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Enantioselective Intermolecular Cyclopropanations for the Synthesis of Chiral Pyrimidine Carbocyclic Nucleosides

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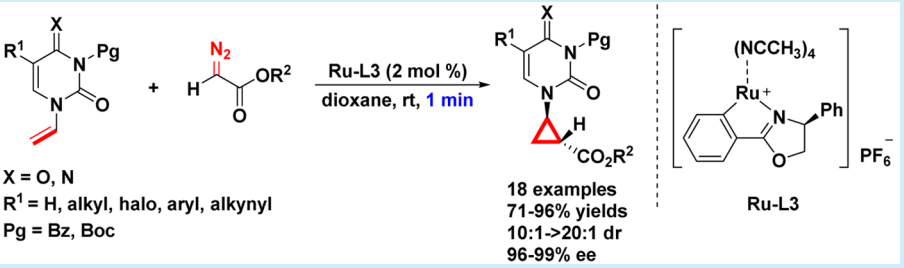
Supporting Information



ABSTRACT: A direct route to chiral cyclopropylpyrimidine carbocyclic nucleoside analogues has been reported via highly enantioselective intermolecular cyclopropanation reactions of N1-vinylpyrimidines with α-diazoesters. With chiral ruthenium(II)−phenyloxazoline complex (2 mol %) as the catalyst, cyclopropyl pyrimidine nucleoside analogues could be obtained in good yields (71−96% yields) with high levels of diastereo- and enantioselectivities (10:1 to >20:1 dr and 96−99% ee) in 1 min.

Chiral nucleosides and their derivatives have shown significant antivirus and antitumor activities.[1] As shown in Figure 1, sofosbuvir is a novel anti-HCV (hepatitis C virus)

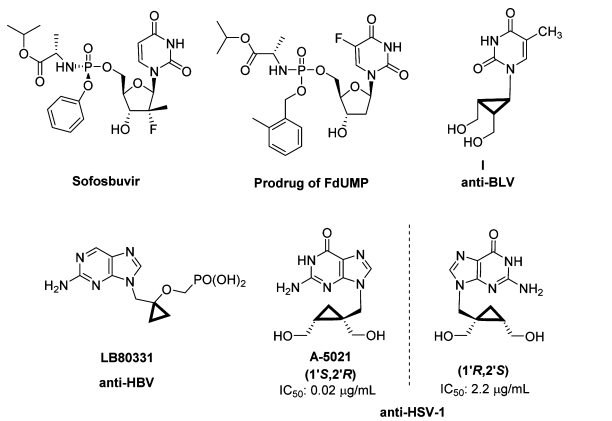


Figure 1. Selected nucleosides with biological activities.

agent that has displayed an impressively excellent treatment effect that has never been seen before in HCV-infected patients.[2] In 2016, Chang's group developed an orally active and liver-targeted prodrug of 5-fluoro-2′-deoxyuridine (FdUMP) for the treatment of hepatocellular carcinoma.[3] Since then, much effort has gone toward the search for new antiviral or anticancer nucleoside agents. Chiral carbocyclic nucleosides containing a cyclopropane moiety have attracted increasing interest owing to their fixed conformation and potent antiviral properties.[4] Cyclopropyl thymidine nucleoside **I** has shown antiviral activity against BLV (bovine leukemia virus).[5] The phase II clinical trials of LB80331 and A-5021 are in progress for the treatment of HBV (hepatitis B virus) and HSV-1 (herpes simplex virus), respectively.[6] In particular, the (1′*S*,2′*R*)-enantiomer A5021 is superior to its enantiomer in its activity against HSV-1.[6b] Therefore, searching for a direct route to synthesize chiral cyclopropyl carbocyclic nucleoside analogues is highly desirable.

The traditional route for the synthesis of chiral cyclopropyl pyrimidine carbocyclic nucleosides is based on a linear approach[7] in which the pyrimidine moiety is constructed from a chiral cyclopropyl urea. However, the generation of the chiral cyclopropyl urea always requires multiple steps from a chiral synthon (Scheme 1a). As we know, the asymmetric cyclopropanation reaction between diazo compounds and alkenes represents an attractive route to construct optically pure cyclopropanes.[8,9] In 2009, the Davies group reported a Rh(II)-catalyzed highly enantioselective cyclopropanation of *N*-vinylphthalimide with α-aryl diazoketone.[10] Later, the Iwasa group developed a ruthenium(II)−phenyloxazoline (Ru−Pheox) complex catalyzed asymmetric cyclopropanation of vinyl carbamates with diazoesters to afford the corresponding cyclopropylamine derivatives in excellent results.[11] In 2014,

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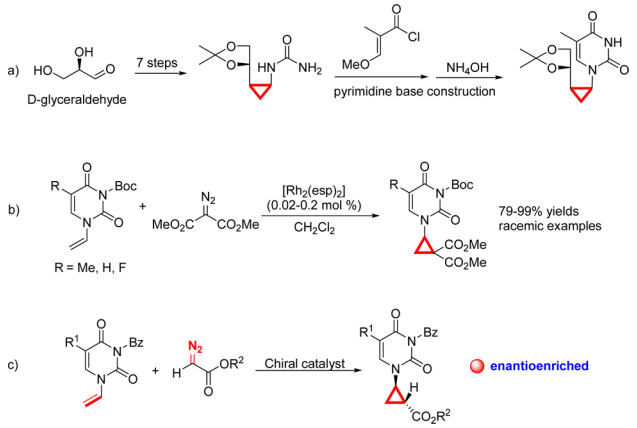
Scheme 1. Different Strategies To Construct Cyclopropyl Pyrimidine Carbocyclic Nucleoside Analogues

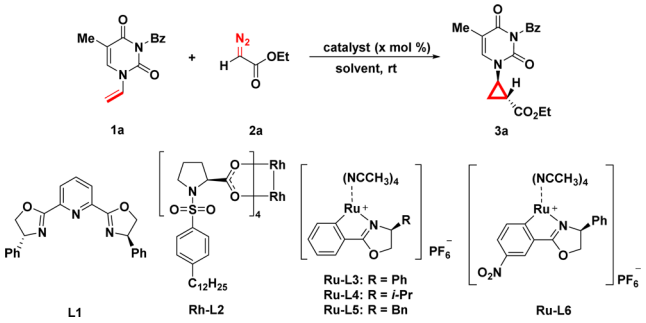


Waser's group reported the first racemic synthesis of cyclopropylpyrimidine carbocyclic nucleoside analogues via the intermolecular cyclopropanation between N1-vinylpyrimidine and diazodimethylmalonate (Scheme 1b).[12] To the best of our knowledge, no example of enantioselective construction of cyclopropylpyrimidine carbocyclic nucleoside analogues in a direct approach has been reported to date. Herein, we report an enantioselective synthesis of cyclopropyl pyrimidine carbocyclic nucleoside analogues via asymmetric intermolecular cyclopropanation reactions of N1 vinylpyrimidine and α-diazoesters (Scheme 1c).[13]

Initially, the reaction between Bz-protected N1-vinylthymine **1a** and ethyl 2-diazoacetate **2a** was chosen as the model reaction (Table 1). When CuCl−pybox **L1** or Rh−**L2** was employed as the catalyst in dioxane at room temperature for 12 h, the cyclopropanation reaction did not occur (entries 1 and 2). To our delight, chiral Ru−Pheox **L3** could give the corresponding carbocyclic nucleoside analogue **3a** in 96% yield, 16:1 dr, and 99% ee (entry 3). It should be noted that the cyclopropanation is complete when N_2 gas is no longer escaping. In the presence of Ru−**L3** as the catalyst, the addition of ethyl 2-diazoacetate **2a** was finished within 1 min, and the cyclopropanation was finished along with the complete consumption of ethyl 2-diazoacetate **2a**. Subsequently, different chiral oxazoline ligands **L4**−**L6** were screened, and the simple phenyl-substituted Ru−**L3** complex provided better results (entries 3−6). Then several solvents were examined, and dioxane was found to be the better one (entries 3 and 7−10). By lowering the catalyst loading to 2 mol %, excellent results could still be maintained (entries 10 and 11). Even 1 mol % of the catalyst still gave excellent diastereo- and enantioselectivity along with the lower yield (entries 11 and 12). Therefore, the optimal reaction conditions were identified as follows: 2 mol % Ru-**L3** in dioxane at room temperature for 1 min (entry 11).

Under the optimized reaction conditions, a series of N1-vinylpyrimidine derivatives with different substituents at the C5 position were examined (Scheme 2). When 5-ethyl- or 5-F-substituted N1-vinylpyrimidine (**1b** or **1c**) was used, the cyclopropanation reactions worked well, affording the desired products **3b**,**c** in 80−93% yields, 10:1−16:1 dr, and 99% ee. In the case of *p*-tolyl- or 2-naphthyl-substituted N1-vinylpyrimidine (**1d** or **1e**), the corresponding cyclopropyl pyrimidine carbocyclic nucleosides **3d**,**e** were obtained in 72−81% yields, 15:1−17:1 dr, and 99% ee. In addition, alkynyl-substituted pyrimidine derivatives (**1f**,**g**) were also suitable

Table 1. Optimization of the Intermolecular Cyclopropanation Reaction Conditions[a]



entry	catalyst	x	solvent	time (min)	yield[b] (%)	dr[c]	ee[d] (%)
1	CuCl−**L1**	5	dioxane	720	NR		
2	Rh−**L2**	5	dioxane	720	NR		
3	Ru−**L3**	5	dioxane	1	96	16:1	99
4	Ru−**L4**	5	dioxane	1	23	1:1	71
5	Ru−**L5**	5	dioxane	1	17	2:3	70
6	Ru−**L6**	5	dioxane	1	94	16:1	99
7	Ru−**L3**	5	CH_2Cl_2	1	25	8:1	99
8	Ru−**L3**	5	$CHCl_3$	1	32	15:1	95
9	Ru−**L3**	5	DCE	1	22	15:1	95
10	Ru−**L3**	5	THF	1	NR		
11	Ru−**L3**	2	dioxane	1	96	16:1	99
12	Ru−**L3**	1	dioxane	1	85	16:1	99

[a]Reaction conditions: **2a** (4.0 equiv) was dissolved in solvent (0.4 mL), catalyst (x mol %) was dissolved in solvent (0.4 mL), then the solution of catalyst (0.4 mL) was added to the solution of **1a** (0.05 mmol) in 0.2 mL of solvent. Subsequently, **2a** (0.4 mL) was added dropwise to the solution of **1a** within 1 min. [b]Isolated yield. [c]The dr values were determined by ^{1}H NMR analysis of the crude products. [d]Determined by HPLC analysis. NR = no reaction.

substrates, giving the cyclopropanation products **3f**,**g** in 71−72% yields, 11:1−12:1 dr, and 96−99% ee. With 4-chlorobenzoyl-protected N1-vinylthymine **1h** as the reactant, the intermolecular cyclopropanation smoothly afforded the carbocyclic nucleoside analogue **3h** in excellent results. The absolute configuration of the chiral carbocyclic nucleoside analogue **3h** was determined to be 1*R*,2*R* by the single-crystal X-ray diffracion analysis (Scheme 3). Subsequently, several Boc-protected N1-vinylpyrimidine derivatives were examined. When Boc-protected N1-vinyluracil (**1i**) and thymine (**1j**) were used, the corresponding cyclopropyl carbocyclic nucleosides **3i** and **3j** were obtained in 93−96% yields, 13:1 → 20:1 dr, and 99% ee. 5-Ethyl- and 5-halo-substituted N1-vinylpyrimidines (**1k**−**o**) were also suitable substrates, delivering the corresponding carbocyclic nucleoside analogues **3k**−**o** in 80−90% yields, 10:1 → 20:1 dr, and 98−99% ee. When α-thymine-substituted acrylate **1p** was examined, the cyclopropanation reaction did not work. In addition, cytosine-substituted alkene **1q** worked well in the intermolecular cyclopropanation reaction to give the chiral cyclopropylcytosine carbocyclic nucleoside analogue **3q** in 90% yield, >20:1 dr, and 99% ee (Scheme 4).

Subsequently, the substrate scope of α-diazoesters was investigated (Table 2). When methyl 2-diazoacetate **2b** or *tert*-butyl 2-diazoacetate **2c** was employed, the corresponding carbocyclic nucleosides **3r**,**s** were obtained in 90−93% yields, 14:1−17:1 dr, and 99% ee (entries 2−3). When ethyl 2-diazopropanoate (**2d**), α-phenyl diazoacetate (**2e**), or diazo-

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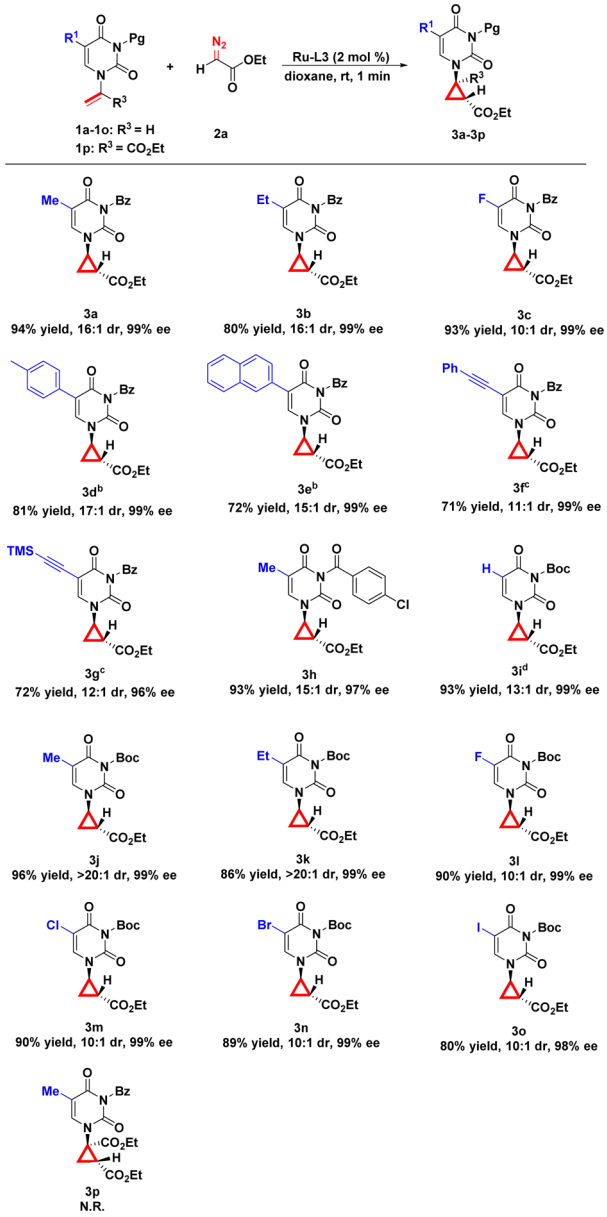
Scheme 2. Substrate Scope of N1-Vinylpyrimidine Derivatives[a]

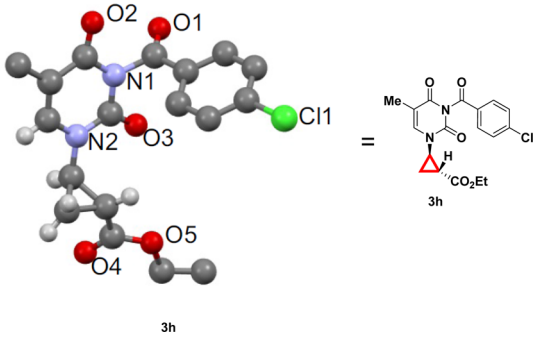


[a]Unless otherwise noted, the reaction conditions were as follows: **2a** was dissolved in dioxane (0.4 mL), Ru−**L3** was dissolved in dioxane (0.4 mL), and then the solution of Ru−**L3** (2 mol %, 0.4 mL) was added to the solution of **1** (0.05 mmol) in 0.2 mL of dioxane. Subsequently, **2a** (0.4 mL) was added dropwise to the solution of **1** within 1 min. Isolated yields are reported. The dr values were determined by ^{1}H NMR analysis of the crude products, and the ee values were determined by HPLC analysis. [b]Catalyst loading: 7 mol %. [c]Catalyst loading: 10 mol %. [d]Catalyst loading: 1 mol %. NR = no reaction.

dimethylmalonate (**2f**) was used, the cyclopropanation reactions did not occur (entries 4−6).

To further evaluate the prospect of the methodology in synthesis, the gram-scale synthesis of chiral cyclopropylthymine carbocyclic nucleoside analogue **3a** was performed. As shown in Scheme 5, by treatment of 5 mmol of Bz-protected N1-vinylthymine **1a** in the presence of 1 mol % of Ru−**L3**, nucleoside analogue **3a** was obtained in 96% yield (1.65 g) with

Scheme 3. X-ray structure of 3h



Scheme 4. Cytosine-Substituted Alkene 1q Involved Cyclopropanation Reaction

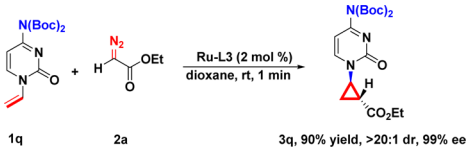
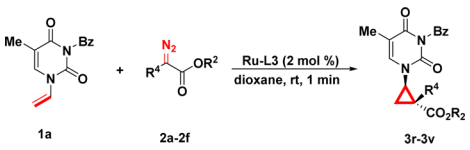


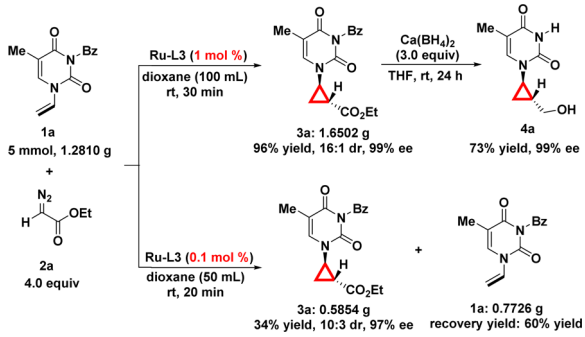
Table 2. Substsubstrate Scope of α-Diazoesters[a]



entry	2	R^2	R^4	3	yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**	Et	H	**3a**	94	16:1	99
2	**2b**	Me	H	**3r**	90	14:1	99
3	**2c**	*t*-Bu	H	**3s**	93	17:1	99
4	**2d**	Et	Me	**3t**	NR		
5	**2e**	Me	Ph	**3u**	NR		
6	**2f**	Me	CO_2Me	**3v**	NR		

[a]Reaction conditions: **2** was dissolved in dioxane (0.4 mL), Ru−**L3** was dissolved in dioxane (0.4 mL), and then the solution of Ru−**L3** (0.4 mL) was added to the solution of **1a** (0.05 mmol) in 0.2 mL of dioxane. Subsequently, **2** (0.4 mL) was added dropwise to the solution of **1** within 1 min. Isolated yields are reported. [b]Isolated yield. [c]The dr values were determined by ^{1}H NMR analysis of the crude products. [d]Determined by HPLC analysis. NR = no reaction.

Scheme 5. Gram-Scale Synthesis of 3a and Reduction of 3a



16:1 dr and 99% ee. When the reaction was performed with 0.1 mol % of Ru−**L3**, the cyclopropanation product **3a** was obtained in 34% yield, 10:3 dr, and 97% ee along with the recovery of the starting material **1a** in 60% yield. After that, in the presence of $Ca(BH_4)_2$, the hydrogenation of the product **3a**

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Org. Lett. XXXX, XXX, XXX−XXX

could occur, affording the deprotected chiral cyclopropyl thymine carbocyclic nucleoside **4a** in 73% yield and 99% ee (Scheme 5).

In summary, we have reported a direct entry to chiral cyclopropyl pyrimidine carbocyclic nucleoside analogues via the highly enantioselective intermolecular cyclopropanation reactions for the first time. With the Ru(II)−Pheox complex as the catalyst, a series of cyclopropyl pyrimidine nucleoside analogues could also be obtained in satisfactory results within only 1 min at room temperature (71−96% yields, 10:1→20:1 dr, and 96−99% ee). In addition, the intermolecular cyclopropanation reaction could be performed on a gram-scale, affording the desired adduct in excellent results, and chiral cyclopropyl pyrimidine carbocyclic nucleoside could be obtained from the cyclopropanation adduct via reduction reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02104.

Experimental procedures, synthesis of the starting materials, and compound characterization data (PDF)
X-ray data for compound **3h** (CIF)

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Notes

The authors declare no competing financial interest.

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