_4	***ent*-4d**	75	98
21	OEt	Ph	2-ClC_6H_4	***ent*-4e**	77	98
22	OEt	Ph	4-MeC_6H_4	***ent*-4f**	86	96
23	OEt	Ph	2-Thienyl	***ent*-4h**	81	99
24	OEt	4-FC_6H_4	Ph	***ent*-4i**	75	98
25	OEt	4-MeC_6H_4	Ph	***ent*-4k**	72	99

[a] Reaction conditions: 0.5 mmol of **1**, 0.5 mmol of **2**, 1 mol% of **I** (entry 1-17) or **II** (entry 18-25), 0.6 mmol of **3** and 20 mol% of TBD (0.1 M in CH_2Cl_2). [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess of the major diastereomer determined by HPLC analysis on a chiral stationary phase.

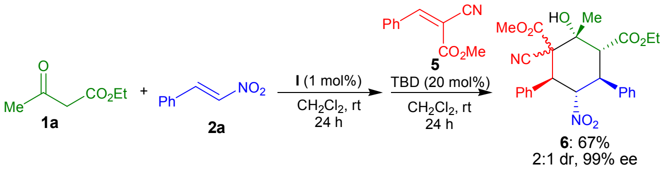
The absolute configuration of the products **4a-q** synthesized by squaramide **I** was assigned as 1*S*,2*S*,3*R*,4*R* and 6*S* on the basis of a X-ray crystallographic analysis of **4a** (Figure 1).[12]

Further we have tried to extend the substrate scope of this one-pot methodology by employing olefin **5**, which gave the adduct **6** bearing six contiguous stereocenters in 67% yield and 99% ee, albeit low diastereoselectivity (Scheme 2).



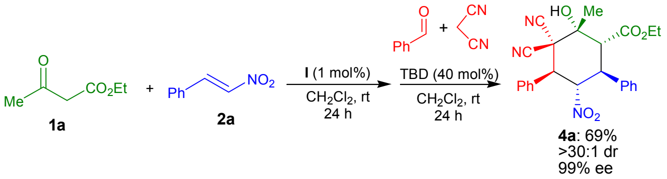
4a

Figure 1. X-ray structure of **4a** [Cu-Kα radiation (λ=1.54178Å), T = 120K, Flack parameter: χ = 0.025(115)].



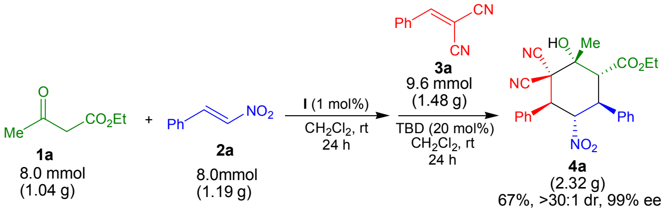
Scheme 2. One-pot organocatalytic Michael/Michael/1,2-addition reaction between **1a**, **2a** and **5**.

A one-pot reaction involving the *in-situ* formation of the α,α-dicyanoolefin was successfully performed, which involves the addition of benzaldehyde and malononitrile followed by TBD (40 mol%) to the initially formed Michael adduct of **1a** with **2a** catalyzed by **I** (Scheme 3). The corresponding product **4a** was obtained in 69% yield, >30:1 dr and 99% ee through this one-pot Michael/Knoevenagel condensation/Michael/1,2-addition sequence.



Scheme 3. One-pot stereoselective organocatalytic Michael/Knoevenagel condensation/Michael/1,2-addition reaction.

A successful gram-scale reaction between **1a**, **2a** and **3a** to form **4a** showed that the reaction efficiency was maintained, thus highlighting the practical and preparative utility of this one-pot process (Scheme 4).



Scheme 4. Gram-scale one-pot stereoselective organocatalytic Michael/Michael/1,2- addition reaction.

In conclusion, we have demonstrated the application of a one-pot sequential organocatalysis for the asymmetric synthesis of functionalized cyclohexanes. A low loading of a chiral organocatalyst and a low cost commercially available achiral base afford a series of highly substituted cyclohexane derivatives *via* one-pot Michael/Michael/1,2-addition reactions in very good yields and excellent stereoselectivities. The enantiomers of the multifunctionalized cyclohexanes are easily accessible by employing a pseudo-enantiomeric amino-squaramide catalyst. This method can be scaled up without any loss of reaction efficiency

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