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Highly Enantioselective Synthesis of 2,3-Dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-ones via Catalytic Asymmetric Intramolecular Cascade Imidization−Nucleophilic Addition−Lactamization

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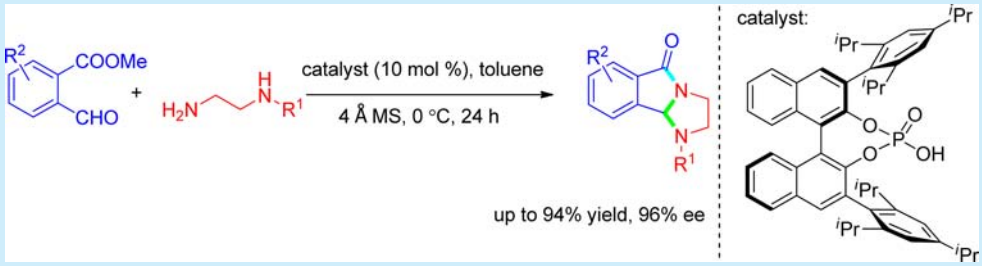
Supporting Information



ABSTRACT: Highly enantioselective catalytic asymmetric intramolecular cascade imidization−nucleophilic addition−lactamization of N^1-alkylethane-1,2-diamine with methyl 2-formylbenzoate catalyzed by a chiral phosphoric acid represents the first efficient method for the preparation of medicinally interesting chiral 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-ones with high yields and excellent enantioselectivities. This strategy has been shown to be quite general toward various methyl 2-formylbenzoates.

Nitrogen-containing cyclic compounds with chiral centers have been in synthetic demand in recent years.[1] In particular, 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-ones possess a unique cyclic chiral center, and many compounds containing this heterocyclic unit in their skeletons have attracted considerable interest, as they consist of commonly used building blocks in a wide range of naturally occurring and/or bioactive substances.[2] The biological activities of these compounds have been well-studied and have shown several promising applications, including anti-inflammatory agents,[3] analgesics,[4] blood pressure lowering agents,[5] spasmolytic agents,[6] antitussives,[7] sedatives, antirheumatics,[8] and anorectic agents.[9]

Although several methods for the synthesis of racemic 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-ones are available currently,[10] limited approaches to enantioselective synthesis of the corresponding chiral compounds have been developed. The first example for the synthesis of chiral 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-ones was successfully accomplished by Katritzky[11] et al. via an intramolecular nucleophilic addition−lactamization cascade between 2-formylbenzoic acid and chiral 1,2-ethylenediamine under Dean−Stark conditions. Afterward, Yamada and co-workers reported a chiral sulfonic auxiliary assisted method for this target synthesis.[12] To date, catalytic asymmetric synthesis of 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-one still remains a grand challenge. To the best of our knowledge, there has been no effective related methodology reported so far. Herein, we disclose the first highly enantioselective synthesis of 2,3-dihydro-1*H*-imidazo[2,1-*a*]-isoindo l-5(9b*H*)-ones via asymmetric catalysis (Figure 1).

Chiral phosphoric acids have proven to be efficient catalysts for many important asymmetric transformations.[13] Antilla[14] showed that many chiral *N*,*N*-aminals, *N*,*O*-acetals, *N*,*S*-acetals,

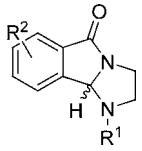


Figure 1. Structure of 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-ones.

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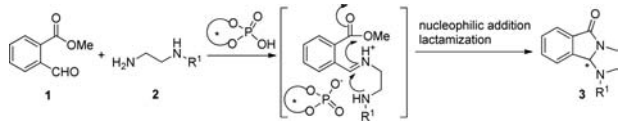
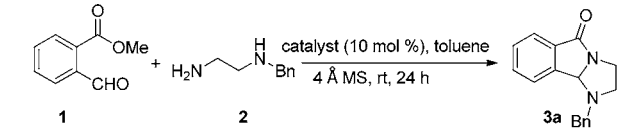
and *N*,peroxide acetals can be prepared using chiral phosphoric acids catalysts via nucleophilic addition of imines. The List group[15] and Rueping group[16] independently developed protocols for enantioselective synthesis of the drug molecules 2,3-dihydroquinazolinones bearing a cyclic *N*,*N*-aminals structure via intramolecular amidation between aldehydes and 2-aminobenzamides. These cyclic aminal compounds were also successfully synthesized with high enantioselectivities by Tian et al. and Lin et al.[17] Meanwhile, Toste[18] and co-workers established a methodology for the synthesis of similar cyclic *N*,*N*-aminals via cross-dehydrogenative coupling catalyzed by axially chiral PAs based on BINOL bearing 1,2,3-triazoles at the 3- and 3′-positions. Among the reactions using chiral phosphoric acid catalysts, most of the nucleophiles were amides, the use of nonsubstituted alkyl amines instead is rare.[19] Inspired by these pioneer works, attempted investigation of the asymmetric synthesis of *N*,*N*-aminal using nonsubstituted alkylamines as nucleophiles directly was made by employing chiral phosphoric acids (Scheme 1).

Scheme 1. Proposed Pathway for the Preparation of Chiral 2,3-Dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-ones



We started our investigations on the Brønsted acid catalyzed reaction of methyl 2-formylbenzoate (1.0 equiv) with N^1-benzylethane-1,2-diamine (1.0 equiv). The reaction was carried out at ambient temperature using a chiral phosphoric acid derived from 3,3′-phenyl-substituted BINOL ((*R*)-**4a**, 10 mol %, Scheme 2) as the catalyst, toluene as the solvent, and 4 Å MS as a desiccant. The intramolecular imidization−nucleophilic addition−lactamization proceeded smoothly, and the desired product 1-benzyl-2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5-(9b*H*)-one was obtained in high yield (89%). However, almost no enantioselectivity (2% ee) was found in the initial experiment. Encouraged by the reactivity, we further examined a number of axially chiral phosphoric acids for the model reaction (Scheme 2). Although most of the tested catalysts aff-orded poor enantioselectivities, phosphoric acid (*R*)-**4i** having a 2,4,6-triisopropylphenyl moiety provided the desired product **3a** in 91% yield with 59% ee.

Scheme 2. Survey of the Catalysts[a]



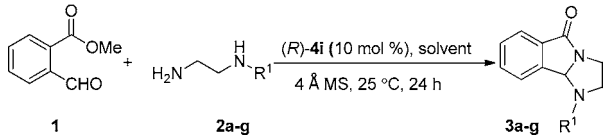
catalyst: **4a-4i**

(*R*)-**4a**, R = Ph	89% yield,	2% ee
(*R*)-**4b**, R = 4-MeC_6H_4	90% yield,	0% ee
(*R*)-**4c**, R = 4-MeOC_6H_4	87% yield,	37% ee
(*R*)-**4d**, R = 3,5-di-^{t}BuC_6H_3	94% yield,	9% ee
(*R*)-**4e**, R = $SiPh_3$	92% yield,	9% ee
(*R*)-**4f**, R = 1-naphthyl	86% yield,	0% ee
(*R*)-**4g**, R = 2-naphthyl	87% yield,	3% ee
(*R*)-**4h**, R = 9-anthracenyl	92% yield,	8% ee
(*R*)-**4i**, R = 2,4,6-tri-^{i}PrC_6H_2	91% yield,	59% ee
(*S*)-**4i**, R = 2,4,6-tri-^{i}PrC_6H_2	90% yield,	-59% ee

[a]All reactions were run on a 0.1 mmol scale in 1.0 mL of toluene; yield refers to isolated yield; % ee was determined by chiral HPLC. See the Supporting Information for details.

In the optimization of the reaction (Table 1), various solvents were screened. Nonpolar solvents (entries 1 and 2) allowed the transformation process proceeded with moderate enantioselectivities, while the polar solvents (entries 3−7) resulted in lower enantioselectivities. The best solvent was toluene for the reaction system, providing **3a** in 59% ee in the trial run (entry 1). It should be noted that steric hindrance of substrates is an important factor in the asymmetric catalysis. Substituents R^1 on N^1-R^1-ethane-1,2-diamine were also explored. The methyl group gave a poor enantioselectivity with high yield (94% yield, 19% ee) while introducing a more bulky group such as diphenylmethyl group was found to be beneficial to the enantioselectivity yet reduced the product yield (entry 10, 55% yield, 77% ee). The benzyl group (entries 11−13) provided a high yield (from 86 to 91%), and the ee value was increased when a more bulky substituent existed in the ortho-position. The 2,6-diisopropylbenzyl group was found to be the optimal group for the transformation with respect to enantioselectivity (entry 13, ee up to 90%). Lower catalyst loading (5 mol %) showed a slight decrease in enantioinduction (entry 14, 88% ee). In the absence of acid catalyst, poor yield for the target product was afforded (entry 15, 45% yield). It is interesting to note that reaction temperature played a key role in rendering the cascade transformation highly enantioselective. When the reaction was conducted at 0 °C, excellent enantioselectivity was observed (entry 16, 96% ee). Both the yield and ee dropped dramatically when the reaction was carried out at −10 °C (entry 17, 88% yield, 86% ee) or −20

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	R^1	product	yield[b] (%)	ee[c] (%)
1	$PhCH_3$	Bn	**3a**	91	59
2	C_6H_6	Bn	**3a**	88	55
3	CH_2Cl_2	Bn	**3a**	87	40
4	$CHCl_3$	Bn	**3a**	90	9
5	Et_2O	Bn	**3a**	87	37
6	THF	Bn	**3a**	86	47
7	CH_3CN	Bn	**3a**	90	0
8	$PhCH_3$	Me	**3b**	94	19
9	$PhCH_3$	^{i}Pr	**3c**	40	29
10	$PhCH_3$	Ph_2CH	**3d**	55	77
11	$PhCH_3$	4-^{i}PrBn	**3e**	88	64
12	$PhCH_3$	2-^{i}PrBn	**3f**	86	72
13	$PhCH_3$	2,6-di(^{i}Pr)Bn	**3g**	91	90
14[d]	$PhCH_3$	2,6-di(^{i}Pr)Bn	**3g**	82	88
15[e]	$PhCH_3$	2,6-di(^{i}Pr)Bn	**3g**	45	0
16[f]	$PhCH_3$	2,6-di(^{i}Pr)Bn	**3g**	90	96
17[g]	$PhCH_3$	2,6-di(^{i}Pr)Bn	**3g**	88	86
18[h]	$PhCH_3$	2,6-di(^{i}Pr)Bn	**3g**	80	70

[a]Unless otherwise noted, all reactions were run on a 0.1 mmol scale in 1.0 mL of solvent with 10 mol % catalyst loading at 25 °C. [b]Isolated yield. [c]The ee was determined by Chiral HPLC; see the Supporting Information for details. [d]Reaction was run with 5 mol % catalyst loading. [e]In the absence of chiral catalyst added. [f]Reaction was run at 0 °C. [g]Reaction was run at −10 °C. [h]Reaction was run at −20 °C.

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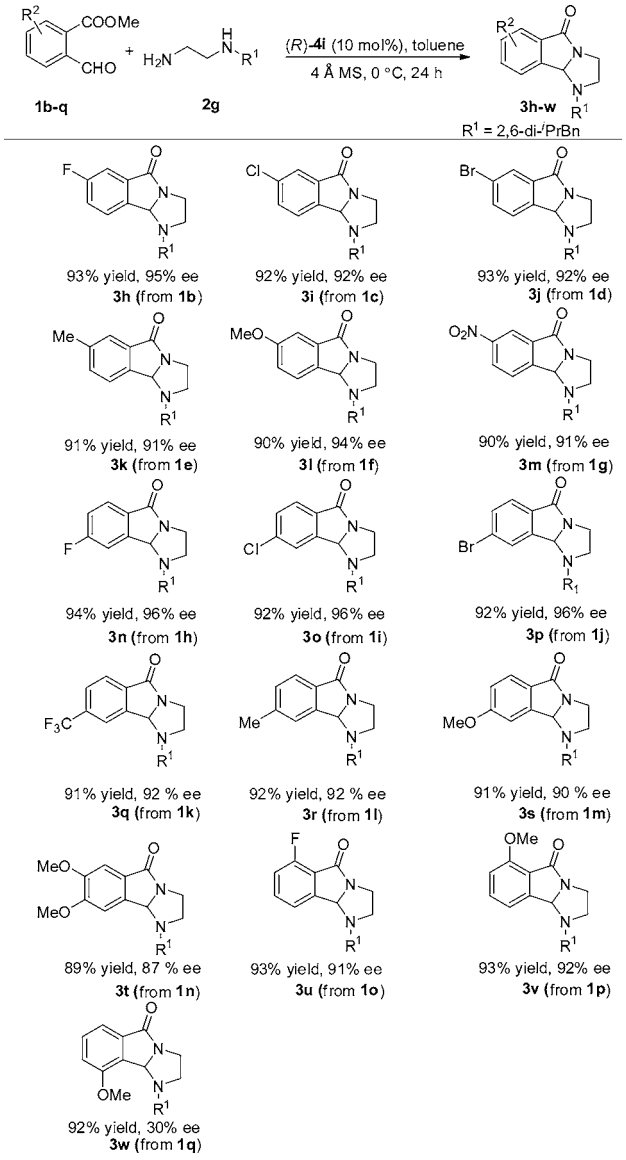
°C (entry 18, 80% yield, 70% ee). Therefore, 0 °C was selected as the optimal temperature for the balance between the catalyst activity and product enantioselectivity (entry 16, 90% yield, 96% ee).

After the optimal conditions were optimized, reaction scope with regard to variation of the aryl substituent of methyl 2-formylbenzoate was investigated (Scheme 3). A variety of

Scheme 3. Scope of Substrates 1[a]



[a]All reactions were run on a 0.1 mmol scale in 1.0 mL of toluene; yield refers to isolated yield; % ee was determined by Chiral HPLC. See the Supporting Information for details.

substitutions were proven to be successful under this catalytic system. For instance, substrates bearing halogen at the 4 or 5 position (**1b**−**d**,**h**−**j**) allowed for excellent enantioselectivities (92% to 96% ee, **3h**−**j**,**n**−**p**). The substrates with an electron-donating group (methoxyl) at the 4, 5, or 6 position (**1f**,**m**,**p**) were all excellent for the reaction, giving the corresponding products with 90−94% ee's (**3l**,**s**,**v**). Substrates possessing an electron-withdrawing substituent 5-nitro (**1g**) or 4-trifluoromethyl (**1k**) provided products **3m** and **3q** in excellent yields and enantioselectivities (90% and 91% yields 90% and 91% ees, respectively). Substrates containing a 4-methyl substituent (**1l**) proved viable and gave product **3r** with 92% ee. Substrates having a 4, 5-dimethoxyl substituent (**1n**) gave product **3t** with 88% ee. An exceptional situation was observed in the reaction of substrate **1q**. The poor enantioselectivity (30% ee) is presumably due to detrimental steric interaction between 3-methoxy and the R^1 group.

The absolute stereochemistry of the chiral 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-one was determined by the single-crystal X-ray diffraction of **3p** (Figure 2). This result unambiguously shows that the absolute configuration of product **3p** to be the (*S*)-form.

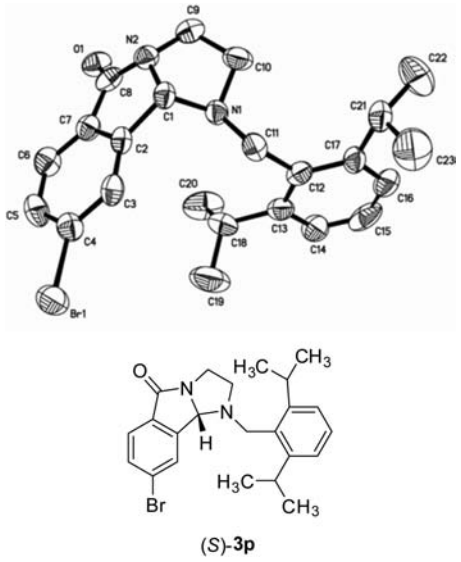


Figure 2. Single-crystal X-ray structure of product **3p**.

In conclusion, we have successfully developed the first catalytic asymmetric synthesis of 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5(9b*H*)-ones via an intramolecular cascade imidization−nucleophilic addition−lactamization. This one-pot sequence using a chiral phosphoric acid as the catalyst provides a simple and efficient approach to the preparation of various medicinally important chiral 2,3-dihydro-1*H*-imidazo[2,1-*a*]isoindol-5-(9b*H*)-ones in high yields with excellent enantiomeric excesses under mild reaction conditions (up to 94% yield and 96% ee). Further work will be directed toward the extension of substrate scope, mechanistic studies, and synthetic application.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and NMR spectra of all new products. 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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