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Enantioselective organocatalytic domino synthesis of tetrahydropyridin-2-ols†

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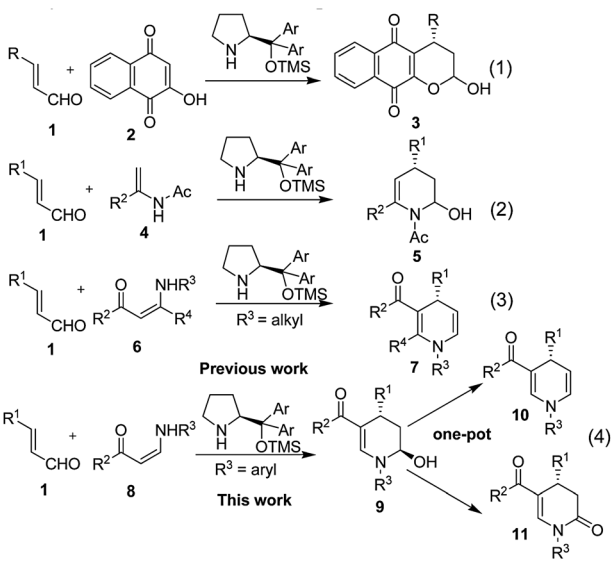
The asymmetric synthesis of tetrahydropyridin-2-ols from enals and enaminones is described. The organocatalytic domino reaction involves a Michael addition–hemiaminalization sequence using the Jørgensen–Hayashi catalyst. Dehydration or oxidation leads to the corresponding 1,4-dihydro-pyridines or 3,4-dihydro-pyridin-2-ones in a one-pot fashion.

Among the various subareas of the rapidly growing field of organocatalysis, Lewis base catalysis employing secondary amines, such as proline, diarylprolinol silyl ethers or imidazolidinones, turned out to be a powerful tool for the asymmetric synthesis of a great variety of highly enantioenriched organic compounds.[1] In particular, the intermediate iminium salts formed from α,β-unsaturated aldehydes and enantiopure secondary amines constitute a prominent activation mode enabling asymmetric Michael additions.[2] As a consequence, such conjugate additions are often used as the first stereogenic step in organocatalytic domino reactions leading to more complex structures.[3] Epoxides,[4] dihydropyridines (DHPs),[5] oxazolidinones,[6] cyclohexanes,[7] tetrahydropyridines (THPs)[8] and dihydrobenzofurans,[9] *etc.*, to name a few, are typical examples known to be easily accessed *via* iminium activation-based enantioselective domino reactions.

1,4,5,6-Tetrahydropyridines (THPs) are important heterocyclic structures and valuable building blocks in organic synthesis, which can be easily converted to the corresponding piperidines, DHPs and pyridines *via* simple reduction or oxidation reactions. More versatile transformations were possible when conventional functional groups such as hydroxyl, allyl, *etc.* are present.[10,11] The synthesis of THPs *via* direct asymmetric catalysis is of particular significance since it provides rapid access to enantioenriched THPs as well as to many other derivatives such as 1,4-DHPs[12] and piperidines. In previous studies, the iminium activation mode *via* secondary amines such as diarylprolinol silyl ethers in the reaction of enals with 1,3-dinucleophiles turned out to be particularly practical in the synthesis of heterocycles. For example, naphthoquinone fused 3,4-dihydropyran-2-ols **3** could be efficiently assembled using 2-hydroxy-1,4-naphthoquinone **2** as a C/O 1,3-dinucleophile in the domino reaction with enals **1** (eqn (1), Scheme 1).[13] On the other hand, the enamides **4** as analogous C/N-1,3-dinucleophiles have been successfully employed in similar transformations to produce the corresponding enantioenriched *N*-acyl THPs **5** (eqn (2), Scheme 1).[11] Recently, Kanger and co-workers reported their results on the direct enantioselective synthesis of 1,4-DHPs **7** *via* the reaction of *N*-alkyl enamines of type **6** and enals in the presence of a diarylprolinol silyl ether catalyst (eqn (3), Scheme 1).[14]

To the best of our knowledge, the asymmetric synthesis of tetrahydropyridin-2-ols **9** bearing *N*-aryl, 5-aroyl and 2-hydroxyl substituents and use of enaminones as C/N dinucleophiles in the reaction with enals have not been reported so far. We now wish to describe our results on the secondary amine-catalyzed diastereo- and enantioselective synthesis of tetrahydropyridin-2-ols **9** *via* domino reactions of enals **1** and *N*-aryl enaminones **8**. The products could be used as precursors for the synthesis of related



Scheme 1 Amine catalyzed enantioselective syntheses *via* domino Michael–hemiacetalization and hemiaminalization reactions.

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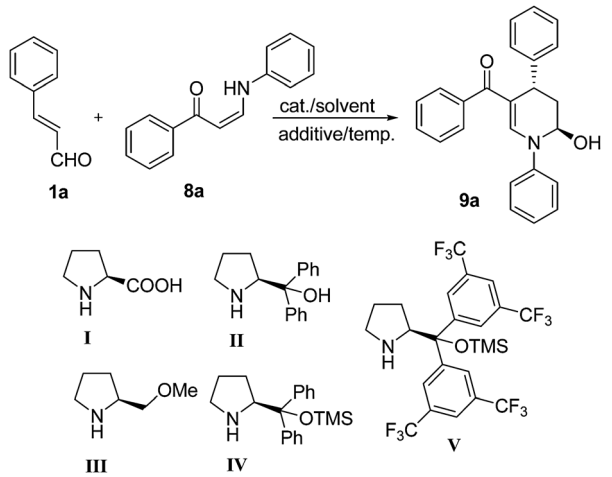
† Electronic supplementary information (ESI) available: Full experimental procedure, characterization data of all products, ^{1}H, ^{13}C NMR spectra, HPLC chromatograms as well as crystal structure of **9a**. CCDC 893719. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc35644a

heterocyclic derivatives, such as 1,4-DHPs and 3,4-dihydropyridin-2(1*H*)-ones (eqn (4), Scheme 1).

As an initial attempt, the reaction of cinnamaldehyde (**1a**) and enaminone (**8a**) was selected as a model to probe the reaction. Different chiral amine catalysts **I–V** were first screened in this model reaction by employing chloroform as solvent at rt. After stirring at rt for 4 days in the presence of catalysts **I–V** with a 20 mol% loading, respectively, it was found that **IV** was the best amine catalyst for the formation of the target product **9a** in terms of yield as well as enantioselectivity. Either lower values were obtained or no reaction took place in the entries using **I–III** and **V** as catalysts (entries 1–5, Table 1). Other parameters of the reaction were then investigated by using **IV** as catalyst (entries 5–22, Table 1). The best results were obtained when EtOAc or mixture of EtOAc–Et_2O (2/1 mL) was employed at 0 °C and with 10 mol% benzoic acid as an additive (entries 16 and 19, Table 1).

During the examination on the application scope we firstly attempted to employ the mixed solvent system (entry 19, Table 1) considering both the product yield and enantioselectivity. When performed in the scale of 0.6 mmol, product **9a** could be produced with good results (entry 1, Table 2). However, lower enantioselectivity was obtained when different substrates such as methoxyphenyl substituted enaminones or enals were used. We then employed EtOAc as the sole solvent in the new entries using different substrates. Typical results are given in Table 2. Good tolerance on substrates was demonstrated by variation of the enaminones (R^2 and R^3) as well as enals (R^1). An electron donating group in the benzoyl fragment (R^2) and the *p*-cyclohexyl group in the aryl amine fragment (R^3) of the enaminones were favorable in this protocol providing the corresponding products with excellent enantioselectivity (**9b–9f**), while an electron withdrawing group in the benzoyl fragment of **9** was not favorable. It is notable that a 4-fluoro functionalized enaminone gave a better er value in mixed EtOAc–Et_2O than in pure EtOAc (**9k**).

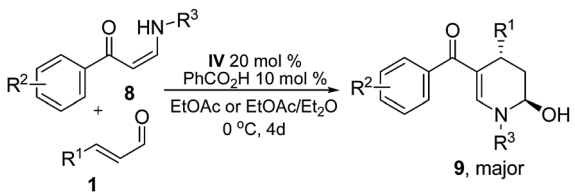
Table 1 Optimization on reaction conditions[a]



Entry	Catal.	*T* (°C)	Solvent	Additive	Yield[b] (%)	dr[c]	er[d] (%)
1	**I**	rt	$CHCl_3$	—	—	—	—
2	**II**	rt	$CHCl_3$	—	—	—	—
3	**III**	rt	$CHCl_3$	—	26	3 : 1	59 : 41
4	**IV**	rt	$CHCl_3$	—	55	2.3 : 1	85 : 15
5	**V**	rt	$CHCl_3$	—	Trace	—	—
6	**IV**	rt	CH_2Cl_2	—	33	2.5 : 1	84 : 16
7	**IV**	rt	Toluene	—	39	5 : 1	88 : 12
8	**IV**	rt	Et_2O	—	56	6.5 : 1	86 : 14
9	**IV**	rt	MeOH	—	—	—	—
10	**IV**	rt	THF	—	20	> 10 : 1	85 : 15
11	**IV**	rt	MeCN	—	28	3 : 1	67 : 33
12	**IV**	rt	EtOAc	—	22	> 10 : 1	91 : 9
13[e]	**IV**	rt	EtOAc	$PhCO_2H$	32	10 : 1	89 : 11
14	**IV**	rt	EtOAc	$PhCO_2H$	59	5 : 1	90 : 10
15[f]	**IV**	rt	EtOAc	$PhCO_2H$	61	5.5 : 1	77 : 23
16	**IV**	0	EtOAc	$PhCO_2H$	38	3 : 1	99 : 1
17	**IV**	0	Et_2O	$PhCO_2H$	59	5 : 1	937
18	**IV**	0	Et_2O–EtOAc (4 : 1)	$PhCO_2H$	64	5.8 : 1	96 : 4
19	**IV**	0	Et_2O–EtOAc (2 : 1)	$PhCO_2H$	75	5.7 : 1	97 : 3
20	**IV**	0	Et_2O–EtOAc (1 : 4)	$PhCO_2H$	43	3.6 : 1	89 : 11
21[g]	**IV**	0	Et_2O–EtOAc (2 : 1)	$PhCO_2H$	38	7 : 1	89 : 11
22[h]	**IV**	0	Et_2O–EtOAc (2 : 1)	$PhCO_2H$	52	5.2 : 1	97 : 3

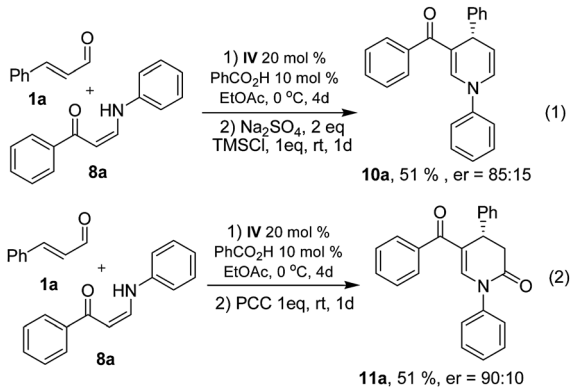
[a] General reactions conditions: **1a** (0.45 mmol), **8a** (0.3 mmol), and chiral amine catalyst (0.06 mmol) in 3 mL solvent, stirred at rt for 4 days. [b] Yield of isolated product. [c] Diastereomeric ratios (dr) was calculated based on the masses of the isolated diastereomers. [d] Measured by HPLC on a chiral stationary phase. [e] 5 mol% $PhCO_2H$. [f] 15 mol% $PhCO_2H$. [g] 10 mol% catalyst IV. [h] 15 mol% catalyst IV.

Table 2 Scope of the tetrahydropyridin-2-ol synthesis[a]



9	R^1	R^2	R^3	Yield[b] (%)	dr[c]	er[d]
9a[e]	Ph	H	Ph	60	6.0 : 1	> 99 : 1
9b	Ph	4-MeO	Ph	57	3.4 : 1	96 : 4
9c	4-ClC_6H_4	4-MeO	4-ClC_6H_4	60	4.1 : 1	96 : 4
9d	4-$MeOC_6H_4$	H	4-*c*-HexylC_6H_4[f]	20	4.1 : 1	98 : 2
9e	Ph	4-MeO	4-MeC_6H_4	72	4.0 : 1	97 : 3
9f	Ph	4-MeO	2-Chloro-pyridin-5-yl	44	10 : 1	> 99 : 1
9g	Ph	H	4-*c*-HexylC_6H_4	44	3.4 : 1	92 : 8
9h	Ph	4-MeO	4-ClC_6H_4	42	7.8 : 1	91 : 9
9i	Ph	4-MeO	4-*c*-HexylC_6H_4	57	5.9 : 1	90 : 10
9j	4-ClC_6H_4	4-MeO	Ph	63	2.5 : 1	89 : 11
9k[e]	Ph	4-F	Ph	30	3.5 : 1	89 : 11
9l	Ph	H	4-MeC_6H_4	48	5.4 : 1	87 : 13
9m	2-$MeOC_6H_4$	H	Ph	52	2.7 : 1	86 : 14
9n	4-$MeOC_6H_4$	H	Ph	22	6.0 : 1	85 : 15
9o	2-$MeOC_6H_4$	4-Me	4-ClC_6H_4	33	2.4 : 1	85 : 15

[a] General reaction conditions: enaminone **8** (0.6 mmol) and cinnamaldehyde **1** (0.9 mmol), catalyst **IV** (0.12 mmol) and $PhCO_2H$ (0.06 mmol) in EtOAc (6 mL), stirred at 0 °C for 4 days. [b] Yield of two isolated diastereoisomeric products. [c] The dr was calculated based on isolated masses of the major (*trans*) and the minor (*cis*) diastereomers. [d] er of the major product measured by HPLC on a chiral stationary phase. [e] The syntheses of **9a** and **9k** were performed in a mixture of EtOAc–Et_2O (4/2 mL). [f] *c*-Hexyl = cyclohexyl.



Scheme 2 One-pot enantioselective synthesis of 1,4-dihydropyridines and 3,4-dihydropyridin-2(1*H*)-ones.

No evident impact of the substituent on the enal was observed, but aliphatic enals such as (*E*)-but-2-enal were not proper reaction partners as sensitive mixed diastereoisomeric products were obtained.

The relative and absolute configuration of the products was assigned by X-ray diffraction on a single crystal of **9a** (see ESI† for the ORTEP structure)[15] and by comparing the optical rotation data of the 1,4-DHP product **10a** with analogous compounds reported in the literature (see Scheme 2).[14,16]

Taking advantage of the unique reactivity of products **9**, we further explored the possibility of establishing a one-pot enantioselective synthesis of other related heterocycles. Indeed, after the prior formation of **9a** with our protocol, Na_2SO_4–TMSCl and PCC were employed to effect a dehydration and oxidation, respectively. Under these conditions we were glad to find that the corresponding 1,4-DHP **10a** and the 3,4-dihydropyridinone **11a** could be obtained both in good enantiomeric excesses (Scheme 2). These results demonstrate the tunable and versatile utility of our one-pot protocol in the asymmetric synthesis of related optically active heterocycles.

In conclusion, we have developed an enantioselective organocatalytic domino reaction for the synthesis of 1,4,5,6-tetrahydropyridin-2-ols from enals and enaminones employing a Michael–hemiaminalization sequence. In addition, our protocol opens a one-pot entry to the corresponding 1,4-dihydropyridines *via* dehydration and 3,4-dihydropyridin-2-ones after oxidation, respectively.

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