Enantiopure cycloalkane fused tetrahydropyrans through domino Michael–ketalizations with organocatalysis†

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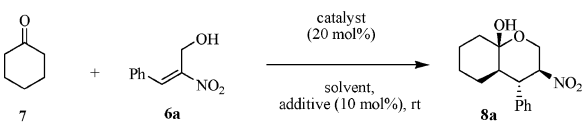
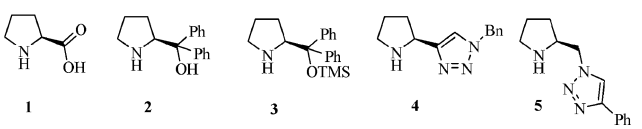
Enantiopure cyclohexane fused tetrahydropyrans have been synthesized using domino Michael–ketalization under organocatalysis.

The conjugate addition of nucleophiles in an enantioselective fashion is a challenging process.[1] This decade has seen an unprecedented focus on the development and exploitation of organocatalysts for achieving this transformation.[2] The seminal works of List *et al.*,[3] Macmillan *et al.*,[4] and Jorgensen *et al.*[5] have inspired researchers to develop newer organocatalysts not only for Michael type reactions but also for aldol reactions and domino processes[6] to synthesize optically pure scaffolds which were hitherto very difficult to access. The cyclic five membered chiral secondary amine structure (pyrrolidine scaffold) has attained the status of being 'privileged' owing to its outstanding performance in organocatalysis.[7] Even though other classes of chiral organocatalysts have proven to be successful, more modifications were attempted while keeping the pyrrolidine ring intact *viz*. biaryl pyrrolidinol (more popularly called a CBS catalyst),[8] trifluoroamido-pyrrolidine,[9] imidazole linked (ionic liquid kind) pyrrolidine,[10] tetrazole linked pyrrolidine,[11] bifunctional pyrrolidine amides,[12] protonated proline-hydrazides,[13] proline diamine,[14] peptide–pyrrolidine,[15] polystyrene-supported pyrrolidine[16] and others.[17] More recently we[18] and Luo *et al.*[19] have efficiently incorporated 'Click' chemistry to synthesize pyrrolidine-triazole organocatalysts to perform aldol and Michael reactions. Our own interest in enantiopure synthesis of substituted tetrahydropyrans has prompted us to adapt a recently explored intramolecular 'oxa-Michael' reaction developed by Evans and Prunet.[20,21] We envisioned a more powerful procedure to synthesize diverse skeletons on this backbone encompassing the synthetically recognized components of atom economy,[22] Click chemistry[23] and 'domino reactions'[24] from two achiral reactants to an enantiopure fused tetrahydropyran with four chiral centres. Our strategy has been to depend on the achievement of complete stereocontrol during the Michael reaction of a 2,3-disubstituted nitro olefin which triggers the second domino ketalization to achieve tetrahydropyranol **8a–h** in an intramolecular fashion.

Towards this endeavour, in the first instance the adduct **6a** (prepared by an atom economical, organocatalyzed Baylis–Hillman reaction between nitro olefin and formaldehyde[25]) was subjected to a domino Michael–ketalization reaction with cyclohexanone in the presence of 20 mol% of L-proline to successfully realize the fused cyclohexyl pyran derivative **8a** in 75% yield (entry 1, Table 1). The enantiopurity was disappointing though. Not discouraged, we screened other pyrrolidine-based catalysts including one we have prepared in our lab (**2** to **5**) and the data pertaining to this study are tabulated (Table 1). We were pleased to note that the pyrrolidine-triazole **5** gave a satisfactory yield of the product and high enantiopurity (97% ee, 62% yield, entry 5, Table 1). Giving a halt at this stage for further improvements in yields, we rather focused on 'diversity' of substrates so that useful scaffolds are accessed (Table 2 and Scheme 1). Based on this optimized protocol,‡ a series of nitro alkenols were prepared using a standard Baylis–Hillman reaction (entries 1–8, **6a** to

Table 1 Catalyst and solvent screening for the stereo- and enantioselective domino reaction





Entry	Catalyst	Solvent[c,d]	Additive	*t*/d	Yield [%][a]	ee [%][b]
1	**1**	DMSO	—	1	75	25
2	**2**	Neat	TFA	15	0	—
3	**3**	Neat	TFA	15	0	—
4	**4**	Neat	TFA	3	50	40
5	**5**	Neat	TFA	7	62	97
6	**5**	MeOH	TFA	10	37	95
7	**5**	*i*PrOH	TFA	10	39	92
8	**5**	Toluene	TFA	14	42	93
9	**5**	CH_3CN	TFA	14	43	89
10	**5**	DMF	TFA	8	44	96
11	**5**	DMSO	TFA	8	43	95

[a] Isolated yield of product after column chromatography. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Conditions for neat reactions: 0.27 mmol **6a**, 10 equiv. cyclohexanone **7**, 20 mol% catalyst **1** at rt. [d] Conditions for solvent reactions: 0.27 mmol **6a**, 6 equiv. cyclohexanone **7**, 20 mol% catalyst **2**, **3**, **4** and **5**, 10 mol% TFA at rt in 0.5 ml solvent.

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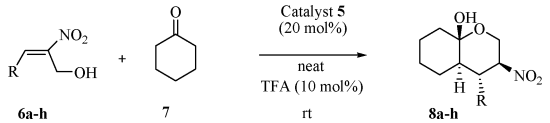
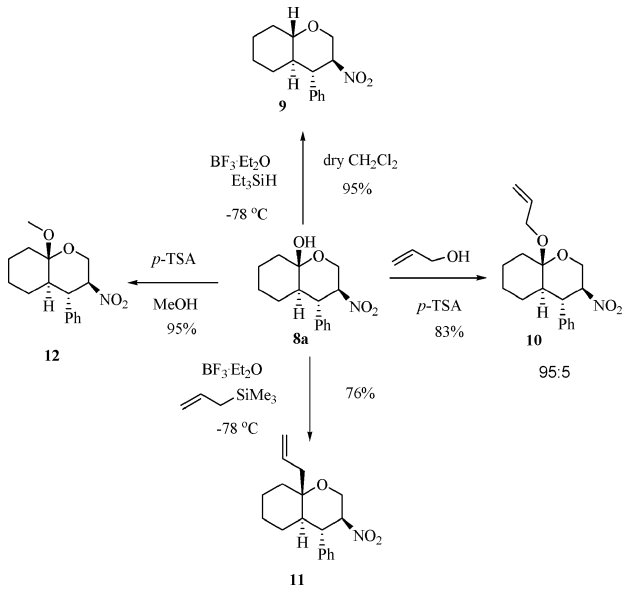
Table 2 Catalytic asymmetric Michael–ketalization reaction of cyclohexanone with various hydroxymethyl nitro olefins



Entry	6	Product	t/d	Yield [%][a]	ee [%][b,c]
1	**6a**	R = Ph, **8a**	7	62	97
2	**6b**	R = *p*-MeO-Ph, **8b**	12	53	99
3	**6c**	R = *p*-Br-Ph, **8c**	10	60	91
4	**6d**	R = *p*-Me-Ph, **8d**	12	41	94
5	**6e**	R = *p*-CN-Ph, **8e**	8	45	88
6	**6f**	R = *m*-F-Ph, **8f**	8	57	89
7	**6g**	R = *m*-NO_2-Ph, **8g**	8	59	92
8	**6h**	R = 2-Furyl, **8h**	10	45	98

[a] Isolated yield of product after column chromatography. [b] Determined by HPLC analysis on a chiral stationary phase. [c] The stereochemistry depicted is relative.



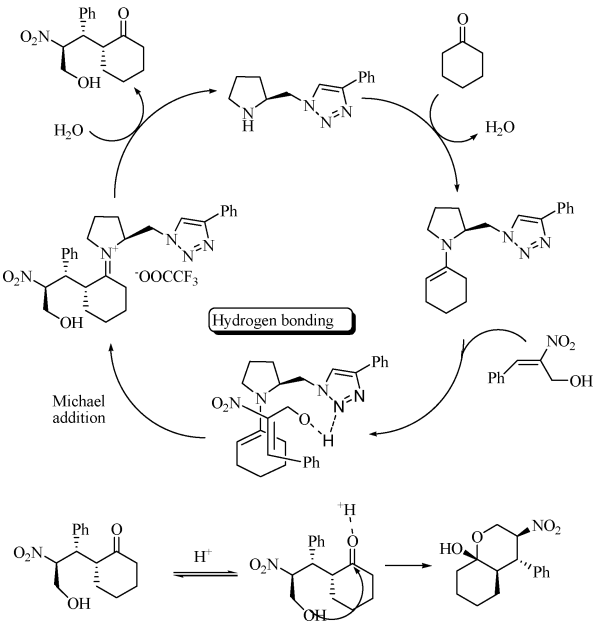
Scheme 1 Transformations of domino product.

6h, Table 2) and the domino Michael–ketalization was attempted on unsubstituted cyclohexanone **7**.

In the presence of 20 mol% of catalyst **5**, 10 mol% of TFA and solvent free conditions, excellent results were obtained in terms of diastereocontrol and enantioselectivity. The products, namely, tetrasubstituted tetrahydropyranol **8** with four contiguous stereocenters were thoroughly characterized using NMR and mass spectroscopy for chemical identity. The relative stereochemistry in the case of **8a** was determined by NOE experiments.

Further **8a** was subjected to high yielding chemical transformations to obtain diverse new chemical entities. For instance, treatment of **8a** with $BF_3{\cdot}OEt_2$ and allyl trimethylsilane at −78 °C furnished **11** having a quaternary allyl group at the ring junction, whereas reduction with triethylsilane provided **9**. Alkylations of the angular ketal to **10** and **12** were also uneventful (Scheme 1).

Even though, no thorough mechanistic insight studies were attempted, a plausible pathway based on literature precedence



Scheme 2 Proposed catalytic cycle of the domino Michael–ketalization reaction.

is drawn, which explains the stereocontrol and specificity of the reaction (Scheme 2).

The highly enantioselective domino Michael–ketalization reaction reported here constitutes a method to build tetrahydropyrans with four contiguous chiral centers fused onto a cycloalkane. The reaction, being catalyzed by a trace amount of TFA, and well-assisted by the pyrrolidine-triazole framework has provided scaffolds hitherto not accessible in optically pure form by other means.[26]

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Notes and references

‡ Typical procedure (entry 1, Table 2): hydroxymethyl nitrostyrene **6a** (50 mg, 0.27 mmol) and catalyst **5** (12 mg, 0.054 mmol) were mixed with cyclohexanone **7** (0.55 ml, 5.5 mmol) in the presence of TFA (0.027 mmol) at room temperature. The homogeneous reaction mixture was stirred at room temperature for 7 days. The reaction mixture was directly loaded onto silica gel column to afford the Michael adduct **8a** (47 mg, 62%) as a white solid. $[\alpha]_D^{27}$ +20.0 (*c* 0.25 M in $CHCl_3$), 97% ee [by HPLC on a chiral phase Eurocel column λ = 225 nm, *i*PrOH–hexane (10 : 90), 1 ml min^{-1}; t_R = 5.8 min (minor), t_R = 6.8 min (major)].

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