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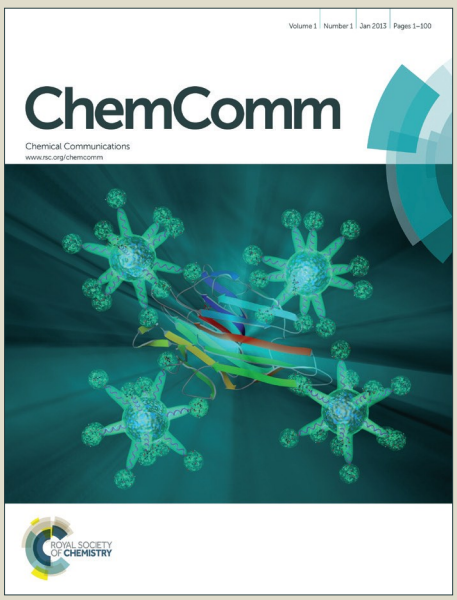

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Asymmetric synthesis of cyclopentanes bearing four contiguous stereocenters *via* an NHC-catalyzed Michael/Michael/esterification domino reaction†

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An NHC-catalyzed Michael/Michael/esterification domino reaction *via* homoenolate/enolate intermediates for the asymmetric synthesis of tetrasubstituted cyclopentanes bearing four contiguous stereocenters is described. A variety of α,β-unsaturated aldehydes and 2-nitroallylic acetates react well with good domino yields and high stereoselectivities.

Cyclopentane motifs are privileged scaffolds present as characteristic structural features in a large number of bioactive natural products and pharmaceuticals such as for instance aristeromycin,[1] travoprost,[2] pactamycin[3] and peramivir[4] (Fig. 1). However, to develop direct and efficient catalytic methods for the stereocontrolled construction of multi-substituted cyclopentanes is still challenging for organic chemists.[5]

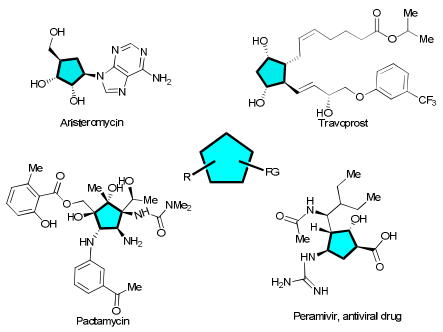

Fig.1 Representative natural products and pharmaceuticals bearing a cyclopentane core.

Nitroalkenes are among the most useful Michael acceptors due to their versatile reactivity and their inherent capacity to undergo further synthetic transformations of the nitro function into other functional groups.[6] NHC-catalyzed cascade reactions have emerged as a powerful tool to construct C-C bonds in organic synthesis[7] and NHC-catalyzed reactions with nitroalkenes gained quite some interest in recent years.[8] The first NHC-catalyzed homoenolate reaction of enals with nitroalkenes to afford *anti* δ-nitroesters was reported by Nair and co-workers.[9a] Later the groups of Liu and Rovis reported complementary asymmetric versions of this reaction affording *anti* and *syn δ*-nitroesters, respectively.[9b-d] Very recently, Wang and co-workers have also developed an NHC-catalyzed reaction of enals with nitroalkenes to prepare enantioenriched dihydrocoumarins.[8i]

Nitroallylic acetates served as versatile dielectrophiles to assemble relatively complex molecules in a domino fashion.[10] Seebach and co-workers developed a [3+3] carbocyclization reaction of 2-nitroallylic acetates and enamines to form bicyclic skeletons with multiple stereocenters using the chiral auxiliary concept under stoichiometric conditions.[10a] An organocatalytic domino reaction of 2-nitroallylic acetates had not been reported until 2009. Tang and Li *et al.* developed a pyrrolidine-thiourea catalyzed tandem reaction of 2-nitroallylic acetates and cyclic ketones to construct bicyclic [3.3.1] skeletons with four or five stereocenters in a single operation.[10b] However, to the best of our knowledge, an NHC-catalyzed cascade reaction employing 2-nitroallylic acetates has not been reported yet. Herein, we describe such an NHC organocatalyzed [3+2]-cycloaddition reaction of enals with *(E)*-2-nitroallylic acetates to afford enantioenriched tetrasubstituted cyclopentanes with four contiguous stereocenters featuring a nitro and an ester group, which can be used for further transformations.

Initially we investigated the reaction of cinnamaldehyde (**1a**) and (*E*)-2-nitroallylic acetate **2a** as model substrates catalyzed by the NHC catalysts derived from the pre-catalysts **A-F** in THF/EtOH using one equivalent of NaOAc as a base. The aminoindanol-based

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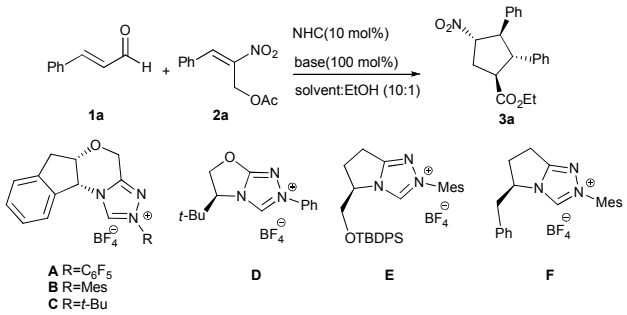
triazolium pre-catalyst **B** provided the desired cyclopentane product **3a** in 30% yield and 78:22 e.r., albeit with a low diastereoselectivity (d.r. 3:1).

Table 1 Optimization of the reaction conditions[a]

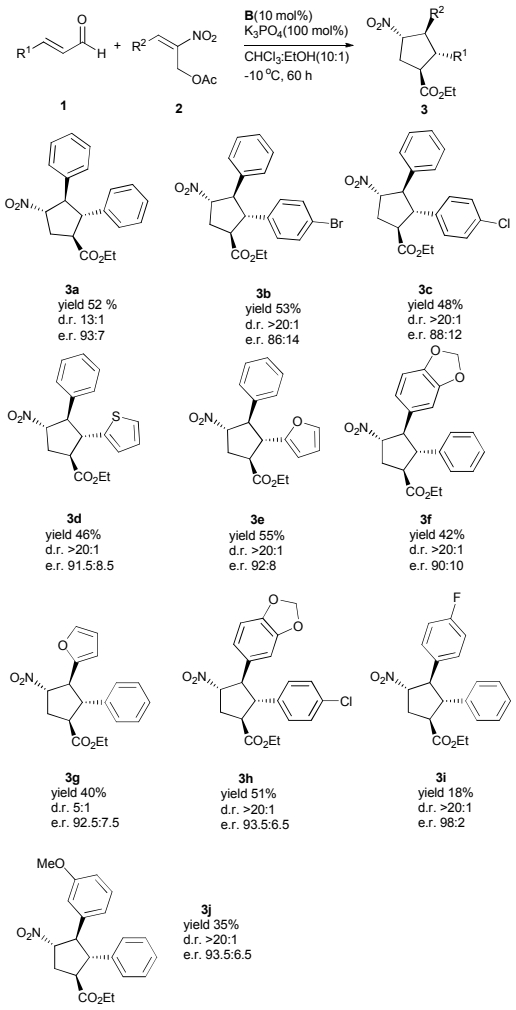


Entry	Cat.	Solvent	Base	Yield (%)[b]	d.r[c]	e.r.[d]
1	**A**	THF	NaOAc	<5	-	-
2	**B**	THF	NaOAc	30	3:1	78:22
3	**C**	THF	NaOAc	n.r	-	-
4	**D**	THF	NaOAc	n.r	-	-
5	**E**	THF	NaOAc	18	6.2:1	63:37
6	**F**	THF	NaOAc	26	8:1	40:60
7	**B**	$CHCl_3$	NaOAc	45	3.6:1	85:15
8	**B**	DME	NaOAc	36	1.7:1	72:28
9	**B**	CCl_4	NaOAc	56	1.5:1	82:18
10	**B**	CH_2Cl_2	NaOAc	30	4.3:1	75:25
11	**B**	TBME	NaOAc	30	1.6:1	78:22
12	**B**	Toluene	NaOAc	42	1.2:1	81:19
13	**B**	$CHCl_3$	NEt_3	45	3.3:1	71:29
14	**B**	$CHCl_3$	DIPEA	40	3:1	75:25
15	**B**	$CHCl_3$	DABCO	26	5:1	70:30
16	**B**	$CHCl_3$	TMEDA	32	3.7:1	69:31
17	**B**	$CHCl_3$	CsOAc	30	1.8:1	68:32
18	**B**	$CHCl_3$	LiOAc	36	2.6:1	74:26
19[e]	**B**	$CHCl_3$	Cs_2CO_3	20	1.3:1	87:13
20[e]	**B**	$CHCl_3$	K_3PO_4	49	7.8:1	91:9
21[f]	**B**	$CHCl_3$	K_3PO_4	40	>20:1	93:7
22[g]	**B**	$CHCl_3$	K_3PO_4	52	16:1	93:7

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), NHC catalyst (10 mol%), base (1.0 equiv.), 24 h at rt. [b] Yield of isolated compound **3a**. [c] d.r. determined by ^{1}H NMR. [d] The e.r. values were determined by HPLC on a chiral stationary phase. [e] The reaction was carried out at −5 °C, 48 h. [f] The reaction was carried out at −15 °C, 96 h. [g] The reaction was carried out at −10 °C, 60 h.

After the screening of the solvents, $CHCl_3$ turned out to be the best solvent, affording **3a** in a good domino yield of 45%, a d.r. of 3.6:1 and an e.r. of 85:15 (entry 7). The reaction proceeded well with different bases (entries 13-20). Using strong organic bases such as DBU or DMAP resulted in complex mixtures without any starting material remained and no desired product could be detected. We also screened some Lewis acid additives such as $Mg(OtBu)_2$, $Ti(OiPr)_4$ and $Sc(OTf)_3$ and also $MgSO_4$ as well as 4Å molecular sieves, but no better result was obtained. Lowering the reaction temperature improved the d.r. and e.r., but the reaction time was extended. The reaction proceeded well at −5 °C (49% yield, 7.8:1 d.r, 91:9 e.r) in 48 h, −15 °C (40% yield, >20:1 d.r., 93:7 e.r.) in 96 h with starting material left and −10 °C (52% yield, 16:1 d.r., 93:7 e.r.) in 60 h. Lowering the loading of the base gave inferior results. Finally, we chose pre-catalyst **B**, $CHCl_3$:EtOH (10:1), K_3PO_4 (100 mol%) at −10 °C as the optimized condition for our reaction (entry 22).

With the optimized conditions in hand, we next evaluated the substrate scope with respect to the enals and 2-nitroallylic acetates. With different substituted cinnamaldehydes, heterocyclic enals or *(E)*-2-nitroallylic acetates, the reaction proceeded well, affording the desired products in good domino yields (18-55%) and enantiomeric ratios (86:14-98:2).



Scheme 1 Substrate Scope. All reactions were performed on a 0.5 mmol scale. The yields of the isolated products are after column chromatography. The diastereomeric ratios were determined by ^{1}H NMR spectroscopy and the e.r. values by HPLC on a chiral stationary phase.

The absolute configuration was unambiguously determined by X-ray crystal structure analysis of compound **3h** and all other cyclopentane products were assigned by analogy (Fig. 2).

A plausible mechanism for the NHC-catalyzed [3+2] Michael/Michael/esterification cascade is shown in Scheme 2. The reaction proceeds via an extended Breslow intermediate, which as a homoenolate **I** undergoes a first Michael addition to the nitroallylic

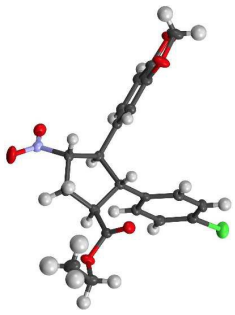
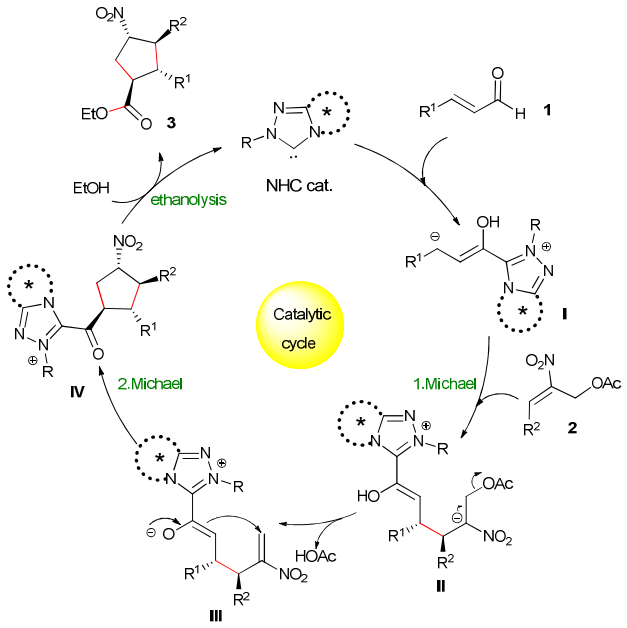


Fig. 2 Absolute configuration of **3h** determined by X-ray structural analysis.[11]

acetates **2**, followed by the elimination of the acetyl group from the adduct **II** to generate the second Michael acceptor intermediate **III**for the intramolecular Michael addition. The resulting acylazolium intermediate **IV** undergoes an ethanolysis with external ethanol to afford the cyclopentane esters **3** and returns the NHC catalyst for further cycles.



Scheme 2 Proposed catalytic cycle.

In conclusion, we have developed a concise protocol for the NHC-catalyzed direct construction of functionalized cyclopetanes bearing four contiguous stereocenters in one single operation with good domino yields and stereoselectivities. A range of functional groups and substituents are tolerated by variation of the enal and nitroallylic acetate substrates. In the novel one-pot protocol two C-C bonds via Michael addition and one C-O bond through a terminating ethanolysis step are formed.

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