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Catalytic Asymmetric Synthesis of the Anti-COVID-19 Drug Remdesivir

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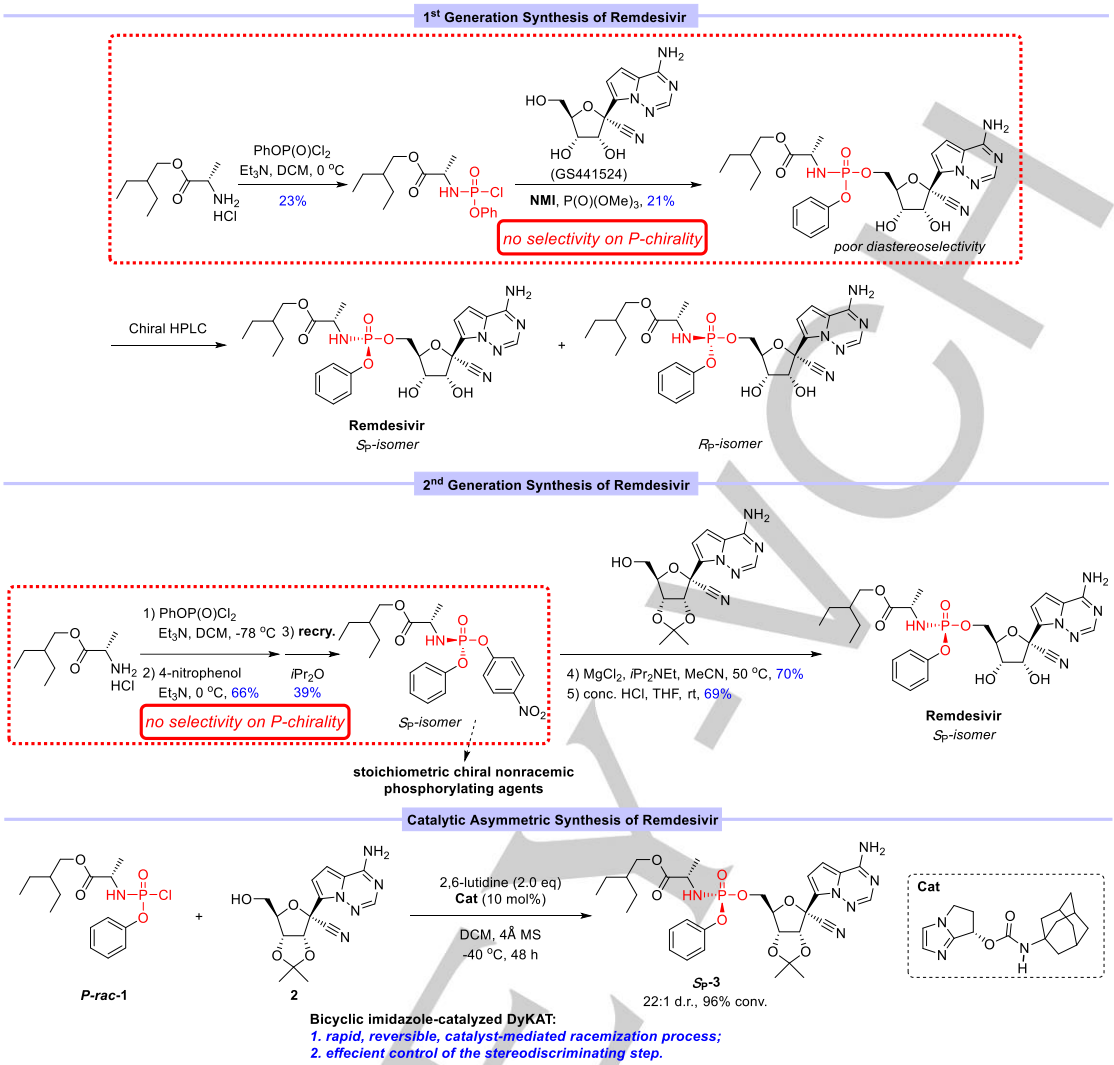
Abstract: The catalytic asymmetric synthesis of the anti-COVID-19 drug remdesivir has been realized via the coupling of the *P*-racemic phosphoryl chloride with protected nucleoside GS441524. The chiral bicyclic imidazole catalyst is crucial for the dynamic kinetic asymmetric transformation (DyKAT) to proceed smoothly with high reactivity and excellent stereoselectivity (96% conv., 22:1 S_P:R_P). Mechanistic studies showed that this DyKAT is a first-order visual kinetic reaction dependent on catalyst concentration. The unique chiral bicyclic imidazole skeleton and carbamate substituent of the catalyst are both required for the racemization process involving the phosphoryl chloride and subsequent stereodiscriminating step. A 10-gram scale reaction was also conducted with comparably excellent results, showing its potential for industrial application.

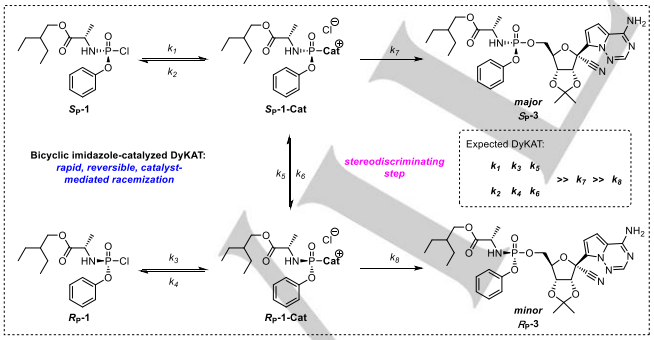
Remdesivir (Veklury, GS-5734) has undoubtedly become an important molecule. It is viewed as one of the world's most promising treatments for COVID-19.[1] To date, COVID-19 has led to approximately 23 millions infections and 800 thousand deaths since the end of 2019. Furthermore, the numbers and rates of infections and related deaths are increasing, with 7 million infections and 150 thousand deaths being reported last month. The urgency of the pandemic has prompted the governments of the United States, the European Union, Japan, etc. to approve the remdesivir as a specific treatment for COVID-19.[2] Recent clinical trial results have shown that it can effectively shorten the recovery period of hospitalized patients and reduce the risk of death by 62% in patients with severe cases of the disease,[3] and so has the potential to greatly lighten the burden on hospitals and doctors during the pandemic. Ensuring that there are sufficient supplies of remdesivir is of paramount importance. Gilead Sciences is striving to provide almost two million remdesivir treatment courses by the end of 2020 and many millions more by 2021.[4] However, the amount is far from sufficient to meet clinical needs and so now remdesivir treatment is rationed due to limited supply. The development of a highly effective synthetic approach to remdesivir is therefore required.

Remdesivir is prepared as a *P*-stereogenic prodrug of a parent nucleoside (GS441524) by introducing an amino acid ester- and aryloxy-substituted phosphoryl group to the hydroxyl functionality of the nucleoside.[5,6] Unlike the progress achieved in the catalytic asymmetric synthesis of carbon centers,[7] stereogenic phosphorus groups are still challenging to construct.[8] Thus, the construction of the phosphorus-based stereogenic center is a key step in the synthesis of remdesivir. The first generation of synthetic methods is shown in Scheme 1(Top). The desired enantiopure S_P-phosphoramidate is prepared from the corresponding *P*-racemic phosphoryl chloride and GS441524 using stoichiometric amounts of *N*-methyl imidazole, followed by separation of the two diastereoisomer products by chiral preparative HPLC.[5] The second generation of synthetic methods is shown in Scheme 1(Middle), which adopted an alternative approach involving the selective nucleophilic displacement of the enantiopure phosphorylating agent separated from the additionally prepared mixture of two diastereoisomer intermediates.[6] Chiral resolution and additonal synthetic steps in the above-mentioned methods are required for the preparation of the enantiomerically pure *P*-stereogenic intermediates, which inevitably leads to low synthetic efficiency and a waste of resources. Herein, we describe the first catalytic asymmetric synthesis of remdesivir via the coupling of the *P*-racemic phosphoryl chloride (**1**) with protected nucleoside (**2**) [Scheme 1(Bottom)]. The synthetic methodology is also promising from an atom-economy and synthetic efficiency perspective.[9,10]

Organophosphorus(V) compounds provide unique binding interactions with a target receptor or enzyme because of their trigonal pyramidal geometry, multiple chelating properties and potential dual functions as a hydrogen donor and acceptor.[8a] These characteristics also present a significant challenge for the construction of *P*-stereocenters due to the crowded three-dimensional space[11] and difficult-to-control interactions between the chiral catalyst and the substrate.[12] Among methodologies for the construction of *P*-stereogenic compounds, catalytic asymmetric substitutions with racemic phosphoryl(V) chloride provide a simple and economic process in terms of both operational simplicity and starting material availability. However, the full conversion of both enantiomers of the racemic starting material into a single, optically pure product in quantitative yield is generally challenging.[13] The crux of the problem lies in the lack of a suitable chiral catalyst that is able to promote the racemization process (k_5/k_6) and control the subsequent stereodiscriminating step (k_7/k_8, Scheme 2).



Scheme 1. Top: 1st Generation synthesis of remdesivir. Middle: 2nd Generation synthesis of remdesivir. Bottom: **This work**: catalytic asymmetric synthesis of remdesivir.

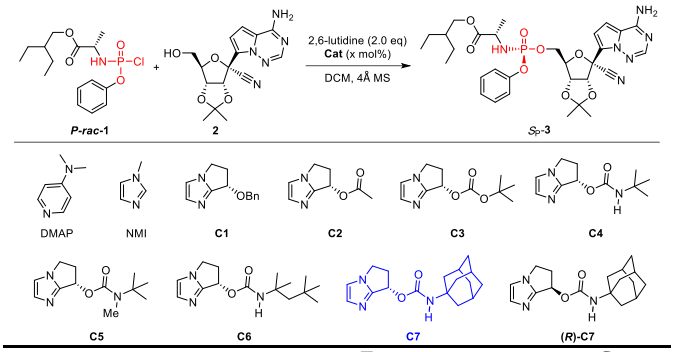


Scheme 2. Bicyclic imidazole-catalyzed dynamic kinetic asymmetric transformation (DyKAT) for the synthesis of remdesivir.

In the early 2010's, the catalytic asymmetric conversion of racemic phosphoryl chloride to phosphoramidate was firstly realized in our group by using the newly developed chiral bicyclic imidazole organocatalysts.[14,15] This represented the first example of the catalytic asymmetric synthesis of *P*-stereogenic phosphoric acid derivatives.[14] Their unique bicyclic imidazole structures provide a good balance between the catalytic activity of the imidazole skeleton and the stereocontrol property of its substituent, making the catalyst almost the only one suitable for asymmetric phosphorylation. This was later confirmed by research scientists at Merck & Co. and the University of Wisconsin in their works concerning the asymmetric synthesis of nucleoside- and glucoside-based phosphoramidate prodrugs, respectively.[16,17] In order to provide sufficient quantities of remdesivir for clinical use, and considering the unique advantages of our chiral bicyclic imidazole catalysts in asymmetric phosphorylation, herein we developed the first highly efficient catalytic asymmetric synthesis of the anti-COVID-19 drug, remdesivir, using our easily accessible catalysts [Scheme 1(Bottom)].

We first explored the specific performance of our chiral bicyclic imidazoles in the catalytic asymmetric synthesis of protected remdesivir using the *P*-racemic phosphoryl chloride **1** and nucleoside **2** (Table 1). Initially, we conducted the reaction in the absence of catalyst and found that only a trace amount of product **3** with 1.1:1 d.r. (S_P:R_P) was obtained (Table 1, entry 1).

Table 1. Optimization of the reaction conditions.[a]

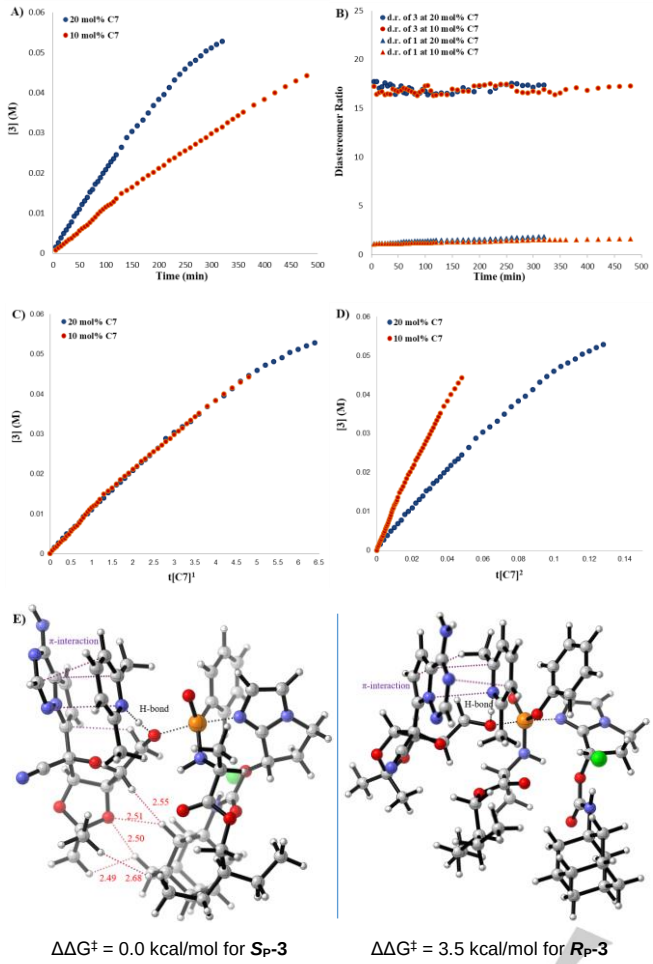


Entry	mol% **Cat**	Base	T [°C]	t [h]	S_P:R_P[b]	Conv. [%][c]
1	none	2,6-lutidine	-10	16	1.1:1	3
2	20% DMAP	2,6-lutidine	-10	16	1.1:1	33
3	20% NMI	2,6-lutidine	-10	16	1.5:1	62
4	20% **C1**	2,6-lutidine	-10	16	3.2:1	45
5	20% **C2**	2,6-lutidine	-10	16	2.6:1	63
6	20% **C3**	2,6-lutidine	-10	16	1.9:1	46
7	20% **C4**	2,6-lutidine	-10	16	9.3:1	91
8	20% **C5**	2,6-lutidine	-10	16	6.2:1	47
9	20% **C6**	2,6-lutidine	-10	16	7.4:1	83
10	20% **C7**	2,6-lutidine	-10	16	11.2:1	91
11	20% **(*R*)-C7**	2,6-lutidine	-10	16	4.3:1	81
12	20% **C7**	none	-10	16	7.8:1	77
13	20% **C7**	2,6-lutidine	-30	16	16.6:1	96
14	20% **C7**	2,6-lutidine	-40	36	21.8:1	96
15	10% **C7**	2,6-lutidine	-30	36	16.4:1	95
16	5% **C7**	2,6-lutidine	-30	48	16.4:1	94
17	10% **C7**	2,6-lutidine	-40	48	21.6:1	96

[a] Reaction conditions: *P-rac*-**1** (104.3 mg, 0.30 mmol, 1.5 equiv), **2** (66.3 mg, 0.20 mmol, 1.0 equiv), 2,6-lutidine (46.6 µL, 0.40 mmol, 2.0 equiv), 4Å MS (80 mg), DCM (2 mL). [b] Determined by ^{31}P NMR analysis. [c] Determined by ^{31}P NMR analysis using $P(O)(OMe)_3$ as the internal standard.

Next, two achiral nucleophilic catalysts were examined to explore the inherent substrate induction in the stereochemical outcome of the *P*-stereogenic product **3**. The desired product was obtained in only 33% conversion with a 1.1:1 d.r. using the commonly employed nucleophilic catalyst *N*,*N*-dimethylpyridine (DMAP) (entry 2). Interestingly, by employing *N*-methyl imidazole (NMI) as the achiral catalyst, the corresponding product **3** was obtained smoothly in 62% conversion with a 1.5:1 d.r. (entry 3). These experimental results suggested that: 1) the nucleophilic catalyst is required for this phosphorylation reaction to proceed with high reactivity; 2) the chiral nucleoside and phosphoryl chloride substrates have negligible impact on the stereochemical induction of the *P*-stereocenter, thus providing an opportunity for the use of a chiral nucleophilic catalyst; 3) the imidazole structure appears to have the potential to improve the reactivity and stereocontrol of this phosphorylation process. Accordingly, a variety of nucleophilic catalysts bearing a chiral bicyclic imidazole framework, which was developed by our group, were screened in this transformation. These catalysts include those modified with a benzyl ether **C1**, acetyl ester **C2**, *tert*-butyl carbonate **C3**, and various carbamates **C4**-**C7** (entries 4-10 and Table S1-S2 in SI). The catalyst **C4** bearing a carbamate group was identified to be the superior catalyst motif, giving the desired phosphoramidate product in high conversion (91%) and 9.3:1 selectivity in favor of the desired (*S*)-configuration at the phosphorus center. This is consistent with the absolute configuration of the *P*-stereocenter in remdesivir (entry 7). The catalyst **C5**, bearing a methyl substituent on the carbamate group, exhibited poorer stereocontrol of the *P*-stereocenter (entry 8). Subsequently, the catalysts **C6** and **C7**, bearing carbamate groups with larger steric hindrance, were synthesized and applied to this reaction to further improve the stereoselectivity (entries 9 and 10). To our delight, the catalyst **C7**, modified with an adamantinyl group, gave the best results (11.2:1 d.r., 91% conv.). A mismatched relationship was observed by changing the configuration of the enantiopure **C7**, suggesting chiral recognition between the chiral catalyst and the substrate (entry 11). In the absence of base, the desired product is obtained in reduced conversion and d.r. (entry 12, 7.8:1 d.r., 77% conv.). The obvious decrease in reactivity and selectivity indicated that the base, 2,6-lutidine, may participate in the transition state of the rate-determining and stereodiscriminating step. To further improve the diastereoselectivity, the reaction temperature was reduced to -30 °C and -40 °C, and the selectivity improved to 16.6:1 and 21.8:1 with comparable reactivities, respectively (entries 13 and 14). When the catalyst loading was decreased to 10 mol% and 5 mol%, a longer reaction time was required but comparable diastereoselectivities were obtained (entries 13-17). These results suggested that the d.r. value is not dependent on the concentration of the catalyst. Thus, the desired product **3** could be obtained in 94% conversion with 16.4:1 d.r. and 96% conversion with 21.6:1 d.r. at 5 mol% (-30 °C) and 10 mol% (-40 °C) catalyst loadings, respectively (entries 16 and 17).

To further understand the specific role of the base and catalyst on the reaction process, a detailed mechanistic study was conducted. At first, the reactions with catalyst loadings of 20 mol% and 10 mol% were monitored over different reaction times by ^{31}P NMR spectroscopy (Figure 1A). The results showed that the d.r. values of the product **3** and starting material **1** do not substantially change as the reaction proceeds, consistent with the catalyst loading screening results (Figure 1B; Table 1, entries 13-17). Furthermore, visual kinetic analysis revealed a first-order dependence on catalyst concentration, which is different from the second order kinetics reported in previous work concerning asymmetric phosphorylation (Figure 1C and 1D).[16] In combination with 2,6-lutidine having an integral effect on the reactivity and stereoselectivity, it was suggested that the reaction pathway involves the simultaneous activation of the phosphoryl chloride **1** and nucleoside **2** by catalyst **C7** and base 2,6-lutidine, respectively. In order to better understand this dual activation mode, a computational study was conducted. Relative transition state energies showed the desired S_P configuration to be favored by 3.5 kcal/mol, in agreement with the experimental results (Figure 1E).

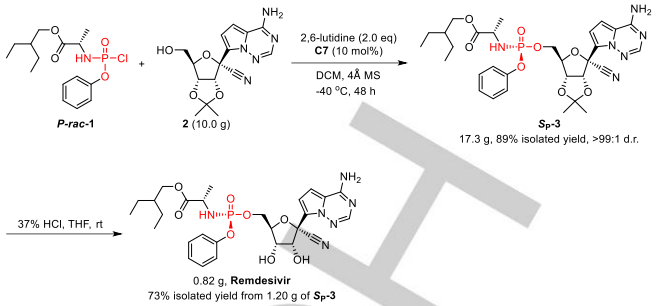


ΔΔG‡ = 0.0 kcal/mol for S_P-**3** ΔΔG‡ = 3.5 kcal/mol for R_P-**3**

Figure 1. Mechanistic study. A) Temporal concentration profiles for the standard reaction at two different catalyst loadings. [**1**]$_0$ = 0.15 M; [**2**]$_0$ = 0.10 M; [lutidine]$_0$ = 0.20 M; [**C7**]$_0$ = 0.02 M for 20 mol% and 0.01 M for 10 mol%. B) Temporal diastereomer ratio of **1** and **3** at two different catalyst loadings. C) The concentration of product was plotted against a normalized time scale, t[**C7**]^1. D) The concentration of product was plotted against a normalized time scale, t[**C7**]^2. E) Transition state model of the stereoselective phosphorylation with **C7**. Calculations were performed at the B3LYP-D3(BJ)/6-31G** level of theory.

We next explored the scalability of the present methodology for the synthesis of remdesivir (Scheme 3). The reaction smoothly proceeded on a 10-gram scale at 10 mol% catalyst loading under -40 °C, affording the desired product in 95% conversion and 21.2:1 d.r.. The enantiopure S_p-**3** was obtained in 89% isolated yield with >99:1 d.r. (85% yield by recrystallization and 4% yield from residual mother liquor by preparative HPLC). To our delight, the catalyst could be easily recovered after column chromatography, which could be successfully applied in the next catalytic cycle without any obvious change in catalytic performance. Following deprotection with 37% HCl in THF, the desired remdesivir could be easily prepared in 73% isolated yield.

In summary, we have developed a bicyclic imidazole-catalyzed DyKAT for the first asymmetric synthesis of remdesivir via the coupling of the *P*-racemic phosphoryl chloride and nucleoside. Mechanistic studies revealed that this DyKAT is a first-order visual kinetic reaction dependent on catalyst concentration. The unique chiral bicyclic imidazole skeleton and



Scheme 3. The gram-scale catalytic asymmetric synthesis of remdesivir.

adamantinyl-substituted carbamate group of the catalyst are both required for the DyKAT to proceed smoothly with high reactivity and excellent stereoselectivity. A 10-gram scale reaction was successfully realized, showing its potential for industrial application.

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Conflict of interest

The authors declare no competing interests.

Keywords: COVID-19 • antiviral drug • asymmetric nucleophilic catalysis • phosphoramidates • ProTide technology

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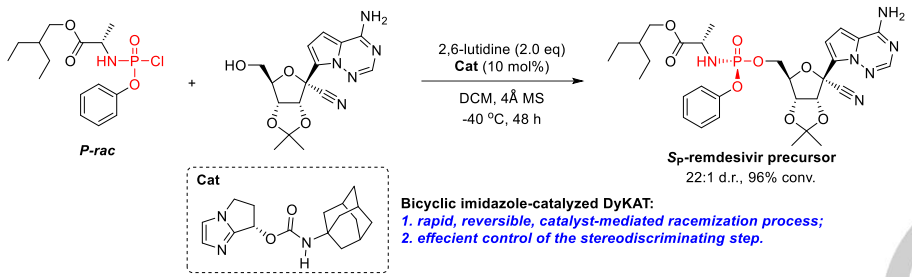

The first catalytic asymmetric synthesis of remdesivir via the coupling of the *P*-racemic phosphoryl chloride with protected nucleoside GS441524 has been realized using the chiral bicyclic imidazole catalyst, which is crucial for the racemization process involving the phosphoryl chloride and subsequent stereodiscriminating step (96% conv., 22:1 S_P:R_P). Furthermore, a 10-gram scale reaction was successfully realized, showing its potential for industrial application.