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A Highly Enantioselective Catalytic Domino Aza-Michael/Aldol Reaction: One-Pot Organocatalytic Asymmetric Synthesis of 1,2-Dihydroquinolidines

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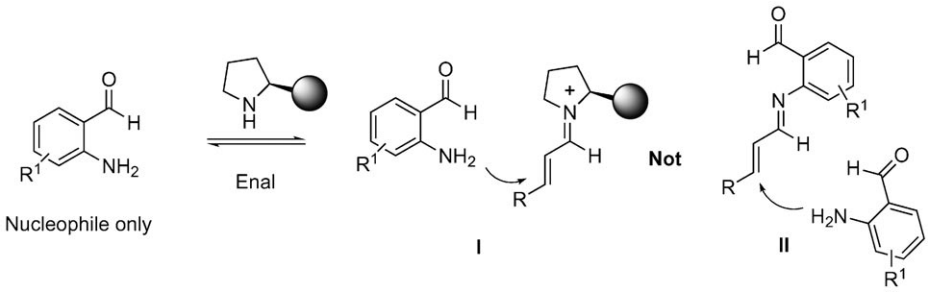
Abstract: The highly enantioselective organocatalytic domino aza-Michael/aldol reaction is presented. The unprecedented, chiral amine-catalyzed asymmetric domino reactions between 2-aminobenzaldehydes and α,β-unsaturated aldehydes proceed with excellent chemo- and enantioselectivity to give the corresponding pharmaceutically valuable 1,2-dihydroquinolines derivatives in high yields with 90 to >99% *ee*.

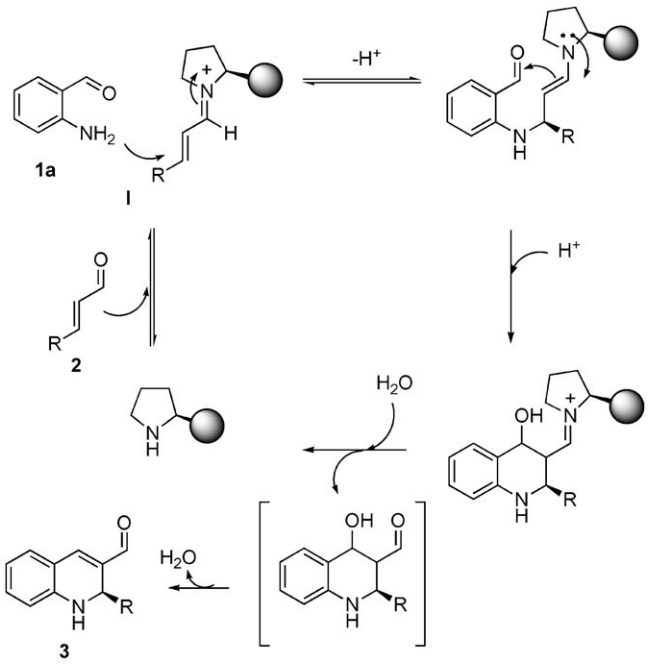
Keywords: asymmetric catalysis; aza-Michael reaction; domino reactions; nitrogen heterocycles; α,β-unsaturated aldehydes

Hetereocycles play an important role in the design and discovery of new compounds for pharmaceutical applications.[1] In this context, 1,2-dihydroquinoline derivatives are of great importance in the preparation of pharmaceuticals and other biologically active compounds.[2] In addition, they can be readily transformed to 1,2,3,4-tetrahydroquinolines, which also are of great value in the synthesis of pharmaceuticals and agrochemicals.[3] Furthermore, several natural products such as alkaloids consist of these structural elements. There are a few methods for the asymmetric synthesis of 1,2-dihydroquinoline derivatives and most of these utilize chiral auxiliaries, reagents or starting materials.[4] There is only one catalytic asymmetric method reported by Shibasaki and co-workers, which relies on the addition of cyanide to quinolines (the Reissert reaction) in the presence of a chiral bifunctional catalyst.[5]

The development of organocatalytic asymmetric reactions has attracted intense attention in recent years.[6] Recently, amine-catalyzed reactions that involve catalytic domino or cascade reaction pathways were developed.[7,8] In this context, we reported the formation of chromene-3-carbaldehyde derivatives *via* an oxa-Michael/aldol condensation pathway.[9] Moreover, Rueping and co-workers have reported an elegant Brønsted acid-catalyzed asymmetric cascade reaction that leads to the synthesis of 1,2,3,4-tetrahydroquinolines.[10] Inspired by these works and the development of catalytic aza-Michael reactions,[11] we envisioned that a chiral amine-catalyzed reaction between 2-aminobenzaldehydes and α,β-unsaturated aldehydes would provide a novel and direct enantioselective entry to 1,2-dihydroquinoline derivatives (Scheme 1). However, there are several chemoselectivity issues that could be problematic.

For instance, the 2-amino group of the benzaldehyde derivative must selectively function as a 1,4-addition nucleophile (**I**) and not participate in imine formation (**II**), which leads to a racemic pathway or that the desired product is not formed. In fact, on mixing anilines and enones in the presence of an amino acid catalyst the imine intermediate rapidly forms.[12] Moreover, an amine catalyst is needed that will form the iminium intermediates at a faster rate than the 2-aminobenzaldehyde derivative. In addition, the 2-aminobenzaldehyde could oligomerize by self-condensation reactions. Despite all these chemoselectivity issues, the subsequent intramolecular aldol addition after a possible initial amine conjugate addition step may kinetically control the desired reaction pathway and push the equilibrium towards product formation (Scheme 1). Herein, we present a highly enantioselective, organocatalytic domino aza-Michael/aldol reaction that gives 1,2-dihydroquinoline derivatives in high yields with 90 to >99% *ee*.





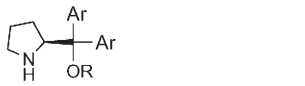
Scheme 1. A plausible reaction pathway for a chiral amine catalyzed enantioselective formation of 1,2-dihydroquinoline-3-carbaldehydes.

In initial experiments on the reaction between 2-aminobenzaldehyde **1a** (0.30 mmol) and cinnamic aldehyde **2a** (0.25 mmol), we found to our delight that protected diarylprolinols **4a**[13] and **4b** were catalysts for the asymmetric domino aza-Michael/aldol reaction [Eq. (1)].

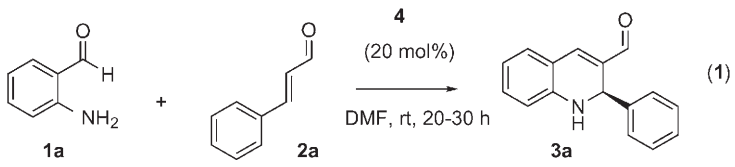
For instance, compound **4a** catalyzed the asymmetric formation of 1,2-dihydroquinoline **3a** in 68% yield and 87% *ee* at room temperature. Thus, we decided to optimize the reaction conditions of the catalytic asymmetric domino aza-Michael/aldol reaction using **4a** as the catalyst (Table 1).

We found that performing the asymmetric domino reactions in DMF or CH_3CN gave a higher reaction efficiency and ee of the 1,2- dihydroquinoline **3a** as compared to other solvents. In addition, the employment of an organic acid as an additive increased the efficiency of the domino reaction. Benzoic acid gave superior results with respect to conversion. For instance, the chiral amine **4a** catalyzed the enantioselective formation of the corresponding 1,2-dihydroquinoline **3a** in 71% yield with 94% *ee* (entry 5). This superior level of enantioselectivity encouraged us to select these reaction conditions for further exploration (Table 2).

The catalytic enantioselective domino reactions were highly chemoselective and the corresponding 1,2-dihydroquinoline-3-carbaldehydes **3** were isolated in high yield with 94–98% *ee*. Hence, enal substituents such as aryl, alkyl and ester groups are readily tolerated. Moreover, when aliphatic α,β-unsaturated aldehydes **2** were used as the substrates, the highest

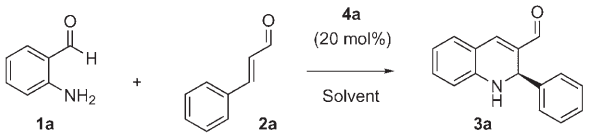


4a: R = TMS, Ar = Ph
4b: R = TMS, Ar = 2-Naphthyl
4c: R = TMS, Ar = 3,5-$(CF_3)C_6H_3$



catalyst **4a**; **3a**: 68% Yield, 87% ee
catalyst **4b**; **3a**: 44% Yield, 82% ee
catalyst **4c**; **3a**: <2% conv., not determined

Table 1. Selected reactions for the **4a**-catalyzed enantioselective domino reactions between **1a** and **2a**.[a]



Entry	Additive (20 mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	none	DMF	rt	20	68	87
2	none	CH_3CN	rt	7	78	79
3	$C_6H_5CO_2H$	DMF	rt	20	80	85
4	$C_6H_5CO_2H$	DMF	–10	20	39	89
5	$C_6H_5CO_2H$	DMF	–25	48	71	94
6	2-$NO_2C_6H_4CO_2H$	DMF	–25	48	20	70
7	4-$NO_2C_6H_4CO_2H$	DMF	–25	48	25	84
8	2-$FC_6H_4CO_2H$	DMF	–25	48	42	91
9	none	CH_3CN	4	5	47	82

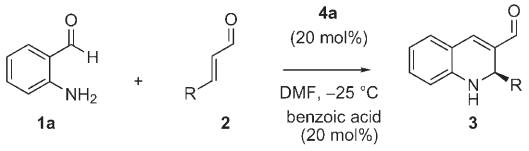
[a] *Experimental conditions:* A mixture of **1a** (0.30 mmol), cinnamic aldehyde **2a** (0.25 mmol) and catalyst (20 mol%) in 0.5 mL solvent was stirred at the temperature and conditions displayed in the table.
[b] Isolated yield of pure compound **3a**.
[c] Determined by chiral HPLC analyses.

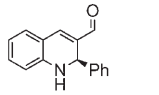
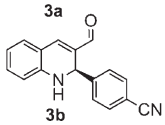
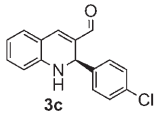
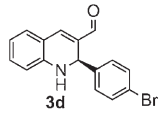
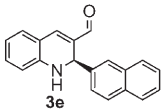
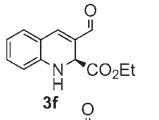
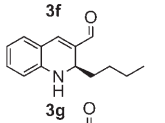
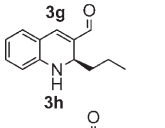
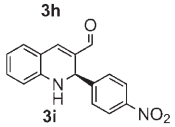
asymmetric induction was achieved in CH_3CN without addition of an organic acid. In fact, the *ee* decreased if benzoic acid was added. For example, chiral amine **4a** catalyzed the formation of 1,2-dihydroquinoline-3-carbaldehyde **3h** in 76% yield with 97% *ee* (entry 7). This is possibly due to the instability of the aliphatic enals under the more acidic conditions. Moreover, ether- and halogen-substituted 2-aminobenzladehydes **1** were explored and the corresponding products **3j–n** were isolated with 90 to >99% *ee* (Table 3). In particular, the organocatalytic asymmetric domino reactions with ether-substituted 2-aminobenzaldehydes were highly enantioselective and in some cases almost enantiopure compounds (>99% *ee*) were obtained (entries 2 and 4).

The absolute stereochemistry of the 1,2-dihydroquinoline-3-carbaldehydes **3** was established by X-ray analyses and is in accordance with previous **4a**-catalyzed heterocycle syntheses (Figure 1).[9,14,15]

Thus, efficient shielding of the *Si*-face of the chiral iminium intermediate by the bulky aryl groups of **4a** leads to stereoselective *Re*-facial nucleophilic conjugate attack on the β-carbon by the amino group of **1**. Next, the generated resulting chiral enamine intermediate undergoes an intramolecular six-*exo trig* aldol reaction (Scheme 1). Hydrolysis of the resulting

Table 2. Scope of the domino aza-Michael/aldol reaction.[a]

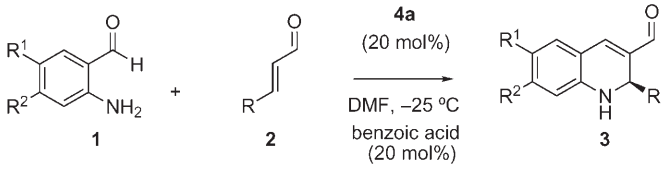


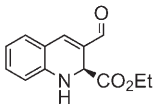
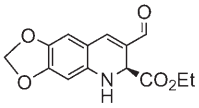
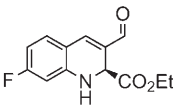
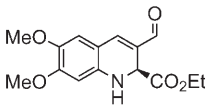
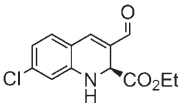
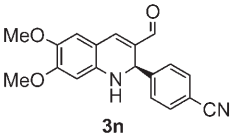
Entry	R	Product	Time (h)	Yield[b]	*ee* (%)[c]
1	Ph	 **3a**	47	71	94
2	4-CNC_6H_4	 **3b**	24	83	98
3	4-ClC_6H_4	 **3c**	24	58	96
4	4-BrC_6H_4	 **3d**	24	90	96
5	2-naphthyl	 **3e**	24	75	94
6	CO_2Et	 **3f**	48	76	97
7	*n*-butyl	 **3g**	48[d]	69	98
8	*n*-propyl	 **3h**	48[d]	78	96
9	4-$NO_2C_6H_4$	 **3i**	48	71	97

[a] *Experimental conditions:* A mixture of **1a** (0.30 mmol), aldehyde **2** (0.25 mmol), benzoic acid (20 mol%) and catalyst **4a** (20 mol%) in DMF (0.5 mL) was stirred at –25 °C. The crude product **3** obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of pure product **3** after silica gel column chromatography.
[c] Determined by chiral HPLC analyses.
[d] Reaction performed in CH_3CN without acid.

iminium intermediate gives the aldol product that can be observed by NMR analyses. Next, subsequent elimination of water leads to the formation of the corresponding 1,2-dihydroquinoline **3**. The addition of a benzoic acid additive may increase the efficiency of the reaction by pushing the equillibrium of the catalyst towards iminium formation.

Table 3. Organocatalytic asymmetric domino aza-Michael/aldol reaction between 2-aminobenzaldehydes **1** and α,β-unsaturated aldehydes **2**.[a]



Entry	Alde. **1**	R^1	R^2	R	Product	Time (h)	Yield[b]	*ee* (%)[c]
1	**1a**	H	H	CO_2Et	 **3f**	48	69	98
2	**1b**	-OCH_2O-		CO_2Et	 **3j**	27	73	>99
3	**1c**	H	F	CO_2Et	 **3k**	24	83	90
4	**1d**	OMe	OMe	CO_2Et	 **3l**	24	67	>99
5	**1e**	H	Cl	CO_2Et	 **3m**	26	31	97
6	**1f**	OMe	OMe	4-CNC_6H_4	 **3n**	48	78	96

[a] *Experimental conditions:* To a stirred solution of catalyst **4a** (20 mol%) and benzoic acid (20 mol%) in DMF (0.5 mL) at −25 °C was added α,β-unsaturated aldehyde **2** (0.25 mmol) followed by addition of 2-aminobenzaldehyde **1** (0.30 mmol). The crude product **3** obtained after aqueous work-up was purified by column chromatography.
[b] Isolated yield of pure product **3** after silica gel column chromatography.
[c] Determined by chiral HPLC analyses.

In summary, we report a highly chemo- and enantioselective organocatalytic asymmetric domino aza-Michael/aldol reaction that gives 1,2-dihydroquinolines in high yields with 90 to >99% *ee*. Hence, the reaction constitutes a simple catalytic, highly enantioselective entry to pharmaceutically valuable quinoline derivatives. Mechanistic studies, synthetic applications of this transformation as well as development of other enantioselective domino conjugate/aldol reactions are ongoing in our laboratory.[15a,16]

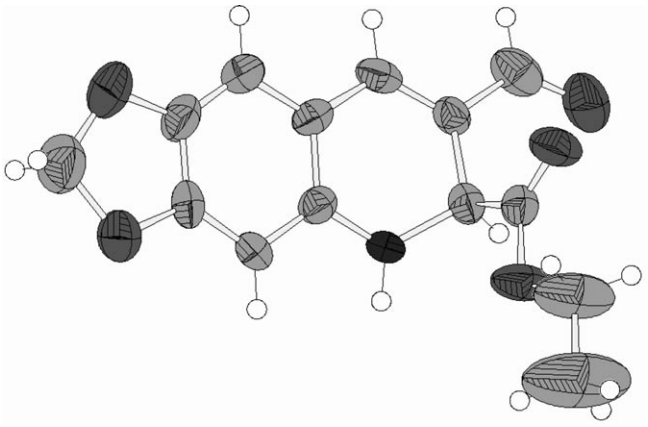


Figure 1. ORTEP picture of 1,2-dihydroquinoline-3-carbaldehyde **3j**.

Experimental Section

General Procedure for the Aza-Michael/Aldol Reaction

To a stirred solution of catalyst **4a** (16 mg, 20 mol%) and benzoic acid (0.006 mg, 20 mol%) in DMF (0.5 mL) at −25 °C was added enal **2** (0.25 mmol) followed by addition of the 2-aminobenzaldehyde **1** (0.30 mmol). The reaction mixture was stirred for the time given in the Tables. Next, the generated compound was directly purified by silica gel chromatography (pentane:EtOAc mixtures) to give the corresponding 1,2-dihydroquinoline-3-carbaldehyde **3**.The *ee* of the product was determined by chiral HPLC analysis.

Acknowledgements

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