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Asymmetric Hydrogenation of α-Purine Nucleobase-Substituted Acrylates with Rhodium Diphosphine Complexes: Access to Tenofovir Analogues

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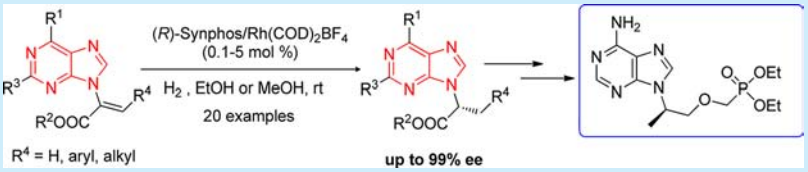
Supporting Information



ABSTRACT: The first asymmetric hydrogenation of α-purine nucleobase-substituted α,β-unsaturated esters, catalyzed by a chiral rhodium (*R*)-Synphos catalyst, has been developed. A wide range of mono- and disubstituted acrylates were successfully hydrogenated under very mild conditions in high yields with good to excellent enantioselectivities (up to 99% ee). This method provides a convenient approach to the synthesis of a new kind of optically pure acyclic nucleoside and Tenofovir analogues.

Acyclic nucleosides and their phosphonates possess a broad spectrum of potential antiviral activity, and some of them are currently used in clinics.[1] Representative examples are shown in Figure 1. The chirality of the aliphatic side chain has proven to play a pivotal role in their relevant bioactivities. For example, introduction of a methyl group into the side chain of Adefovir, leading to Tenofovir, improved its anti-HBV (hepatitis B virus) activity.[2] In addition, the *S*-enantiomer of Cidofovir shows high antiviral activity, whereas the *R*-isomer is devoid of effect.[3] Therefore, the development of new methods for the synthesis of chiral acyclic nucleosides and their phosphonates has received more attention in recent years.[4] Among the various reported approaches for synthesizing such chiral compounds, including chiral pool and chiral auxiliary strategies,[4] the more efficient and atom-economic asymmetric catalysis is less studied.[5]

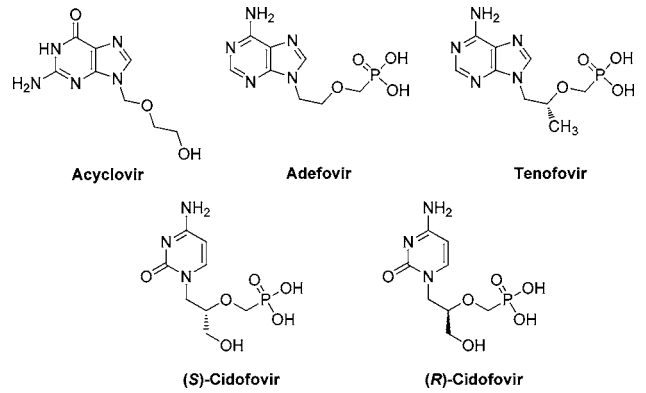


Figure 1. Representative acyclic nucleosides and nucleoside phosphonates possessing antiviral activities.

Transition-metal-catalyzed asymmetric hydrogenation has been established as one of the most powerful tools for preparing enantiomerically pure compounds in organic synthesis.[6] Many efficient chiral rhodium and ruthenium diphosphine catalysts have been developed for the hydrogenation of C═C bonds bearing an adjacent coordinating functional group (CFG) with excellent activities and enantioselectivities. However, hydrogenation of unsaturated substrates bearing a N-containing heterocyclic group remains a great challenge because of the strong coordinating ability of the nitrogen moiety, which often results in catalyst deactivation. Successful examples in the hydrogenation of such types of substrates are rare.[7] For example, Zhou and co-workers recently reported a highly efficient iridium-catalyzed asymmetric hydrogenation of pyridyl-containing cyclic imines using a substituent-controlled strategy.[7l] It was found that the introduction of a substituent at the *ortho* position of the pyridyl ring could reduce its coordinating ability. In contrast to the strategies of preventing coordination of the nitrogen atom to the metal center,[6,7b−e,l] we envisioned that a suitable N-containing heterocyclic group may be used to serve as a CFG

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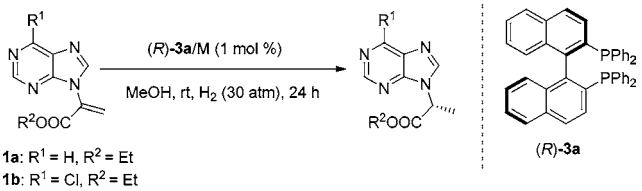
to facilitate the asymmetric hydrogenation. Given the importance of nucleosides in medicinal chemistry, as described above, we exemplified this new strategy with the asymmetric hydrogenation of α-nucleobase-substituted acrylates. To the best of our knowledge, this is the first highly enantioselective hydrogenation of nucleobase-containing α,β-unsaturated acid esters with chiral rhodium diphosphine catalysts at ambient temperature and pressure with excellent enantioselectivity.[8]

In our initial attempt, we examined the asymmetric hydrogenation in methanol using rhodium and ruthenium complexes of (*R*)-BINAP as the catalysts. The effect of a substituent on the 6-position of the purine skeleton and the ester or acid groups on catalytic performance was investigated. As shown in Table 1, the

Table 1. Asymmetric Hydrogenation of Acrylates 1a−c with Different Chiral Metal Catalysts[a]



1a: R^1 = H, R^2 = Et
1b: R^1 = Cl, R^2 = Et
1c: R^1 = Cl, R^2 = H

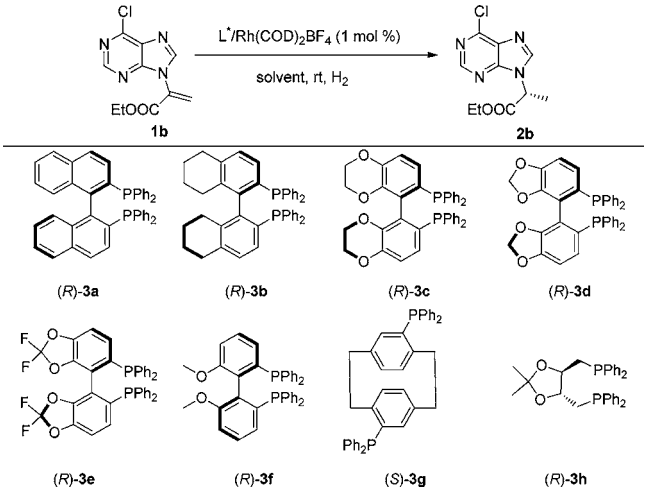
entry	R^1/R^2	metal	conv (%)[b]	ee (%)[c]
1	H/Et (**1a**)	$[Ru(C_6H_6)Cl_2]_2$	<5	
2	H/Et (**1a**)	$[Rh(COD)Cl]_2$	43	44
3	Cl/Et (**1b**)	$[Ru(C_6H_6)Cl_2]_2$	>95	58
4	Cl/Et (**1b**)	$[Rh(COD)Cl]_2$	>95	93
5	Cl/H (**1c**)	$[Rh(COD)Cl]_2$	>95	86

[a]Reaction conditions: substrate **1** (0.15 mmol), MeOH (2 mL), chiral metal catalyst (1 mol %) generated in situ by mixing a metal precursor with (*R*)-**3a** (1.1 equiv), H_2 (30 atm), stirred at rt for 5 h. [b]Determined by ^{1}H NMR analysis. [c]Determined by chiral HPLC analysis with a chiral OD-H column.

ruthenium catalyst was found to be inactive in the hydrogenation of ethyl 2-(6*H*-9*H*-purine-9-yl)acrylate **1a** (entry 1). Low conversion and enantioselectivity were observed for the rhodium catalyst (entry 2). In sharp contrast, introducing a chloro group on the 6-position of the purine skeleton (**1b**) improved the reactivity and enantioselectivity significantly (entries 3 and 4), and excellent ee value was achieved for the rhodium catalyst. Particularly, the acid substrate **1c** was hydrogenated smoothly, giving the product with the same configuration, albeit with low enantioselectivity (entry 5). These results suggested that the substituent on the purine skeleton could tune the coordination strength of nitrogen atoms, and consequently, the heterocyclic purine ring (not the acid group) might act as the CFG (instead of the poison) to facilitate the hydrogenation process (for a proposed coordination model, see Scheme S2 in the Supporting Information).

Encouraged by this exciting result, we then chose the asymmetric hydrogenation of **1b** with chiral rhodium diphosphine catalysts as the model reaction for optimizing the reaction conditions. The solvent effect was first investigated at room temperature under 30 atm of hydrogen for 24 h. As shown in Table 2 and Table S1, the reaction was found to be sensitive to solvent. Hydrogenation proceeded smoothly in alcoholic solvents and acetone (entries 1−5), and ethanol was the optimal solvent in terms of both reactivity and enantioselectivity (entry 15 vs 16 in Table S1). Interestingly, in contrast to other functional olefins,[9] the enantioselectivity was insensitive to

Table 2. Optimization of Conditions for Asymmetric Hydrogenation of 1b[a]



entry	solvent	ligand	H_2 (atm); t (h)	conv (%)[b]	ee (%)[c]
1	MeOH	(*R*)-**3a**	30; 24	>95	93
2	EtOH	(*R*)-**3a**	30; 24	>95	95
3	IPA	(*R*)-**3a**	30; 24	>95	90
4	*t*-BuOH	(*R*)-**3a**	30; 24	>95	89
5	acetone	(*R*)-**3a**	30; 24	>95	96
6	CH_2Cl_2	(*R*)-**3a**	30; 24	70	76
7	THF	(*R*)-**3a**	30; 24	12	90
8	EtOAc	(*R*)-**3a**	30; 24	38	87
9	EtOH	(*R*)-**3a**	10; 5	>95	95
10	EtOH	(*R*)-**3a**	1; 5	>95	95
11	EtOH	(*R*)-**3b**	1; 5	94	92
12	**EtOH**	**(*R*)-3c**	**1; 5**	**>95**	**97**
13	EtOH	(*R*)-**3d**	1; 5	70	94
14	EtOH	(*R*)-**3e**	1; 5	38	92
15	EtOH	(*R*)-**3f**	1; 5	>95	93
16	EtOH	(*S*)-**3g**	1; 5	86	−23
17	EtOH	(*R*)-**3h**	1; 5	81	28
18[d]	EtOH	(*R*)-**3c**	1; 5	>95	93
19[e]	EtOH	(*R*)-**3c**	1; 5	44	93

[a]Reaction conditions (unless otherwise noted): substrate **1b** (0.15 mmol), solvent (2 mL), Rh catalyst (1 mol %), stirred at rt for 5 h. IPA = isopropyl alcohol. [b]Determined by ^{1}H NMR analysis. [c]Determined by chiral HPLC analysis with a chiral OD-H column. [d]Substrate **1b** (2.5 mmol), EtOH (5 mL), S/C = 1000, 48 h. [e]Substrate **1b** (2.5 mmol), EtOH (5 mL), S/C = 2000, 48 h.

hydrogen pressure (Table 1 and Table S2). Remarkably, even if the reaction proceeded at ambient temperature and pressure, full conversion and the same ee value were obtained in 5 h (entry 10). Subsequently, some comercially available chiral diphosphine ligands were screened (entries 10−17), and the best result (97% ee) was achieved with (*R*)-Synphos (entry 12). Furthermore, the reaction proceeded smoothly at a low catalyst loading of 0.1 mol % in full conversion with a slightly low enantioselectivity (93% ee) upon prolonged reaction time (entry 18). When the substrate to catalyst ratio (S/C) was furthered increased to 2000, the excellent enantioselectivity still remained unchanged (entry 19).

With the optimal reaction conditions in hand, a series of α-purine nucleobase-containing monosubstituted acrylates were then hydrogenated, and the data are collected in Scheme 1. In most cases, the reaction proceeded smoothly at ambient

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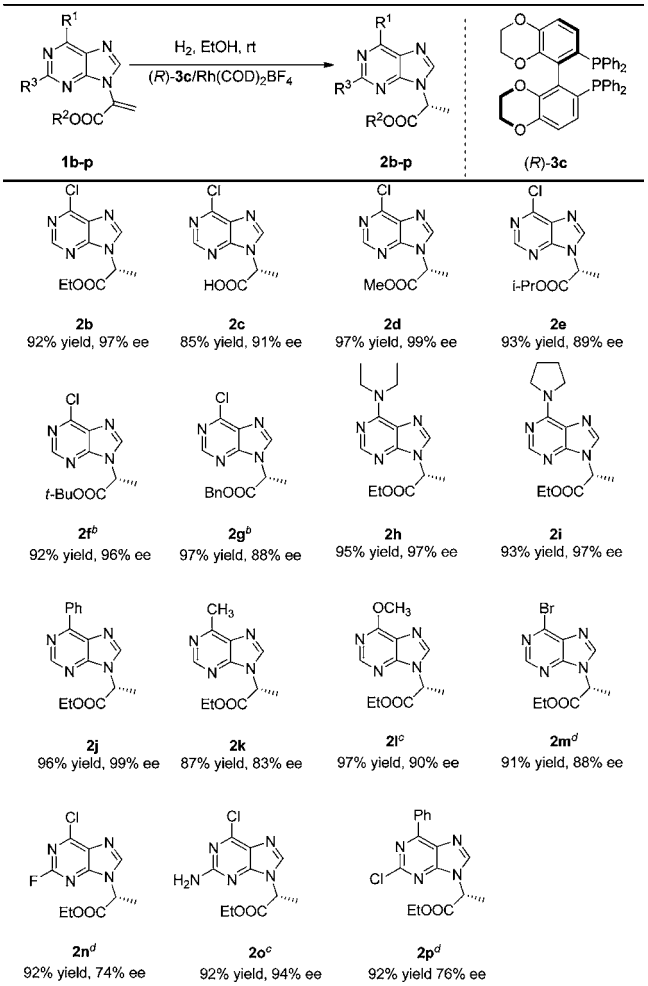
Scheme 1. Asymmetric Hydrogenation of Acrylates 1b−p[a]

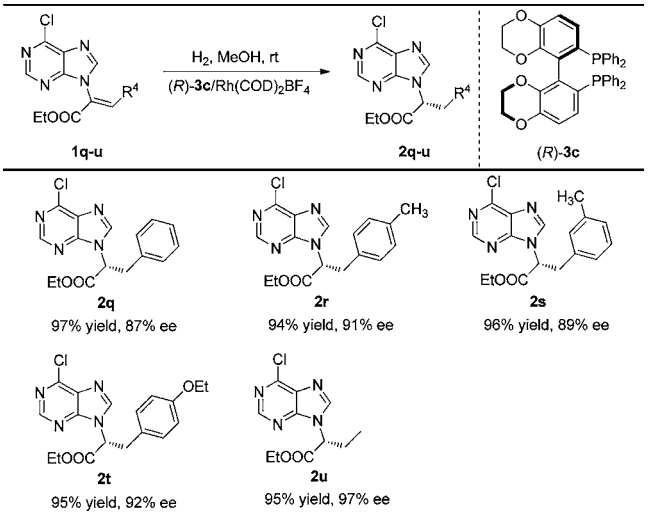


[a]Reaction conditions (unless otherwise noted): substrates **1b−p** (0.15 mmol), EtOH (2 mL), 1 mol % of Rh catalyst, H_2 (1 atm), stirred at rt for 5 h. Yield of isolated product was given. The ee values were determined by chiral HPLC analysis. The absolute configuration of **2b** was determined to be *R* based on single-crystal X-ray analysis of its corresponding alcohol **2ba** (Scheme S1). The configurations of the other products are proposed by analogy. [b]Reaction for 24 h. [c]With 5 mol % of Rh catalyst, H_2 (30 atm), 24 h. [d]H_2 (30 atm), 24 h.

temperature and pressure to give the chiral acyclic nucleosides in high yields with excellent enantioselectivities (up to 99% ee). It was found that the substrates bearing small ester groups (**1b** and **1d**) gave excellent enantioselectivity. Hydrogenation of substrate **1f** bearing bulky ester also proceeded smoothly with excellent ee value, albeit with low reactivity. Notably, hydrogenation of the corresponding acid **1c** gave very good enantioselectivity (91% ee). Moreover, introducing different substituents onto the skeleton of purine (**1h−1p**) was found to influence the reaction. Substrates bearing ethylamino, pyrrolidinyl, and 6-phenyl groups on the 6-position of the purine skeleton were smoothly hydrogenated at ambient temperature and pressure in high yield and excellent enantioselectivity. Low yield and ee value were observed in the hydrogenation of **1k** bearing a small methyl group. The substrate bearing electron-rich methoxyl group (**1l**) led to very low reactivity and enantioselectivity, and full conversion could be achieved with 5 mol % of Rh catalyst under 30 atm of hydrogen. Unlike the 6-chloro derivative, the hydrogenation of a substrate bearing a bromo group on the 6-position (**1m**) was carried out under higher hydrogen pressure for longer reaction time with good enantioselectivity. Notably, substrates bearing two substituents on the purine skeleton (**1n−p**) could also be hydrogenated but gave low reactivity or enantioselectivity.

Intrigued by the results described above, we extended this catalyst system to the hydrogenation of the more challenging α-purine nucleobase-containing disubstituted acrylates (Scheme 2). After reaction condition optimization (Table S4), all

Scheme 2. Asymmetric Hydrogenation of Acrylates 1q−u[a]

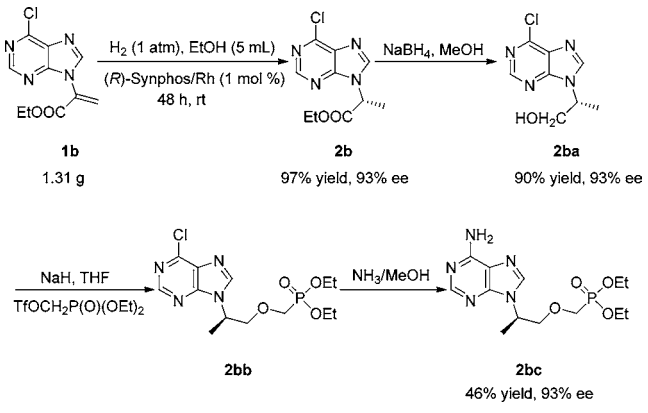


[a]Reaction conditions: substrates **1q−u** (0.15 mmol), MeOH (2 mL), 5 mol % of Rh catalyst, H_2 (30 atm), stirred at rt for 24 h. Yield of isolated product was given. The enantiomeric excesses were determined by chiral HPLC analysis.

disubstituted acrylates **1q−t** bearing an aryl group were successfully hydrogenated with 5 mol % of Rh catalyst under 30 atm of hydrogen pressure to give the chiral acyclic nucleosides in high yields with very good enantioselectivities regardless of different substituents on the aryl group. Notably, excellent enantioselectivity (97% ee) and reactivity were observed in the hydrogenation of substrate **1u** bearing a methyl group.

To demonstrate the synthetic utility of the current methodology, the Tenofovir analogue **2bc**[8b] was synthesized as shown in Scheme 3. The asymmetric hydrogenation of **1b** was carried out

Scheme 3. Asymmetric Synthesis of Tenofovir Analogue (*R*)-2bc



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on a gram scale (1.31 g) in the presence of 1 mol % of Rh catalyst under 1 atm of H_2 in 10 mL of EtOH at room temperature for 48 h, producing (*R*)-**2b** in 97% yield with 93% ee. Then, further reduction of **2b** with $NaBH_4$ in MeOH afforded (*R*)-**2ba** in 90% yield and 93% ee. **2ba** was subsequently treated with NaH and $TfOCH_2P(O)(OEt)_2$ in THF at −20 °C to produce **2bb**, which was used without further purification. Finally, crude product **2bb** underwent aminolysis, giving (*R*)-**2bc** in 46% yield in two steps without any loss of ee.

In conclusion, we have developed the first highly effective asymmetric hydrogenation of α-purine nucleobase-substituted α,β-unsaturated acid esters using chiral rhodium (*R*)-Synphos catalyst. A wide range of mono- and disubstituted acrylates were successfully hydrogenated under very mild conditions in high yields and good to excellent enantioselectivities (up to 99% ee). This new method thus provides a practical and facile approach to the synthesis of a new kind of optically pure acyclic nucleoside and Tenofovir analogues. In addition, a N-containing heterocyclic purine ring was proposed as the CFG to facilitate the asymmetric hydrogenation process. We believe that this new strategy will stimulate future work on the asymmetric hydrogenation of other more challenging unsaturated substrates bearing heterocyclic groups.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00869.

Experimental procedures, synthesis method of the starting materials, and compound characterization data (PDF)

X-ray data for compound **2ba** (CIF)

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Notes

The authors declare no competing financial interest.

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