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COMMUNICATION

Organocatalytic One-pot Asymmetric Synthesis of 2-Aryl-2,3-dihydro-4-quinolones

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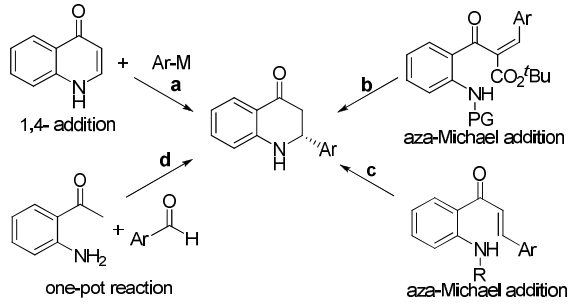
Abstract: A highly efficient organocatalytic one-pot enantioselective synthesis of (*R*)-2-aryl-2,3-dihydro-4-quinolones from *o*-aminoacetophenones and aryl aldehydes has been developed. The approach was characterized by metal free, solvent free and protecting group free. A variety of 2-aryl-2,3-dihydro-4-quinolones could be obtained in good yields up to 99% ee.

2-Aryl-2,3-dihydro-4-quinolones, also known as azaflavanones, are a family of heterocyclic compounds with broad-spectrum biological activities,[1,2] such as antimalarial activity and potent cross-species microRNA inhibitors.[3] Additionally, they represent a new class of antimitotic antitumor agents against a panel of human tumor cell lines.[4] Interestingly, the two enantiomers of 2-aryl-2,3-dihydro-4-quinolones were found to display distinctly different activities.[4] Therefore, the enantioselective synthesis of these compounds is highly desirable. To date, there are only several reports of the catalytic enantioenriched synthesis of 2-aryl-2,3-dihydro-4-quinolones,[5-9] mainly employing two strategies: one is the asymmetric intermolecular 1,4-addition of organometallic reagents to 4-quinolones (Scheme 1, a);[5] the other is the asymmetric intramolecular aza-Michael addition (Scheme 1, b and c).[6] In 2013, Pitchumani et al. reported an elegant cyclodextrin-mediated one-pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones from *o*-aminoacetophenone and aldehydes (Scheme 1, d).[7] Compared to above approaches, the method neither needed the synthesis of starting materials (e.g. quinolone, aminochalcone), nor required removal of activating groups (ester group) or protecting groups. Nevertheless, a stoichiometric amount of chiral per-6-amino-*β*-cyclodextrin (per-6-ABCD) was used in this approach. Due to per-6-ABCD being macrocyclic oligosaccharides possessing high molecular weight (MW: 1127), the amount of per-6-ABCD in the reaction was very huge compared to reaction substrate. More recently, Akiyama et al. reported a chiral phosphoric acid catalyzed asymmetric synthesis of 2-substituted 2,3-dihydro-4-quinolones using a protecting-group-free aza-Michael addition (Scheme 1, c, R = H).[8] Herein, we described a highly efficient and green organocatalytic one-pot approach to asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones from *o*-aminoacetophenones and aldehydes, featured by metal free, solvent free and protecting group free.

Scheme 1. Synthetic Approaches to 2-Aryl-2,3-dihydro-4-quinolones



Recently, our group has developed a kind of organocatalysts based on aminoquinoline and pyrrolidine.[10] We evaluated their catalytic ability by catalyzing the cyclization of 2-hydroxychalcones to yield chiral flavanones. These organocatalysts presented excellent enantioselectivities and good yields. Then we envisioned that this kind of organocatalysts might promote the one-pot synthesis of 2-aryl-2,3-dihydro-4-quinolones from *o*-aminoacetophenones and aldehydes. Initially, *o*-aminoacetophenone **(1a)** and benzaldehyde **(2a)** were chosen as model substrates. The reaction was performed in the presence of 20 mol % catalyst **4a** in toluene. To our delight, the reaction proceeded smoothly to give the desired (*R*)-2-benzyl-2,3-dihydro-4-quinolone **(3a)** in 30% yield with 67% ee (Table 1, entry 1). This result indicated that this kind of catalyst indeed supported the enantioselective one-pot transformation. Switching from catalyst **4a** to the catalysts **4b** and **4c** gave only trace amounts

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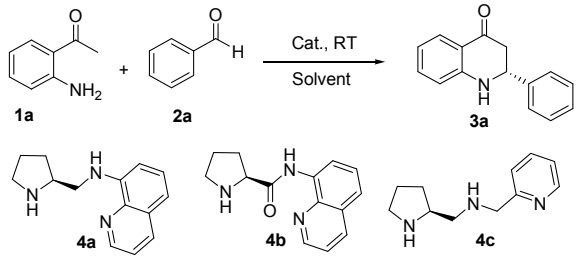
† Electronic Supplementary Information (ESI) available: Characterization data and experimental procedures. CCDC 1418014-1418015. For ESI and crystal graphic data in CIF or other electronic format see DOI:10.1039/x0xx00000x

Table 1. Optimization of the Reaction Conditions [a]

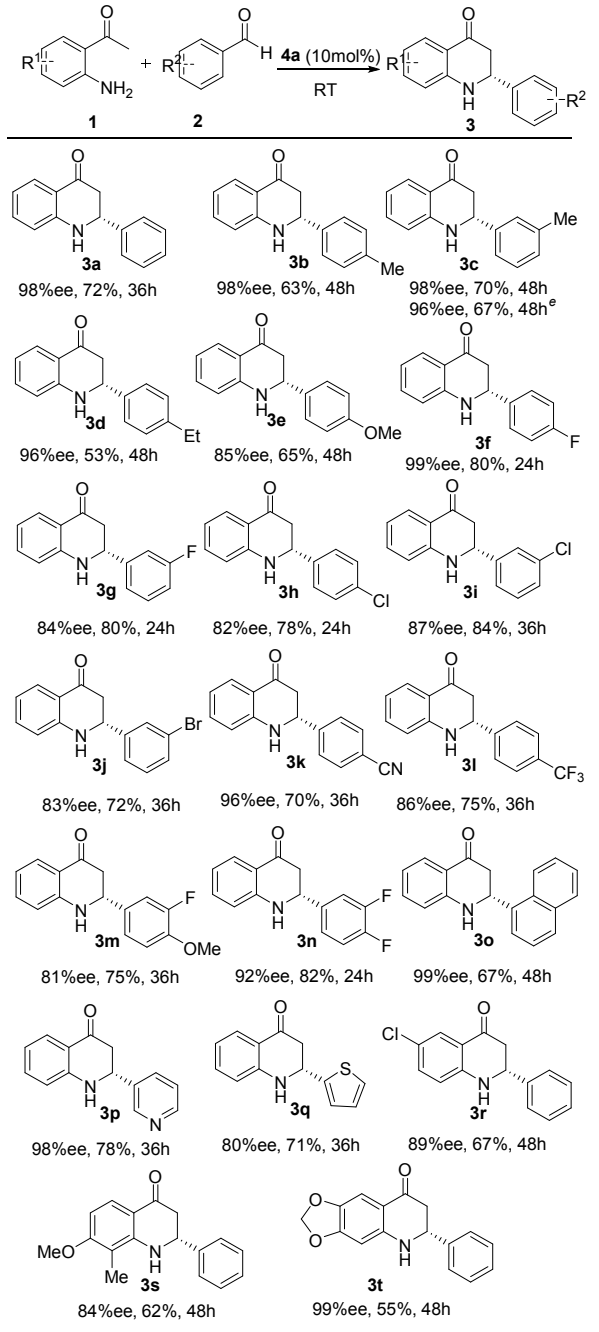


Entry	Cat.	Solvent	Yield [b] [%]	ee [c] [%]
1	**4a**	Toluene	30	67
2	**4b**	Toluene	<5	ND
3	**4c**	Toluene	<5	ND
4	**4a**	DMF	NR	-
5	**4a**	$CHCl_3$	12	61
6	**4a**	CH_2Cl_2	15	33
7	**4a**	$ClCH_2CH_2Cl$	53	77
8	**4a**	DMSO	48	63
9	**4a**	Methanol	10	23
10	**4a**	Ethanol	<5	ND
11	**4a**	CCl_4	<5	ND
12	**4a**	Dioxane	<5	51
13	**4a**	CH_3CN	53	73
14	**4a**	Chlorobenzene	53	0
15	**4a**	(Trifluoromethyl)benzene	62	57
16	**4a**	Xylene	12	49
17	**4a**	Ethyl acetate	<5	43
18	**4a**	THF	NR	-
19[d]	**4a**	Solvent-free	67	98
20[d,e]	**4a**	Solvent-free	72	98
21[e]	**-**	Solvent-free	0	-
22[e]	**4b**	Solvent-free	<5	ND
23[e]	**4c**	Solvent-free	35	6

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (20 mol%) in solvent (0.3 mL) at RT (25 °C) for 24 h. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase (See the Supporting Information). [d] Absolute configuration was determined as *R* by comparison of optical rotation to literature values (See the Supporting Information). [e] 10 mol% catalyst was used and the reaction time was 36 h. RT = room temperature. NR = no reaction. ND = no detective.

of the desired product (Table 1, entries 2, 3). Therefore, the catalyst **4a** was used to screen other reaction conditions. After extensive screening of solvents, it was found that solvent dramatically affected the outcome of the reaction (Table 1, entries 4-18). 1, 2-Dichloroethane and acetonitrile offered better results than toluene (entries 7 and 13). To our surprise, when the reaction was carried out in absence of solvent, the

Scheme 2. Substrate Scope of Organocatalytic One-pot Enantioselective Synthesis of 2-Aryl-2,3-dihydro-4-quinolones [a-d]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), **4a** (10mol%) at RT (25 °C). [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase (See the Supporting Information). [d] Absolute configuration was determined as *R* by comparison of optical rotation to literature values (See the Supporting Information). [e] Recovered catalyst **4a** was used.

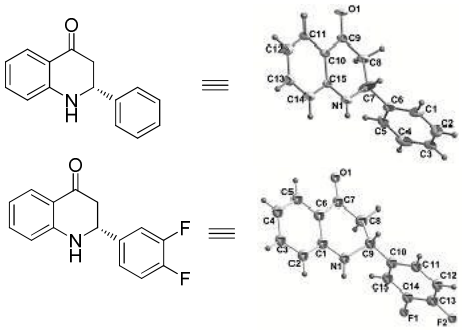
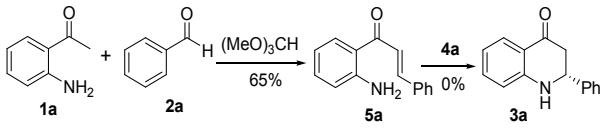


Figure 1. X-Ray for the products **3a** and **3n**

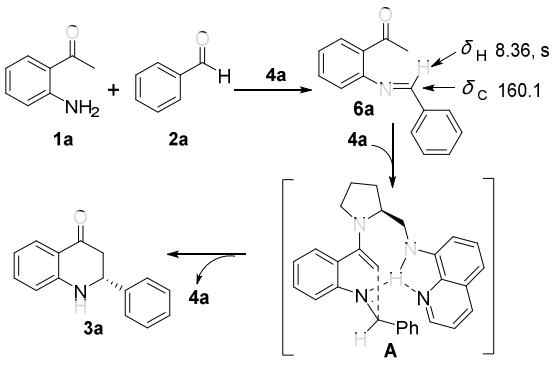
reaction was accelerated obviously, affording the desired (*R*)-2-benzyl-2,3- dihydro-4-quinolone in 67% yield with up to 98% ee after 24 h (Table 1, entry 19). Next, we investigated the catalyst loading. Gratifyingly, the excellent enantioselectivity was maintained and the yield increased a little when the catalyst amount was decreased to 10 mol %, albeit a little longer time was needed (Table 1, entry 20). When the loading of catalyst **4a** was lowered, e.g., to 5 mol %, the reaction was much slow. The reaction did not work without catalyst **4a** (Table 1, entry 21). Under the same solvent-free conditions, catalyst **4b** led to poor conversion (Table 1, entry 22), and catalyst **4c** obtained low enantioselectivity (Table 1, entry 23).

With the optimal reaction conditions in hand, we moved onto explore the scope of the organocatalytic one-pot synthesis of 2-aryl-2,3-dihydro-4-quinolones from o-aminoacetophenones and aryl aldehydes. The results were summarized in Scheme 2. The different substituted aryl aldehydes were first investigated with *o*-aminoacetophenone **(1a)** as a partner. Aryl aldehydes possessing either electron-donating groups or electron-withdrawing groups smoothly reacted and provided the corresponding (*R*)-2-aryl-2,3-dihydro-4-quinolones in good to excellent yields and ee values (Scheme 2, **3a**-**3l**), which indicated that the electronic properties of the substituents only had a minor effect on this transformation. Several important functional groups such as –F, –Cl, –Br, –CN, $–CF_3$ and –OMe were well tolerated, which allows further functionalization toward the synthesis of structural diversely 2-aryl-2,3-dihydro-4-quinolones. It is noted that aryl aldehyde with ortho substituent gave much low yield (not shown), implying that the reaction is sensitive to the steric properties of the aryl aldehyde. Pleasingly, 3,4-disubstituted aryl aldehydes were compatible with the reaction (Scheme 2, **3m**, **3n**). Other aromatic aldehydes, e. g. 2-naphthaldehyde, 3-pyridine carboxaldehyde and 2-thiophenaldehyde were also suitable substrates, affording **3o** (67% yield, 99% ee), **3p** (78% yield, 98% ee) and **3q** (71% yield, 80% ee), respectively. Other o-aminoacetophenones were also examined. To our delight, 5-chloro-2-aminoacetophenone (**2r**), 3-methyl-4-methoxyl-2-aminoacetophenone (**2s**) and 4, 5-methylenedioxy-2-aminoacetophenone **(2t)** reacted smoothly with benzaldehyde, providing the desired products **3r** (67% yield, 89% ee), **3s** (62% yield, 84% ee) and **3t** (55% yield, 99% ee), respectively. In addition, the catalyst was conveniently recovered by column chromatography. The recovered catalyst could promote the one-pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolone albeit with slightly decreased yield and enantioselectivity (Scheme 2, **3c**). The structures of products

Scheme 3. Synthesis of *o*-Aminochalcone and aza-Micheal Addition



Scheme 4. Proposed Mechanism



HRMS: $[M+H]^+$: found 433.2381
calcd 433.2387

3a and **3n** were confirmed by X-ray crystallography analysis (Figure 1).

As for the mechanism of the one-pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones from *o*-aminoacetophenones and aldehydes, Pitchumani et al suggested that, with the promotion of per-6-amino-*β*-cyclodextrin, *o*-aminoacetophenone and aldehyde first formed *o*-aminochalcone, then underwent an asymmetric aza-Micheal addition to afford the product.[7] To validate the similar mechanism in our approach, we synthesized *o*-aminochalcone **(5a)**, and treated it with above optimal reaction conditions, but the aza-Micheal addition did not proceed (Scheme 3). We then supposed that the one-pot reaction probably formed the imine at first, then suffered from the intramolecular asymmetric Mannich reaction to provide 2-aryl-2,3-dihydro-4-quinolone (Scheme 4). The formation of imine in the reaction system was confirmed by the NMR spectroscopy experiment of the reaction mixture. The chemical shift (δ_H 8.36, s, -N=CHPh) was found in ^{1}H NMR and the chemical shift (δ_C 160.1, -N=CHPh) was found in ^{13}C NMR (see Supporting information). We attempted to isolate the imine **6a** from the reaction system or prepare the imine **6a** by other method, but failed, which were probably ascribed to the unstability of **6a**. Catalyst **4a** might promote the subsequent Mannich reaction via intermediate **A**, in which the carbony group of **6a** was activated by the formation of an enamine with the pyrrolidine moiety of catalyst **4a**, while the C=N of the imine was also activated by the forming hydrogen-bond between the nitrogen atom and the N-H. We believed that phenyl ring of the substrate and quinolinyl ring of the catalyst possess arene π-π stacking from molecular modelling studies, which might have contributed to the high enantioselectivities. The intermediate **A** was supported by the molecular ion peak from high-resolution mass spectrometry (HRMS) of the reaction mixture ($[M+H]^+$: m/z found 433.2381, calcd 433.2387) (see Supporting

information). The enamine attacked the carbon atom of the C=N on *Re* face, leading to the formation of (*R*)-2-aryl-2,3-dihydro-4-quinolone.

Conclusions

In summary, we have developed a highly efficient organocatalytic one-pot synthesis of (*R*)-2-aryl-2,3-dihydro-4-quinolones from *o*-aminoacetophenones and aryl aldehydes. The products were obtained in good yields up to 99% ee. Compared to previous approaches, the approach was characterized by metal free, solvent free and protecting group free. Preliminary mechanistic study showed that the protocol probably underwent an asymmetric Mannich process. Due to easy operation and high efficiency, this method would be prospective in the synthesis of bioactive 2-aryl-2,3-dihydro-4-quinolones, thereby facilitating biological and medicinal chemistry studies of such compounds.

Acknowledgements

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Notes and references

†**General procedure for 2-Aryl-2,3-dihydro-4-quinolones synthesis:** To a 1.5 mL test tube were added 0.01mmol (10 mmol%) of organocatalyst **4a**, 0.1 mmol of 2'-hydroxyacetophenones **1** and 0.1 mmol of aryl aldehydes **2**. Then the reaction mixture was left at room temperature for sufficient time (based on monitoring by thin-layer chromatography), and finally purified by column chromatography with 10% EtOAc / hexanes as eluent to give the products **3**.

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A highly efficient organocatalytic one-pot approach for enantioselective synthesis of (R)-2-aryl-2,3-dihydro-4-quinolones from o-aminoacetophenones and aryl aldehydes has been achieved.