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H_8-BINOL Chiral Imidodiphosphoric Acids Catalyzed Enantioselective Synthesis of Dihydroindolo-/-pyrrolo[1,2-*a*]quinoxalines

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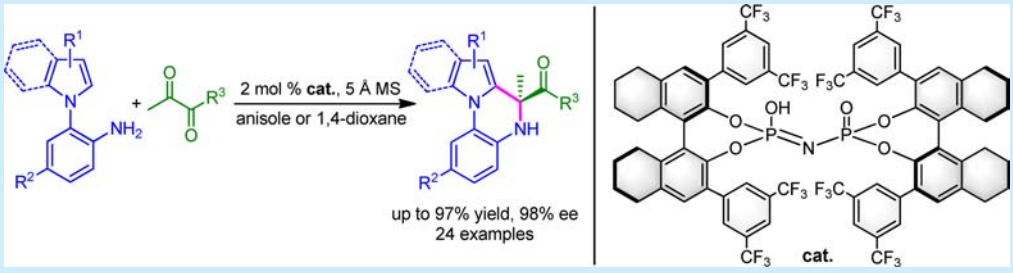
Supporting Information



ABSTRACT: The first enantioselective synthesis of 5,6-dihydroindolo[1,2-*a*]quinoxalines is achieved by using a newly developed H_8-BINOL-type imidodiphosphoric acid catalyst with low catalyst loading through efficient Pictet−Spengler-type reactions of indolyl anilines with ketones. This methodology also generates phenyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalines with high yields and excellent enantioselectivities. Moreover, this method was utilized to synthesize an HIV-1 inhibitor with high yield and good enantioselectivity through a one-step procedure.

Quinoxalines are relatively common nitrogen-containing heterocycles found in numerous pharmaceuticals.[1] Among them, dihydroindolo-/-pyrrolo[1,2-*a*]quinoxalines and their derivatives exhibit a wide range of important physiological and biological properties, including anticancer[2] (Figure 1, compound **A** and **D**), anti-HIV[3] (compound **B**), and polycystic kidney disease inhibition[4] (compound **C**) activities. The most common approach for generating dihydroindolo-/-pyrrolo[1,2-*a*]quinoxalines is an acid-catalyzed Pictet−Spengler-type reaction,[2b,5,6] which is more economical and less toxic when compared with precious-metal-mediated cascade reactions[7] and N-arylation reactions.[8] Although the demand for constructing the absolute configuration of the pharmacological active molecules is growing rapidly to maximize treatment effects or mitigate drug toxicity,[9] the enantioselective synthesis of chiral dihydroindolo-/-pyrrolo[1,2-*a*]quinoxalines is rare. Only Tian and co-workers have reported the chiral boron Lewis acid-catalyzed enantioselective synthesis of dihydropyrrolo[1,2-*a*]-quinoxalines very recently.[10] To the best of our knowledge, the enantioselective synthesis of dihydroindolo[1,2-*a*]quinoxalines remains unexplored. Thus, developing strategies toward highly enantioselective synthesis of dihydroindolo-/-pyrrolo[1,2-*a*]-quinoxalines is an unmet challenge.

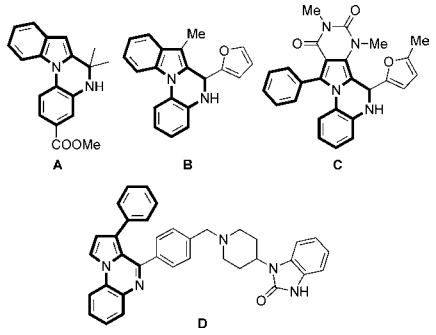


Figure 1. Biologically active dihydroindolo-/-pyrrolo[1,2-*a*]-quinoxalines and their derivatives.

Chiral imidodiphosphoric acids, which are composed of two chiral BINOL scaffolds, have shown impressive catalytic efficiency and stereocontrolled ability in several highly enantioselective transformations.[11] However, the structural diversity of chiral imidodiphosphoric acids has remained undeveloped. As part of our ongoing interest in developing new organocatalysts, we have reported VAPOL-type chiral imidodiphosphoric acid in our previous work,[11d] which showed complementary catalytic performance compared to BINOL type catalysts. To fully exploit the great structure advantage of the chiral imidodiphosphoric acids, introducing other fascinating C_2-symmetric scaffolds is a worthwhile endeavor. H_8-BINOL scaffolds, which were first reported by Cram and co-workers in 1978,[12] have showed attractive chiral controlled ability in many enantioselective transformations when applied as chiral phosphoric acids[13] and metallic organophosphates.[14] Inspired by the above work, we developed H_8-BINOL-type chiral imidodiphos-

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phoric acid catalysts **1** (Figure 2) for the first time to further expand the application scope of the newly emerging

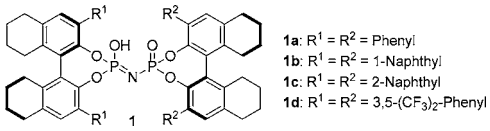


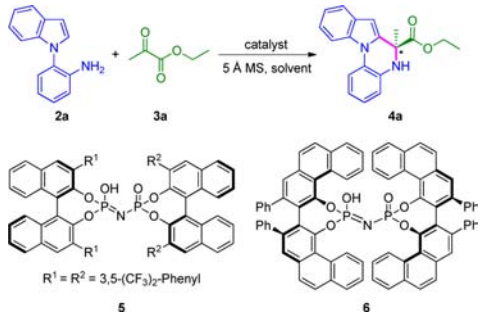
Figure 2. H_8-BINOL-type imidodiphosphoric acids **1**.

imidodiphosphoric acid catalyst. Herein we report the highly enantioselective synthesis of quaternary carbon-centered 5,6-dihydroindolo[1,2-*a*]quinoxalines (DHIQs) and phenyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalines (PDHPQs) via a Pictet–Spengler-type reaction. The chemistry employs an H_8-BINOL type chiral imidodiphosphoric acid catalyst **1d** and shows excellent catalytic activity (up to 98% ee, 98% yield) and high efficiency (as low as 2 mol %) in this capacity.

As shown in Figure 2, H_8-BINOL-type chiral imidodiphosphoric acids **1a–d** were synthesized successfully with modified procedures reported in our previous work[11c,d] by using corresponding H_8-BINOL phosphoryl chlorides and phosphoramides.[15] Unexpectedly, better chemoselectivities and higher yields were observed through the entire synthetic routes compared with the synthesis of BINOL type imidodiphosphoric acid catalysts (see the Supporting Information).[11c] Optically active imidodiphosphoric acids **1a–d** were then tested for the enantioselective synthesis of DHIQs and PDHPQs.

Our preliminary studies revealed that equimolar ratios of unprotected indolyl aniline **2a** and activated ketone pyruvate **3a** were viable substrates for the Pictet–Spengler-type reaction to generate enantiomeric excess of DHIQ product **4a** containing a quaternary stereogenic center in the presence of 2 mol % of imidodiphosphoric acid catalysts **1**. The 3,5-$(CF_3)_2$-phenyl substituted H_8-BINOL catalyst **1d** gave higher yield and enantioselectivity (96% yield, 83% ee, Table 1, entry 4) compared with other phenyl- or naphthyl-substituted H_8-BINOL imidodiphosphoric acids (Table 1, entries 1–4). By comparison, 3,5-$(CF_3)_2$-phenyl-substituted BINOL catalyst **5**, which was similar to H_8-BINOL catalyst **1d** in structure, was also tested and found to be less effective and led to an apparent decrease of stereochemical induction (Table 1, entry 5). It might be because the dihedral angel of H_8-BINOL scaffold is slightly larger than that of the BINOL scaffold,[16] which makes the chiral environment of **1d** more rigid and stereoselective than **5**. VAPOL-type imidodiphosphoric acid **6** was also evaluated under the same conditions but gave inferior enantioselectivity (Table 1, entry 6). Further screening of solvents showed that diethyl ether could improve the stereoselectivity slightly but decrease the reaction rate and yield dramatically (Table 1, entry 7). To our delight, switching the solvent to anisole further enhanced both the ee and yield (Table 1, entry 8). Increasing the catalyst loading of **1d** to 5 mol % did not improve the catalytic profile or stereochemical outcome, while decreasing the catalyst loading to 1 mol % led to depressed chemo- and stereoselectivity (Table 1, entries 9 and 10). The ee value was further increased as the reaction temperature was lowered, although longer reaction time was required (Table 1, entries 11 and 12). The best enantioselectivity was achieved when the reaction was run at −20 °C in anisole by using 2 mol % of catalyst **1d** (Table 1, entry 12). In addition, molecular sieves were essential to this reaction for the dehydration step.

Table 1. Optimization of the Reaction Conditions for DHIQs[a]



entry	cat. (mol %)	solvent	temp (°C)	time	yield[b] (%)	ee[c] (%)
1	**1a** (2)	toluene	rt	12 h	61	34
2	**1b** (2)	toluene	rt	12 h	73	37
3	**1c** (2)	toluene	rt	12 h	69	33
4	**1d** (2)	toluene	rt	12 h	96	83
5	**5** (2)	toluene	rt	12 h	87	75
6	**6** (2)	toluene	rt	12 h	90	8
7	**1d** (2)	diethyl ether	rt	2 d	52	85
8	**1d** (2)	anisole	rt	12 h	95	89
9	**1d** (5)	anisole	rt	8 h	95	89
10	**1d** (1)	anisole	rt	2 d	89	87
11	**1d** (2)	anisole	0	1 d	94	91
12	**1d** (2)	anisole	−20	2 d	96	93

[a]Reactions were performed with 0.1 mmol of **2a**, 0.1 mmol of **3a**, 70 mg 5 Å MS, and 1 mL of solvent. [b]Yield of the isolated product. [c]Determined by HPLC analysis on Chiralcel AD-H or OD-H columns.

Using the optimized reaction conditions (Table 1, entry 12), the substrate scope was subsequently investigated. The synthesis of DHIQs **4** from indolyl anilines **2** and activated ketones **3** was shown to tolerate a variety of different substitution patterns. As summarized in Scheme 1, substrate **2** with a methyl group on 3-position of the indole moiety gave rise to DHIQ **4b** in high yield with excellent enantioselectivity (92% yield, 95% ee). Changing ethyl pyruvate **3a** to phenyl pyruvate **3b** afforded DHIQ **4c** with even better enantioselectivity (98% ee). Substrate **2c** with a bromo-group on 4-position of the indole moiety and phenyl pyruvate **3b** provided the corresponding product **4d** in 96% yield and 94% ee, and its absolute configuration was further confirmed by X-ray crystallography (Scheme 1).[17] Substrate **2** bearing either electron-donating, electron-withdrawing, or aryl groups on the 5-position of the indole moiety reacted with either ethyl pyruvate **3a** or phenyl pyruvate **3b** to furnish the chiral DHIQs **4e–j** with high yields and enantioselectivities (74–97% yield, 84–93% ee). Modification of the aniline moiety on substrate **2** was also examined, and DHIQ **4k** was obtained with the best result in Scheme 1 (97% yield and 98% ee). Then we investigated the tolerance for substrate **3**. Benzyl, 2-naphthyl, or *tert*-butyl pyruvates **3c–e** were employed and smoothly underwent the standard conditions to give DHIQs **4l–n** with excellent yields and enantioselectivities (78–92% yield, 92–96% ee). In addition to pyruvates, butanedione was also used to give the corresponding DHIQ **4o** in high yield with excellent enantioselectivity. Furthermore, this transformation could be performed on gram scale (Scheme 1, **4c**) without any loss of yield (96%) but with slightly decreased enantioselectivity (97% ee).

Aldehydes were also screened for this reaction. However, only moderate enantioselectivities were achieved in most cases.

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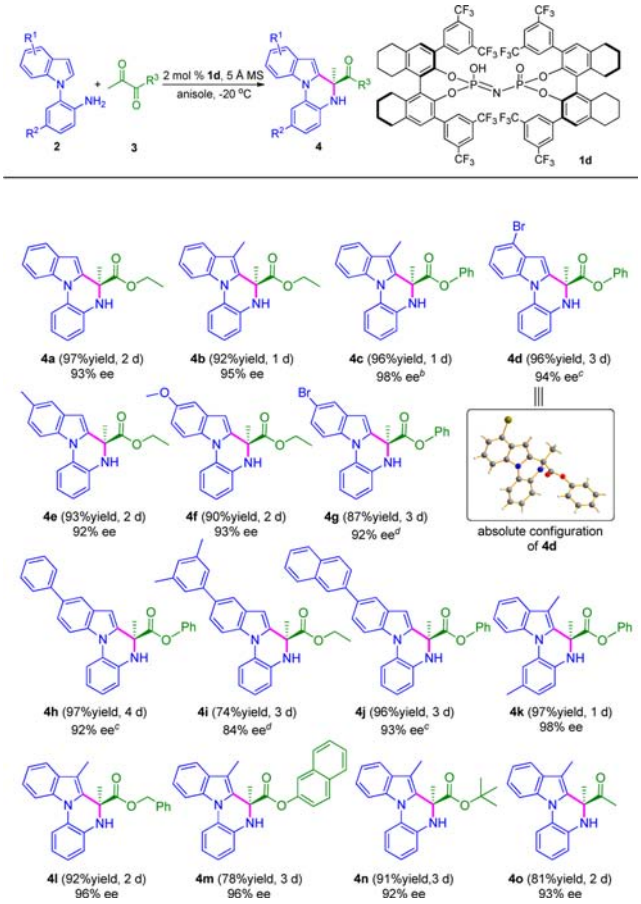
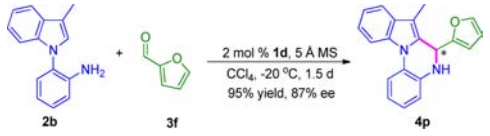
Scheme 1. Pictet−Spengler−Type Reaction for DHIQs[a]



[a]Reactions were performed with 0.1 mmol of **2**, 0.1 mmol of **3**, 70 mg 5 Å MS, and 2 mol % of catalyst **1d** in 1 mL of anisole at −20 °C. Isolated yields. The ee value was determined by HPLC analysis on Chiralcel AD-H or OD-H column. [b]1.11 g of product (3.02 mmol, 97% ee, 96% yield) was obtained when the gram-scale reaction was carried out. [c]Reactions were run at 5 °C. [d]Reactions were run at 25 °C.

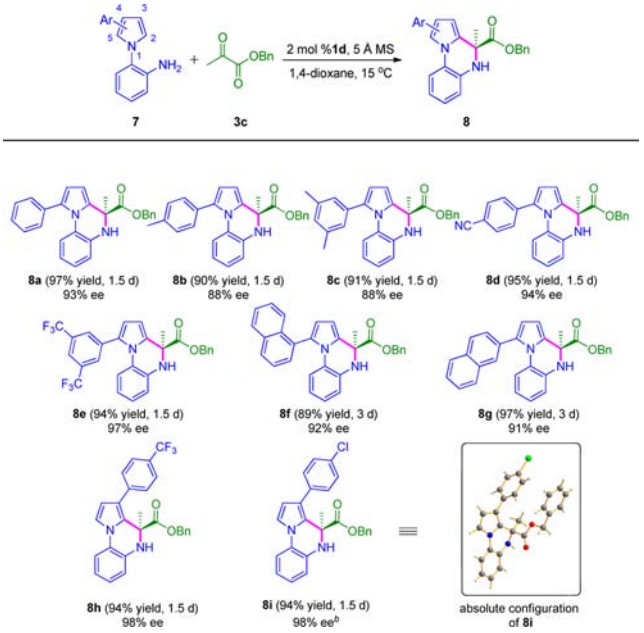
Fortunately, when methylindolyl aniline **2b** and furaldehyde **3f** were employed as the substrates, DHIQs **4p** (compound **B** in Figure 1) was obtained with high yield and good enantioselectivity (Scheme 2). Notably, DHIQ **4p** has recently been discovered as a new HIV-1 inhibitor in vitro, which showed promising anti-HIV-1 activities.[3]

Scheme 2. One-Step Enantioselective Synthesis of HIV-1 Inhibitor 4p



Encouraged by successful enantioselective synthesis of chiral DHIQs **4**, we next turned our attention to enantioselective synthesis of chiral PDHPQs. Although similar work has been reported by Tian and co-workers,[10] the substrates with substituents on the pyrrole ring were not investigated and only tertiary chiral carbon centers were constructed in their products. In addition, their catalyst loading was high (10 mol %). In our work, we have constructed two kinds of PDHPQ frameworks containing a crowded quaternary chiral carbon center by the newly developed H_8-BINOL imidodiphosphoric acid catalyst **1d** with low catalyst loading (2 mol %). The reaction conditions were reoptimized, and the best result was obtained in 1,4-dioxane at 15 °C. When benzyl pyruvate **3c** was selected as the activated ketone, substrate **7** with a range of aryl groups on the 2- or 3-position of pyrrole ring reacted smoothly to give 3- or 5-PDHPQs **8** with high yields and enantioselectivities. The C-5 position of the pyrrole ring in 2-phenylpyrrolyl substrates **7a−g** attacked their intramolecular imine intermediates and produced 5-PDHPQ **8a−g** as the products. The introduction of electron-donating groups on the phenyl moiety was found to slightly decrease the ee value (Scheme 3, **8b** and **8c**). On the other hand,

Scheme 3. Pictet−Spengler-Type Reaction for PDHPQs and NDHPQs[a]



[a]Reactions were performed with 0.1 mmol of **7**, 0.1 mmol of **3c**, 70 mg of 5 Å MS, and 2 mol % of catalyst **1d** in 1 mL of 1,4-dioxane at 15 °C. Isolated yields. The ee value was determined by HPLC analysis on a Chiralcel AD-H or OD-H column. [b]1.05 g of product (2.45 mmol, 98% ee, 96% yield) was obtained when the gram-scale reaction was carried out.

the presence of electron-withdrawing substituents on the phenyl moiety were favored, and 5-PDHPQs **8d** and **8e** were formed with excellent yields (94−95%) and enantioselectivities (94−97% ee). 1-Naphthyl- and 2-naphthyl-substituted substrates could also give satisfying results and 5-naphthyl-4,5-dihydropyrrolo[1,2- *a*]quinoxalines (5-NDHPQs) **8f** and **8g** were obtained with excellent yields (89−97%) and enantioselectivities (91−92% ee). 3-Phenylpyrrolyl substrates **7h** and **7i** were also tested, and the more crowded C-2 position of the pyrrole ring attacked their intramolecular imine intermediates and produced 3-PDHPQ **8h** and **8i** as the main products with excellent yields and remarkable enantioselectivities (94% yield and 98% ee in both cases). The absolute configuration of the optically active **8i** was established by single-crystal X-ray structure analysis (Scheme 3).[18] Moreover, **8i** could also be obtained through gram-scale reaction without any loss of chemo- and stereoselectivity (Scheme 3).

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In conclusion, we have developed H_8-BINOL chiral imidodiphosphoric acids, which enabled the highly efficient and enantioselective synthesis of quaternary carbon-centered DHIQs and PDHPQs with low catalyst loading. These two Pictet−Spengler-type reactions were both amenable to gram scale, which provided practical and convenient ways for the further biological activity studies of DHIQs and PDHPQs. In addition, a straightforward one-step procedure has been developed for the rapid synthesis of promising HIV-1 inhibitor DHIQ **4p** with high yield and good enantioselectivity. Further applications of H_8-BINOL chiral imidodiphosphoric acid catalysts and the transformations mentioned above are currently being investigated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds and CIF files for compounds **4d** and **8i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) CCDC 1008679 (compound **4d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(18) CCDC 1011722 (compound **8i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.