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Chiral Phosphoric Acid Catalyzed Asymmetric Synthesis of 2-Substituted 2,3-Dihydro-4-quinolones by a Protecting-Group-Free Approach

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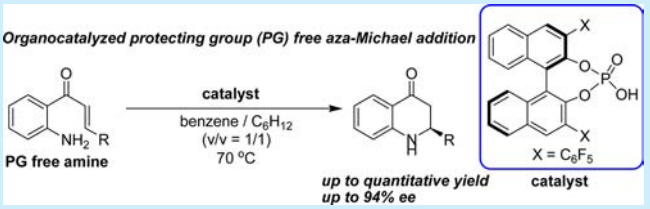
Supporting Information

ABSTRACT: Chiral 2-substituted 2,3-dihydro-4-quinolones were synthesized based on the chiral phosphoric acid catalyzed intramolecular aza-Michael addition reaction using N-unprotected 2-aminophenyl vinyl ketones as substrates in good yields with high enantioselectivities.



Step economy is generally defined by the streamlining of reaction steps by refraining from the use of protection−deprotection reactions, redox, etc.,[1] thereby enabling ready access to target molecules. Protection and deprotection reactions, although representing an important protocol in synthetic organic chemistry, generally require much time and cost, making the approach less step-economical.

The organocatalyzed aza-Michael addition was extensively studied in recent years[2] and is recognized as one of the most powerful tools for the synthesis of enantioenriched nitrogen heterocycles. The key issue is how to effect the cyclization in an efficient and stereocontrolled manner. To achieve that goal, any removable activating group on the nitrogen atom is frequently required for stereocontrol and increasing the acidity of the nitrogen. To that end, the development of a protecting-group-free aza-Michael addition is highly desired to decrease the number of reaction steps.[3]

The quinolone skeleton is found in many natural products and is regarded as a "privileged" structure in medicinal chemistry because it can be easily accessed with flexible synthetic approaches that allow the production of large chemical libraries having potential biological activities. Consequently, numerous synthetic strategies have been developed to gain access to a range of quinolone skeletons. 2-Substituted 2,3-dihydro-4-quinolone derivatives represent a new class of antimitotic antitumor agents (Figure 1).[4] A highly enantioselective synthesis of those structures is strongly desired because their enantiomers often exhibit distinct properties. There are several reports of the catalytic enantioselective synthesis of 2-aryl-2,3-dihydro-4-quinolones.[5] However, activating groups on the nitrogen atom were required in those approaches. Pitchumani et al. developed a cyclodextrin-mediated asymmetric synthesis in aqueous media based on the sequential aldol-Michael reaction of *o*-aminoacetophenone with various aldehydes in a one-pot manner.[5f] This method requires more than a stoichiometric amount of chiral reagent to realize a highly enantioselective addition.

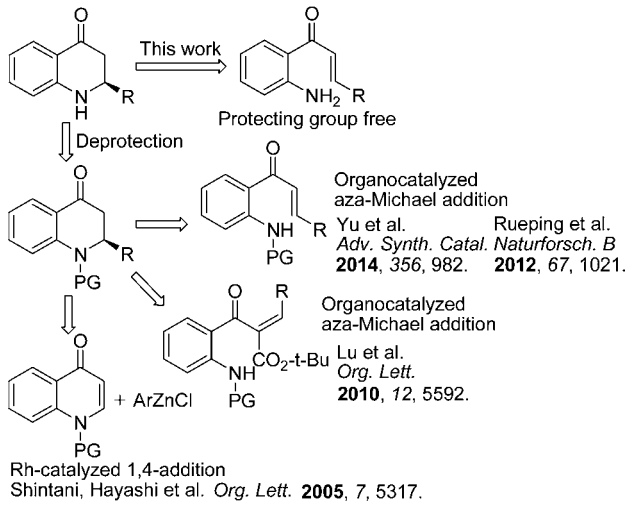


Figure 1. Synthetic approaches to 2-substituted 2,3-dihydro-4-quinolones.

Chiral phosphoric acid, a representative organocatalyst, has a Brønsted acidic part (P−OH) and a Lewis basic part (P═O) and functions as a bifunctional catalyst.[6] Although Rueping et al. reported a chiral *N*-triflylphosphoramide catalyzed synthesis of 2-substituted 2,3-dihydro-4-quinolone derivatives using N-protected 2-aminophenyl vinyl ketone, the enantioselectivity of this reaction was unsatisfactory (49−63% ee).[5h] We report herein a chiral phosphoric acid catalyzed intramolecular aza-Michael addition of N-unprotected 2-aminophenyl vinyl ketone to furnish 2-substituted 2,3-dihydro-4-quinolones in a highly enantioselective manner.

At the outset, we selected **1a** as the model substrate and treated it with a range of phosphoric acids **3** bearing aryl groups at 3,3′-

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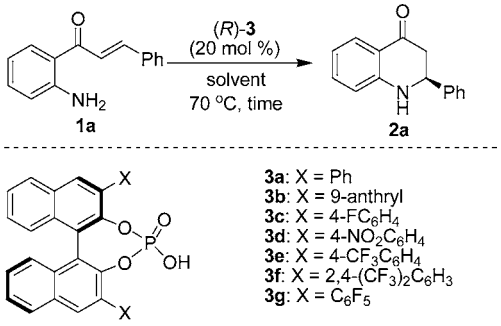
positions in benzene at 70 °C to give aza-Michael adduct **2a** in 24% yield with 23% ee. Investigation of the 3,3′-substituents revealed that the introduction of an electron-withdrawing group has a beneficial effect on the enantioselectivity. Finally, we found that **3g** bearing a pentafluorophenyl C_6F_5 group was the catalyst of choice for the aza-Michael addition reaction.[7,8] Solvent screening revealed that the mixed solvent of benzene and cyclohexane gave the best result (Table 1, entry 9). The loading of (*R*)-**3g** could be reduced to 10 mol % without any deleterious effect on the yield and enantioselectivity (entry 10).[9]

Table 1. Examination of Reaction Conditions[a]



entry	catalyst	solvent	yield[b] (%)	ee[c] (%)
1	**3a**	benzene	24	23
2	**3b**	benzene	84	−13
3	**3c**	benzene	3	52
4	**3d**	benzene	48	70
5	**3e**	benzene	34	67
6	**3f**	benzene	quant	85
7	**3g**	benzene	91	90
8	**3g**	toluene	quant	90
9	**3g**	benzene/C_6H_{12} (v/v = 1/1)	quant	93
10[d]	**3g**	benzene/C_6H_{12} (v/v = 1/1)	95	93

[a]Reactions were carried out on a 0.1 mmol scale with starting material **1a** (0.1 mmol) and (*R*)-**3** (20 mol %) in benzene (0.1 M) at 70 °C (details in Supporting Information). [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d](*R*)-**3g** (10 mol %) was used.

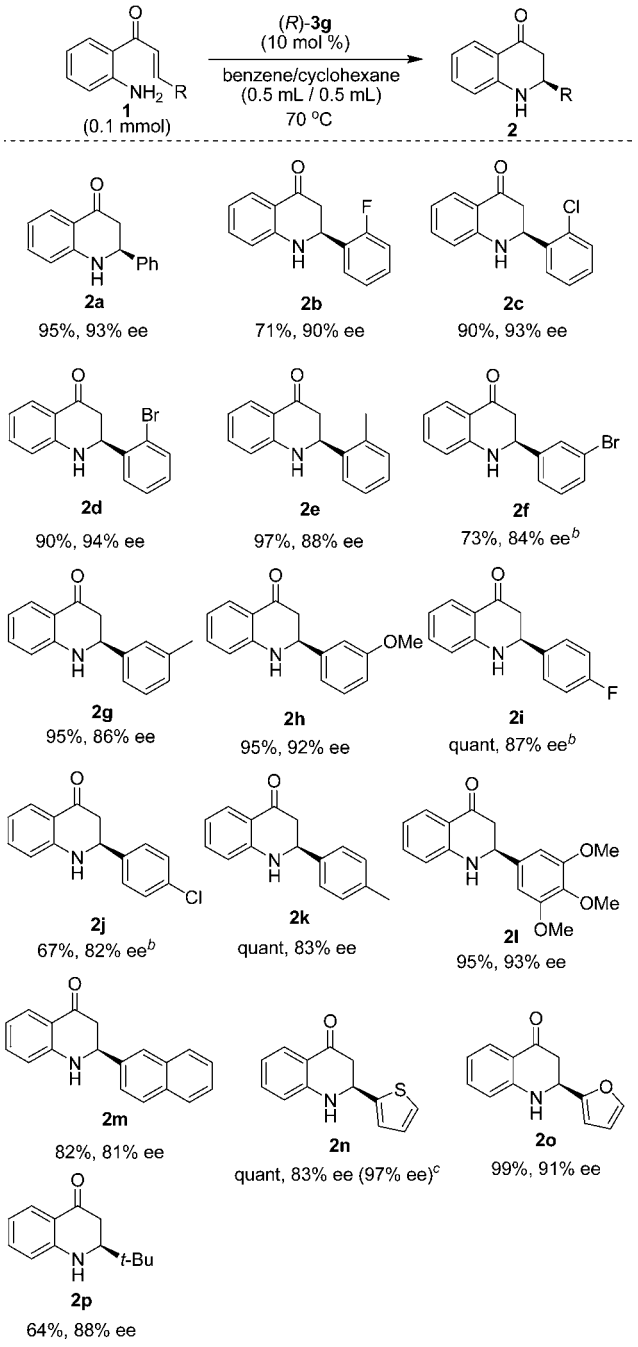
To extend the scope of the aza-Michael addition, substrates **1b**−**1o** were subjected to the optimum reaction conditions (Scheme 1). Substrates **1b**−**1e** bearing *ortho*-substituted arene at the *β*-position exhibited high reactivity and stereoselectivity. Electron-withdrawing (**1b**−**1d**) and electron-donating (**1e**) group substituted substrates were converted into the corresponding products in 71−97% yield with 88−94% ee. Similar efficient cyclization was observed in the reaction of substrates **1f**−**1h** containing *meta*-substituted arenes to give **2f**−**2h** in 73−95% yield with 84−92% ee. *para*-Substituted aromatics on the substrates were also robust to the conditions, furnishing **2i**−**2k** in good to high yields with high ee. 2-Naphthyl (**1l**), 2-thienyl (**1m**), 2-furyl (**1n**), and *tert*-butyl (**1o**) group substituted substrates participated in the reaction with good to high efficiencies, and **2m** could be further purified by a single recrystallization.

Single-crystal X-ray analysis indicated that the absolute configuration of **2d** produced by the intramolecular aza-Michael reaction was *S* (Figure 2). The absolute configuration of the other products was surmised by analogy.

Further transformation of chiral 2,3-dihydroquinolones was explored (Scheme 2). When (*S*)-**2a** was reduced with $NaBH_4$, an alcohol with 15:1 dr was obtained.[10] This crude product was converted into sulfide (*S*,*S*)-**4a** under Mitsunobu conditions in 89% yield without loss of optical purity.[11] (*S*)-**2a** was efficiently converted into tetrahydroquinoline (*S*)-**5a** using $LiAlH_4$ and $AlCl_3$.

We investigated the reaction of N-protected substrates (Scheme 3): when N-acetylated substrate **6a** was subjected to the same optimum reaction conditions as for **6a**, **7a** was obtained

Scheme 1. Substrate Scope of Chiral Phosphoric Acid Catalyzed Asymmetric Aza-Michael Addition[a]



[a]Reactions were carried out on a 0.1 mmol scale with starting material **1** (0.1 mmol) and (*R*)-**3g** (10 mol %) in benzene (0.5 mL)/cyclohexane (0.5 mL) at 70 °C (details in Supporting Information). Isolated yields. Determined by chiral HPLC analysis. [b](*R*)-**3g** (20 mol %) was used. [c]After recrystallization.

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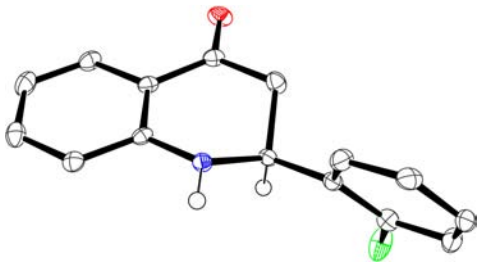
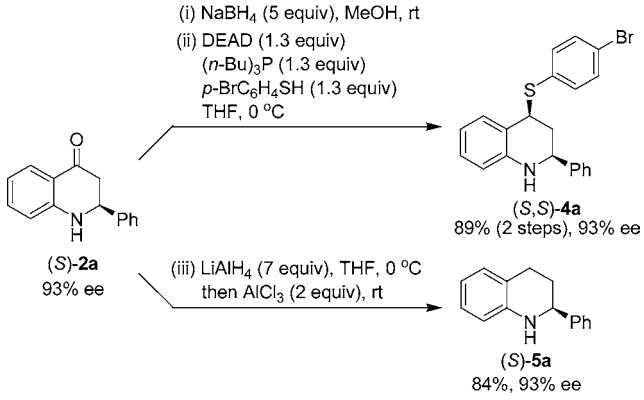
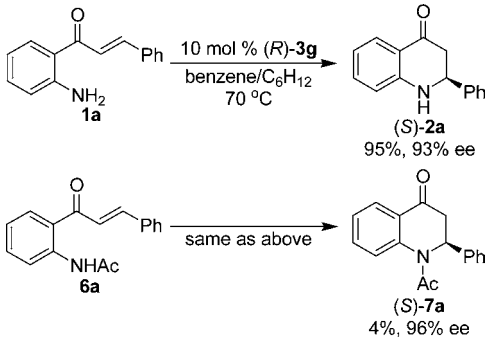


Figure 2. ORTEP drawing of (*S*)-**2d**.

Scheme 2. Derivatization of Chiral 2,3-Dihydroquinolones



Scheme 3. Reaction of N-Protected Substrate under Optimum Reaction Conditions[a]



[a]Reactions were carried out on a 0.1 mmol scale with starting material **6a** (0.1 mmol) and (*R*)-**3g** (10 mol %) in benzene (0.5 mL)/cyclohexane (0.5 mL) at 70 °C (details in Supporting Information). Isolated yields. Determined by chiral HPLC analysis.

in 4% yield with 96% ee. This indicates that the nucleophilicity of the nitrogen atom plays an important role.

In conclusion, we have developed a chiral phosphoric acid catalyzed asymmetric synthesis of 2-substituted 2,3-dihydro-4-quinolones using a protecting-group-free aza-Michael addition reaction. This method could be applied to various substrates to furnish the corresponding products in good to high yields with high to excellent enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for all new compounds, NMR spectra for the products, and HPLC charts. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01654.

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Notes

The authors declare no competing financial interest.

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(8) Regarding this reaction mechanism, one of the reviewers suggested that the substrate activates another substrate by the formation of an iminium intermediate. We examined the reactions in the presence of aniline (both 10 mol and 100 mol %) to form iminium intermediate, but the products were obtained in much lower yields (8 and 2%, respectively).

(9) Use of 5 mol % of the optimized catalyst decreased both yield and ee.

(10) The alcohol product of the reduction reaction was slightly decomposed to 2-phenylquinoline during silica gel chromatography. Therefore, the crude of the reduction reaction was used directly without further purification.

(11) Mitsunobu reaction using a carboxylic acid as a nucleophile did not work well. 2-Phenylquinoline was rapidly formed under the reaction conditions.

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