Literature Report

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

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Checker: Xiao-Qing Wang
Date: 2020-11-30

Wang, M.; Zhang, L.; Zhang. W.; et al.
Angew. Chem. Int. Ed. **2020**, *59*, 20814-20819.

CV of Prof. W. Zhang

Background:

- **1981 - 1985** B.S. ECUST
- **1985 - 1988** M.S. ECUST
- **1993 - 1997** P.D. Osaka University
- **2003 - now** Professor, SJTU

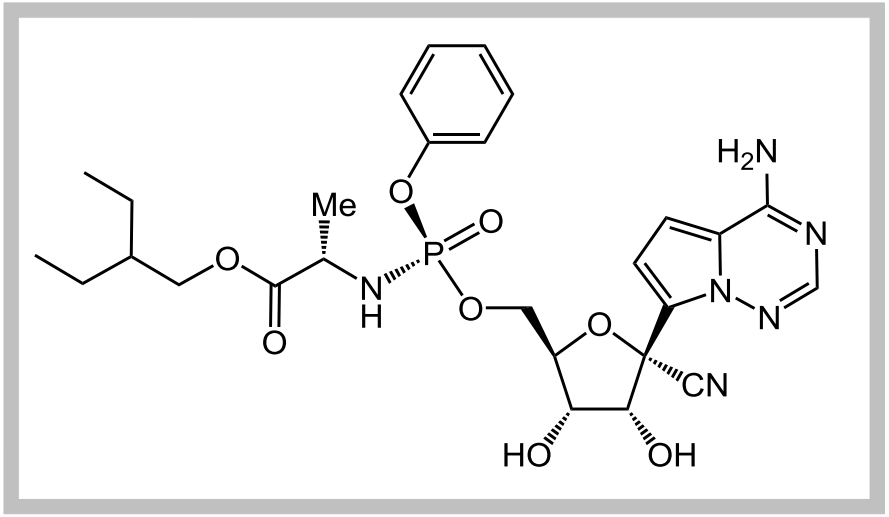
Research:

Design and synthesis of novel chiral ligands and organocatalysts; Development of an efficient method for synthesis of drugs and their key intermediates; Development of highly efficient asymmetric catalytic reactions.

Contents

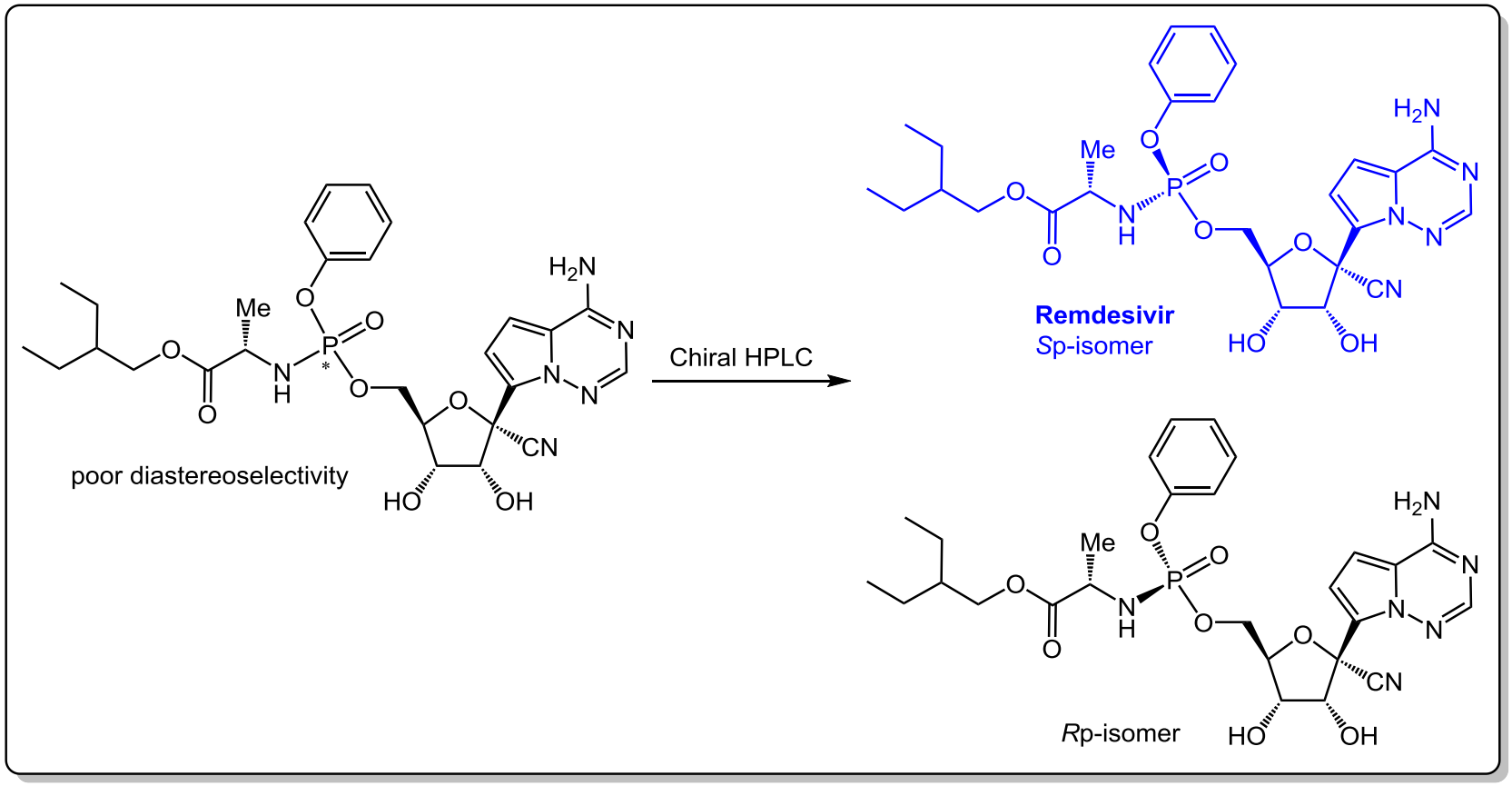
Remdesivir

瑞德西韦(Remdesivir)是美国吉利德科学公司研发的一种小分子广谱抗病毒药物。该药物最初被发现具有抗埃博拉和马尔堡病毒活性且并被用于治疗埃博拉感染者的临床试验中。后续研究表明，该药物可能对新型冠状病毒引起的传染性疾病也有效。

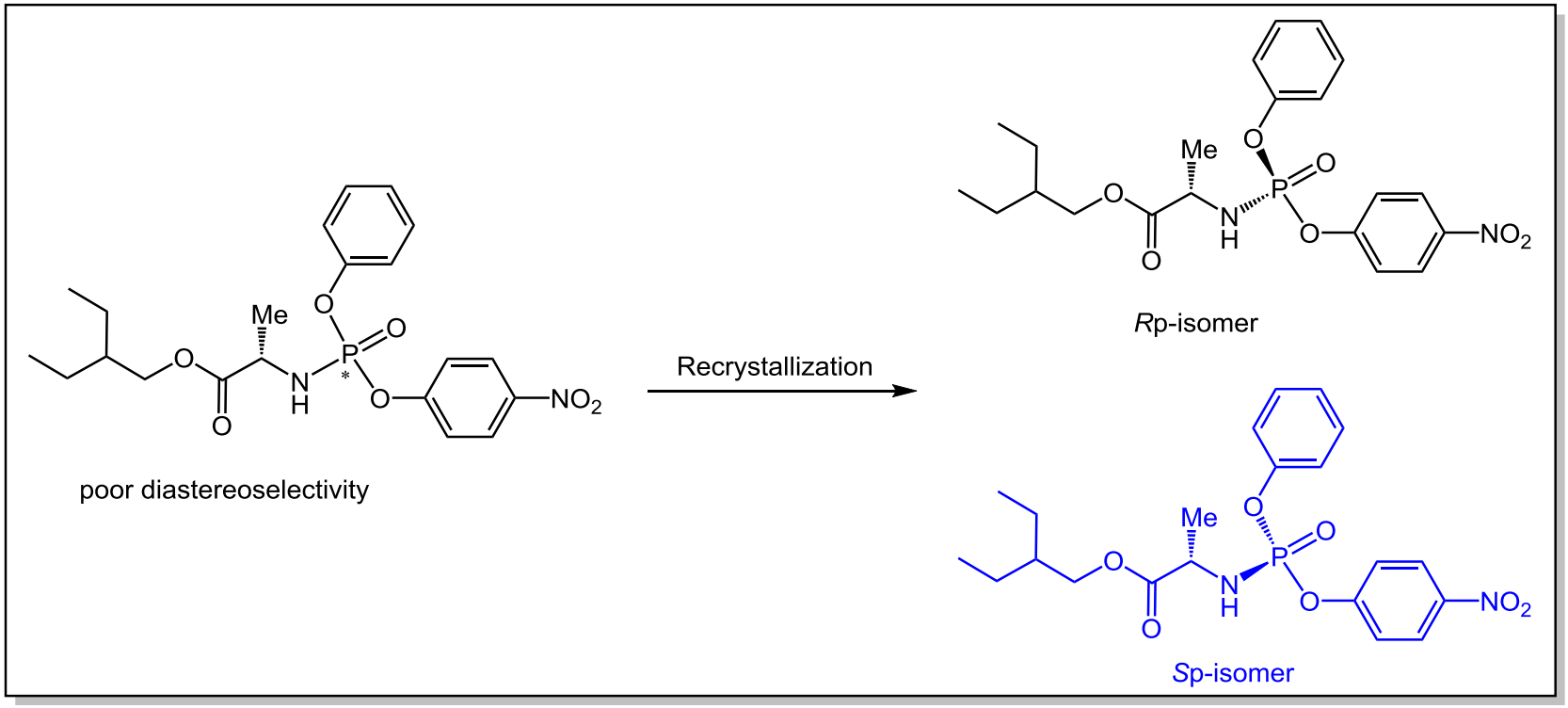


作用机制：和RNA聚合酶（RdRp）结合，阻止病毒复制

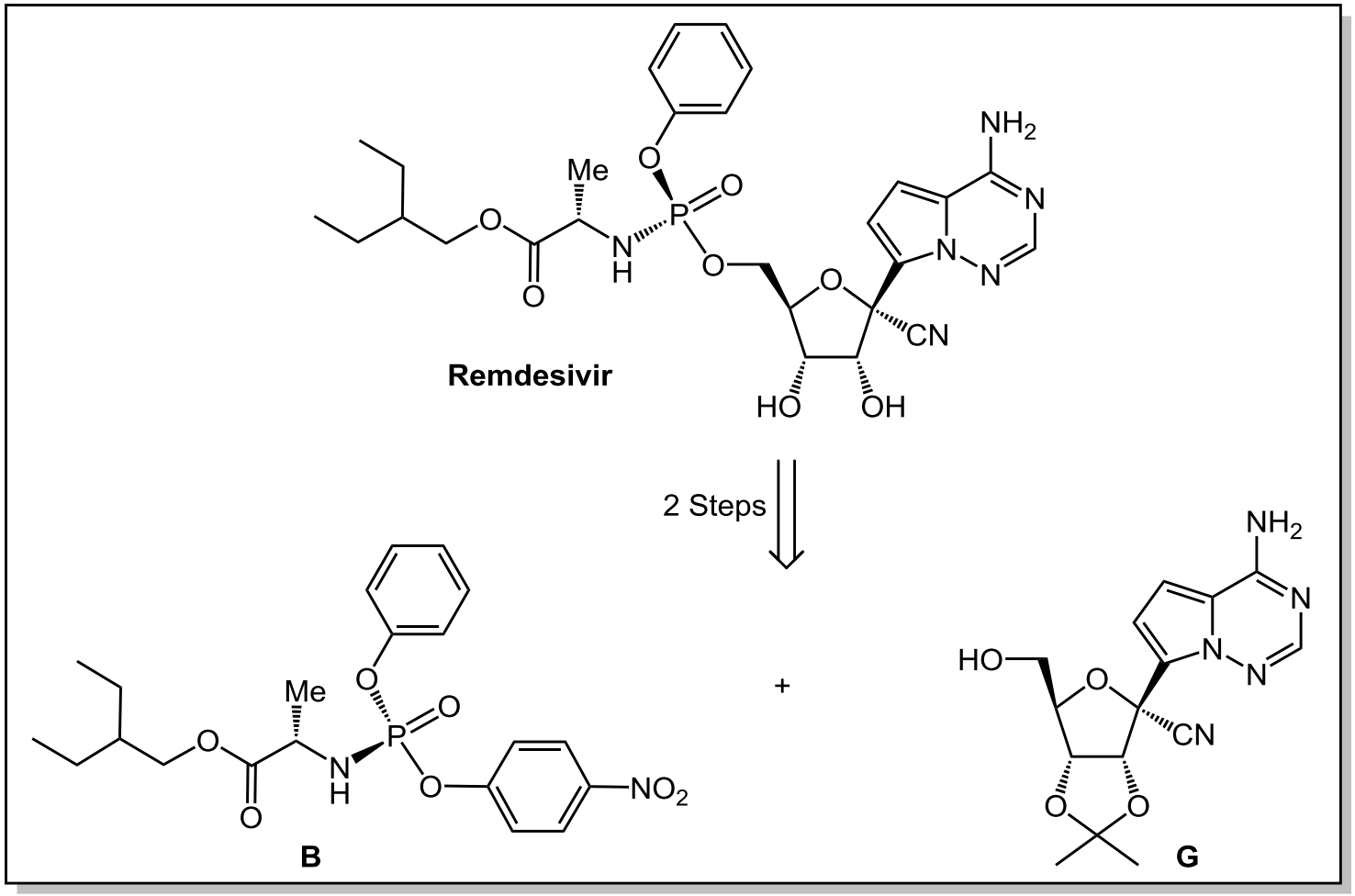
1st Generation Synthesis of Remdesivir



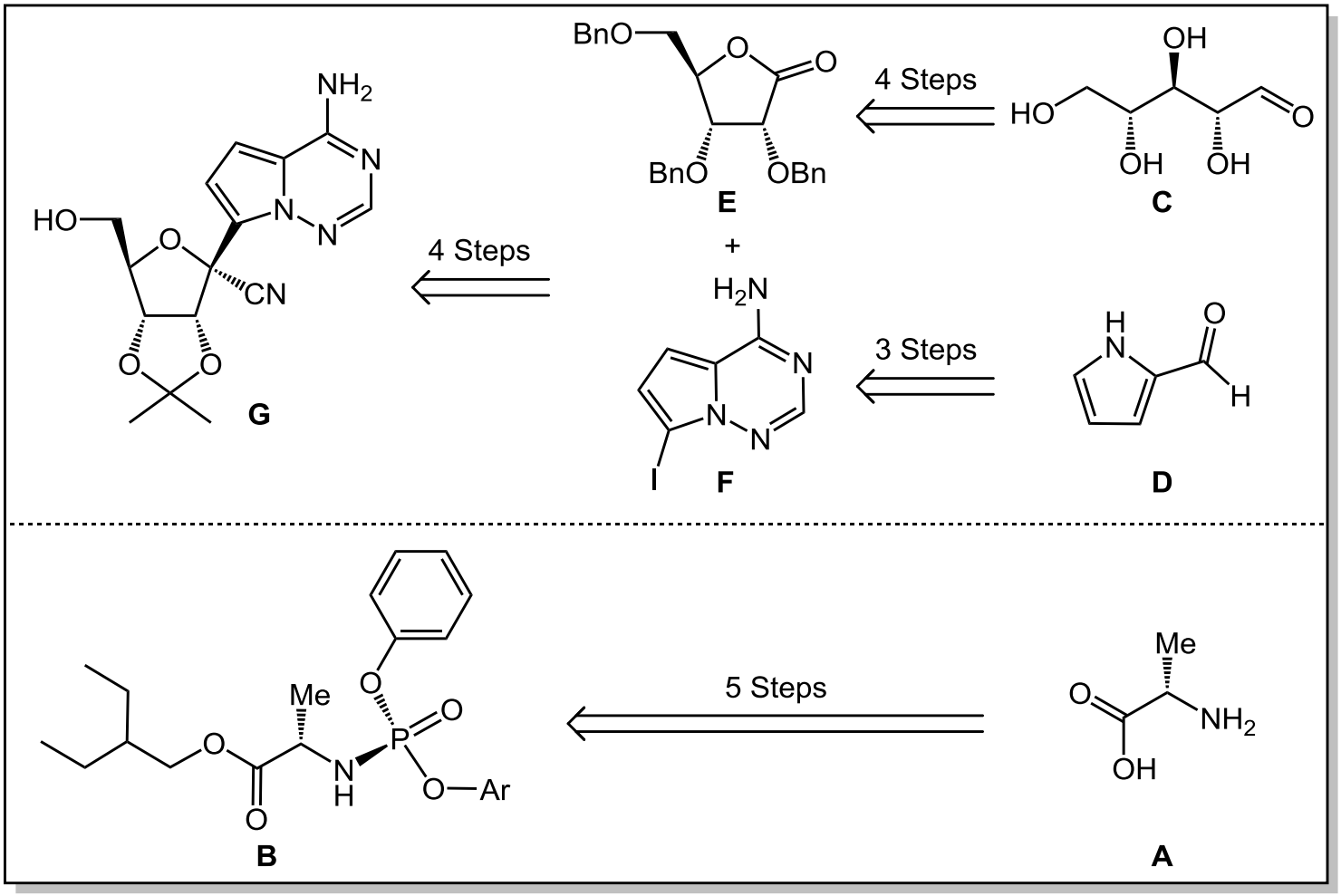
2st Generation Synthesis of Remdesivir



Retrosynthetic Analysis

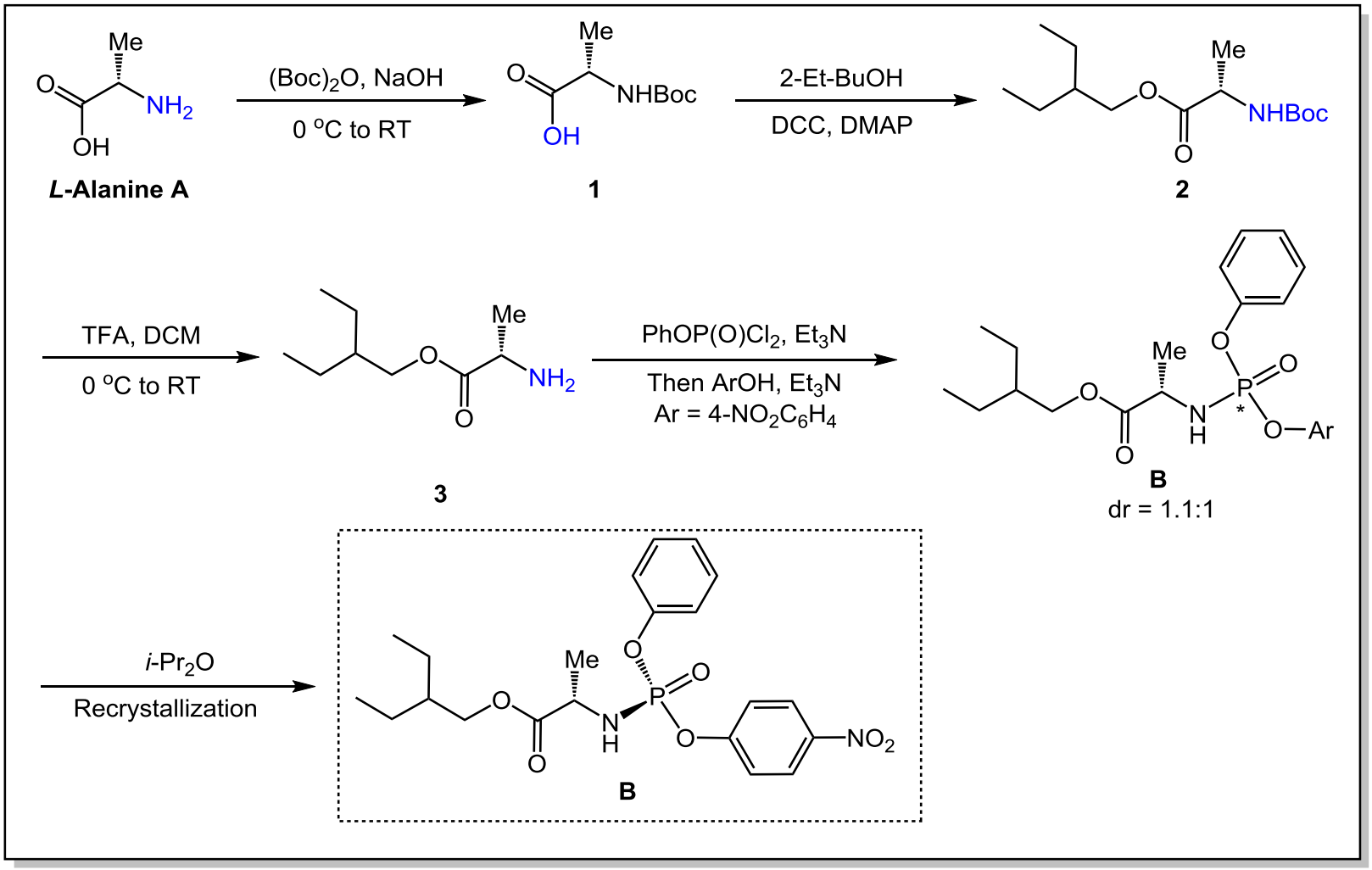


Retrosynthetic Analysis

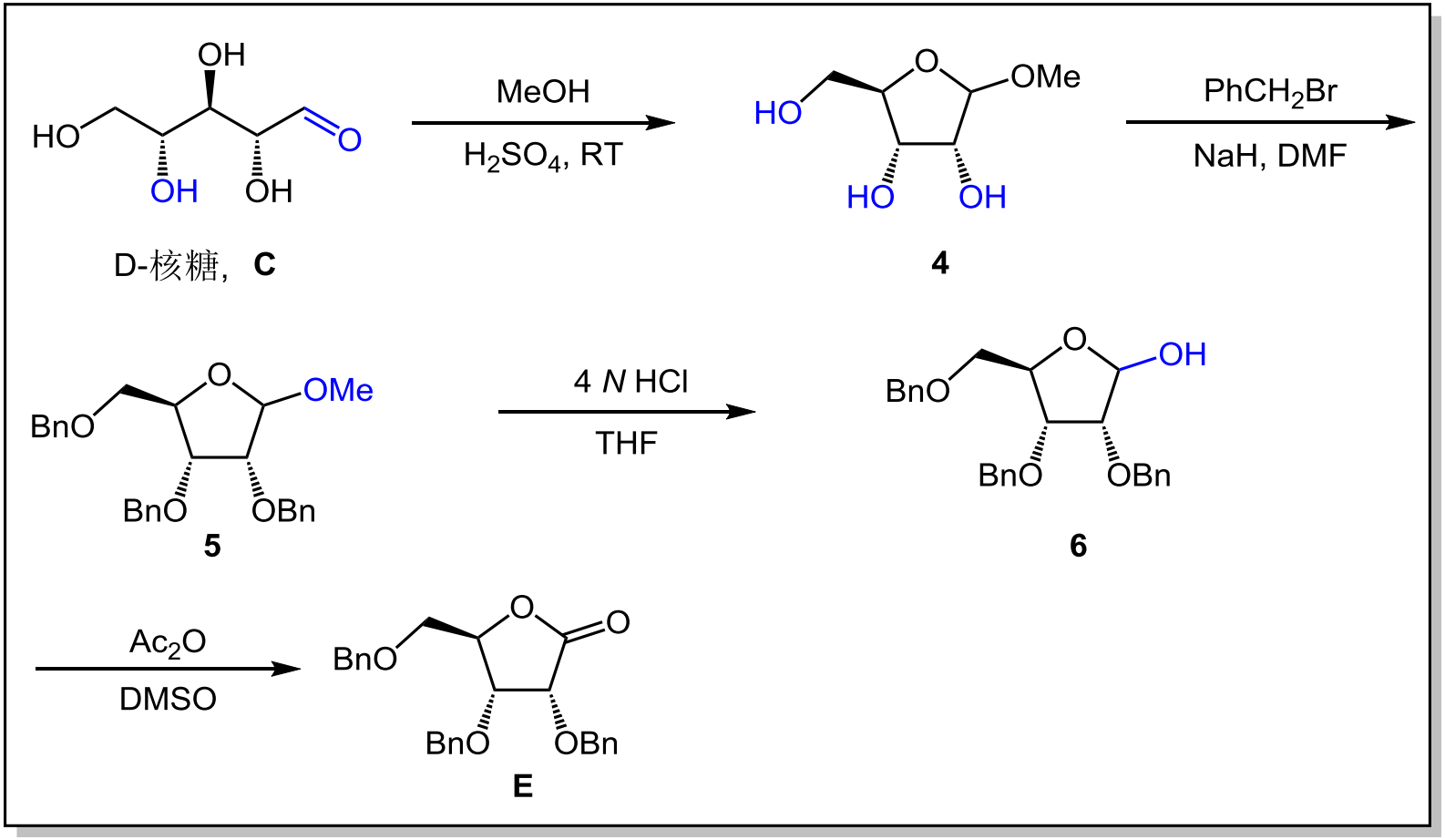


A. S. Ray, *Nature*, **2016**, *531*, 381-385; *J. Med. Chem.* **2017**, *60*, 1648-1661.

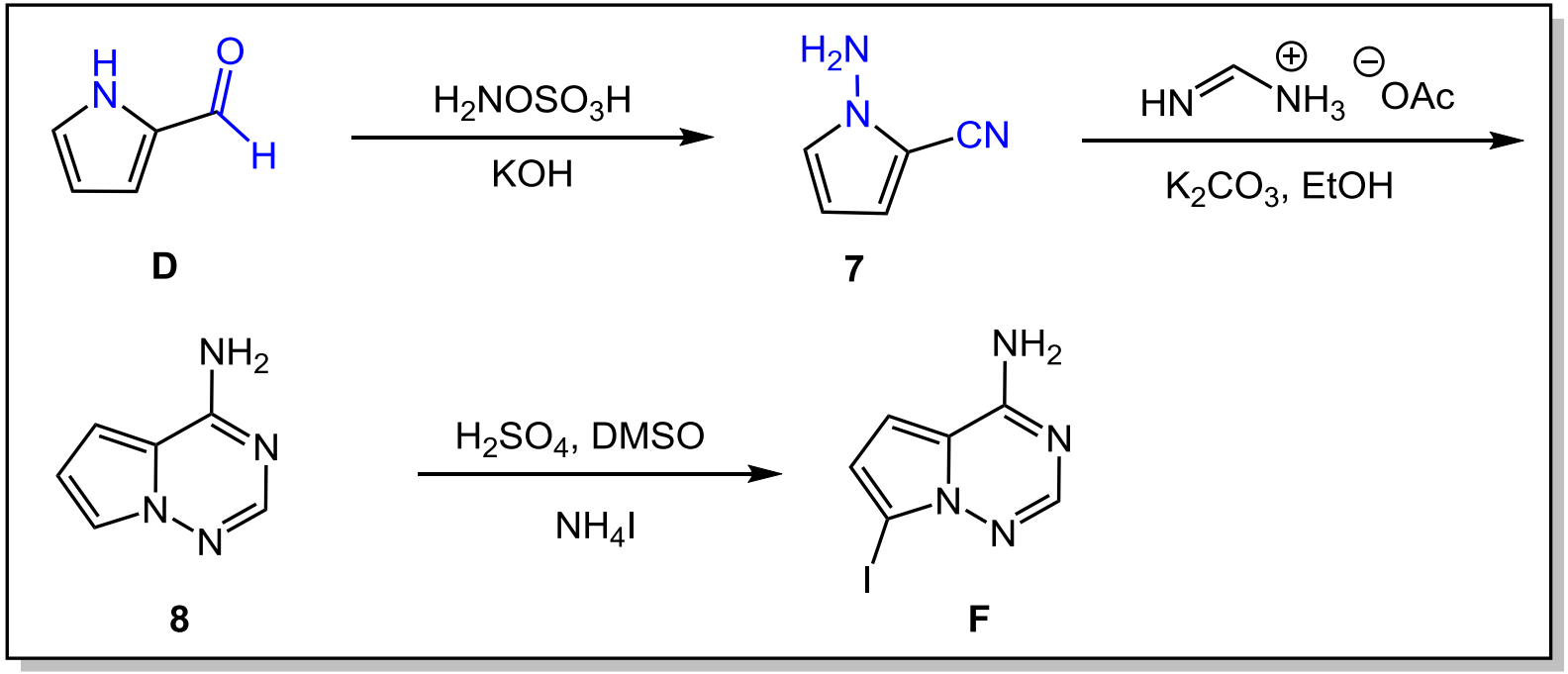
Synthesis of B



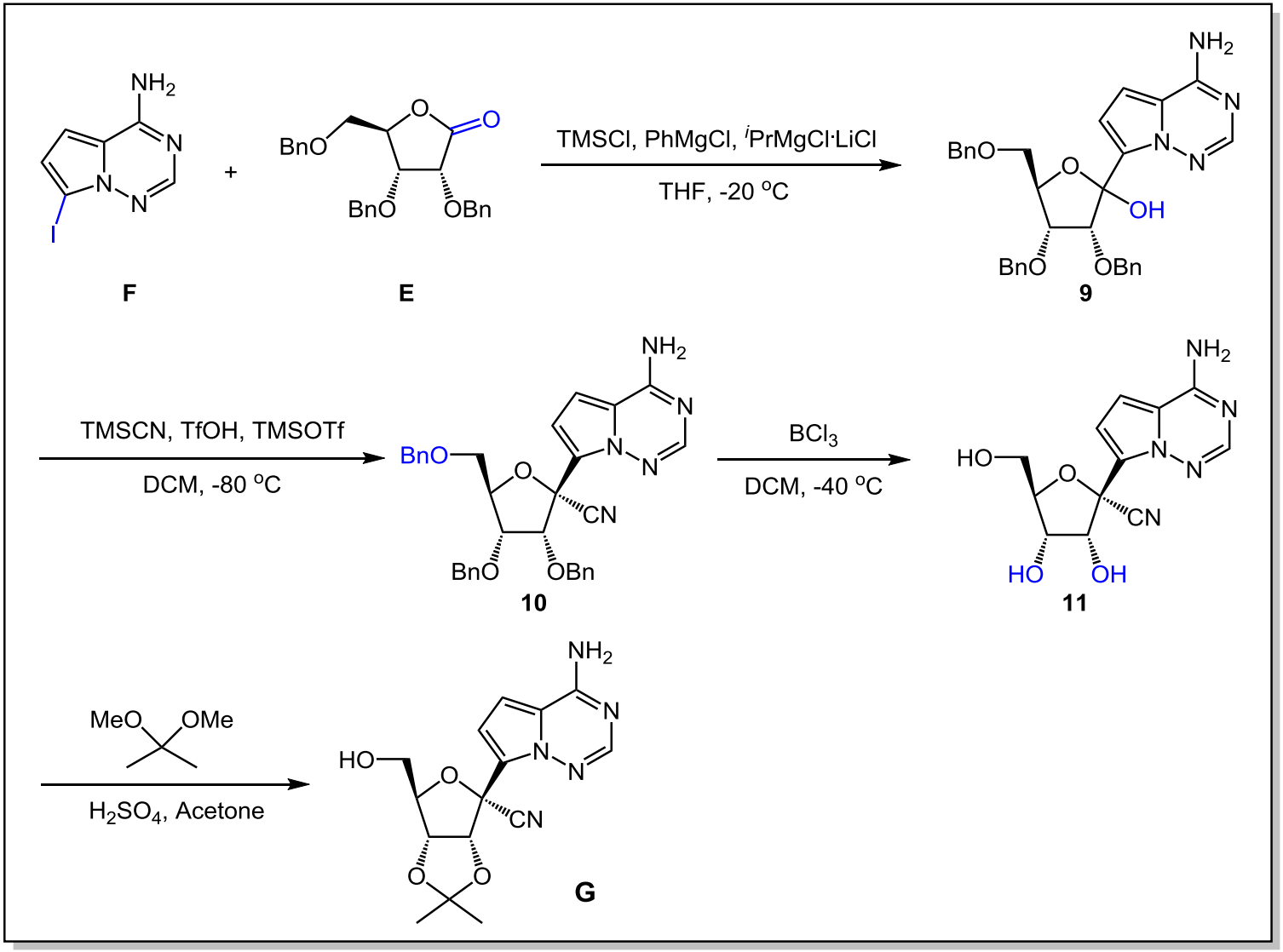
Synthesis of E



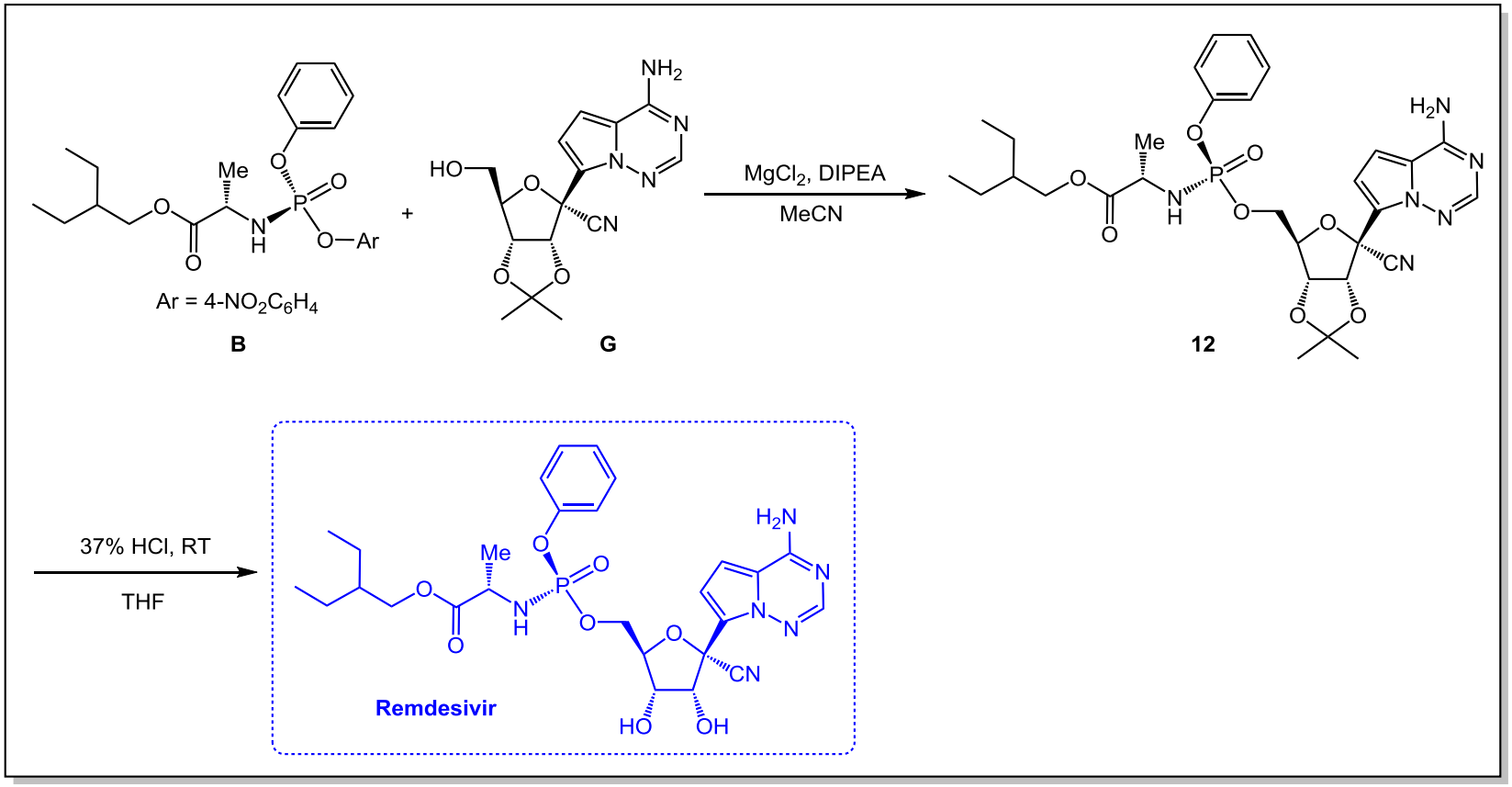
Synthesis of F



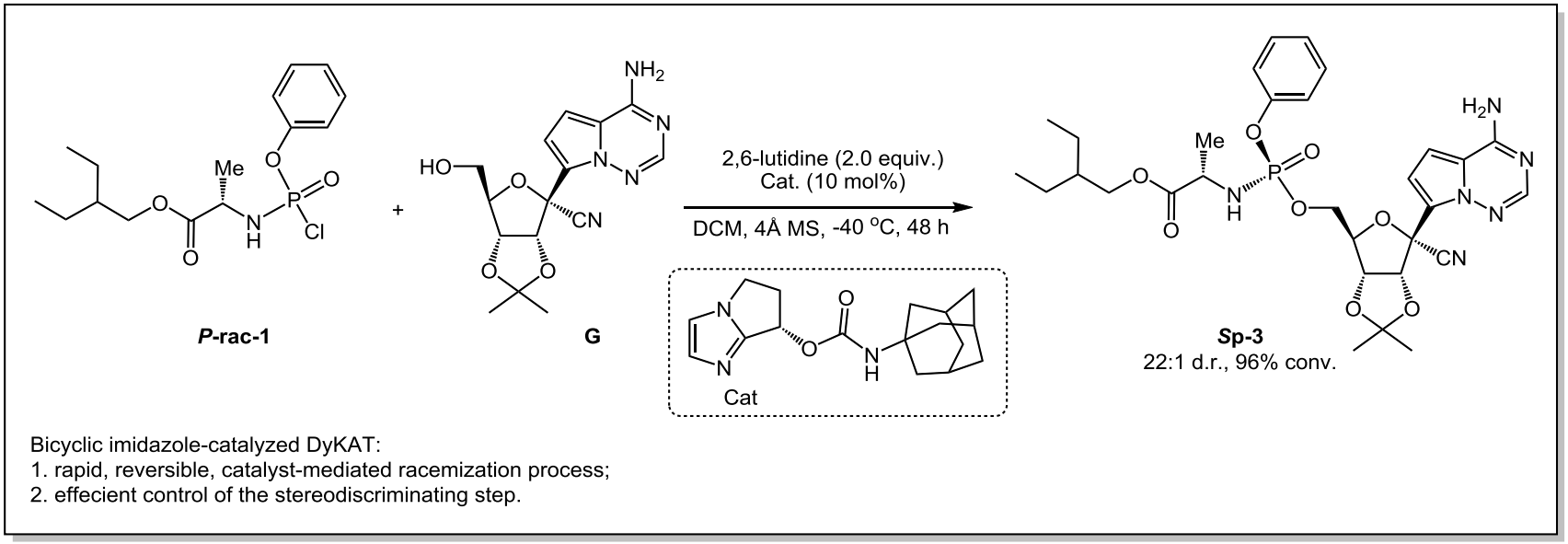
Synthesis of G



Synthesis of Remdesivir

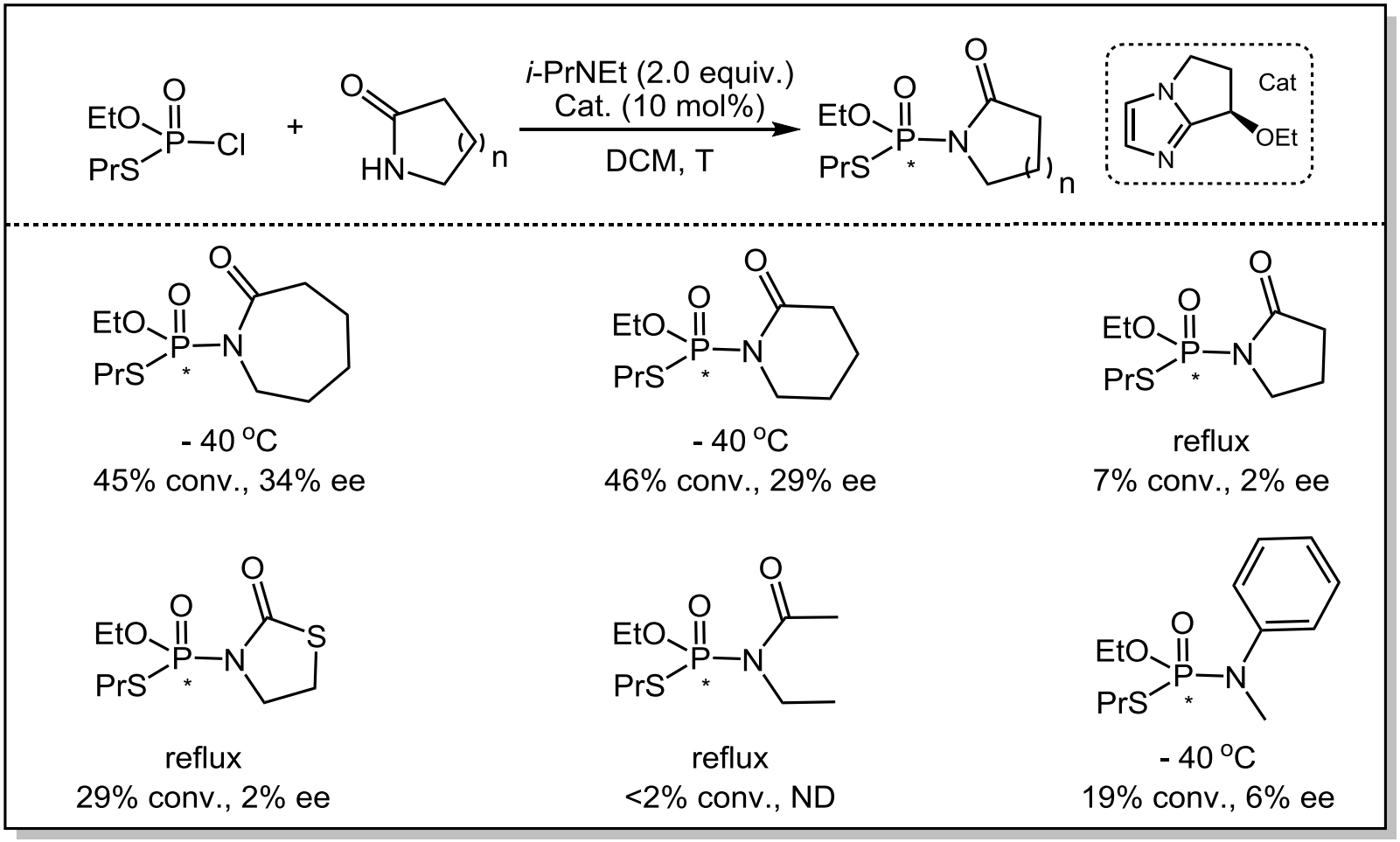


3st Generation Synthesis of Remdesivir



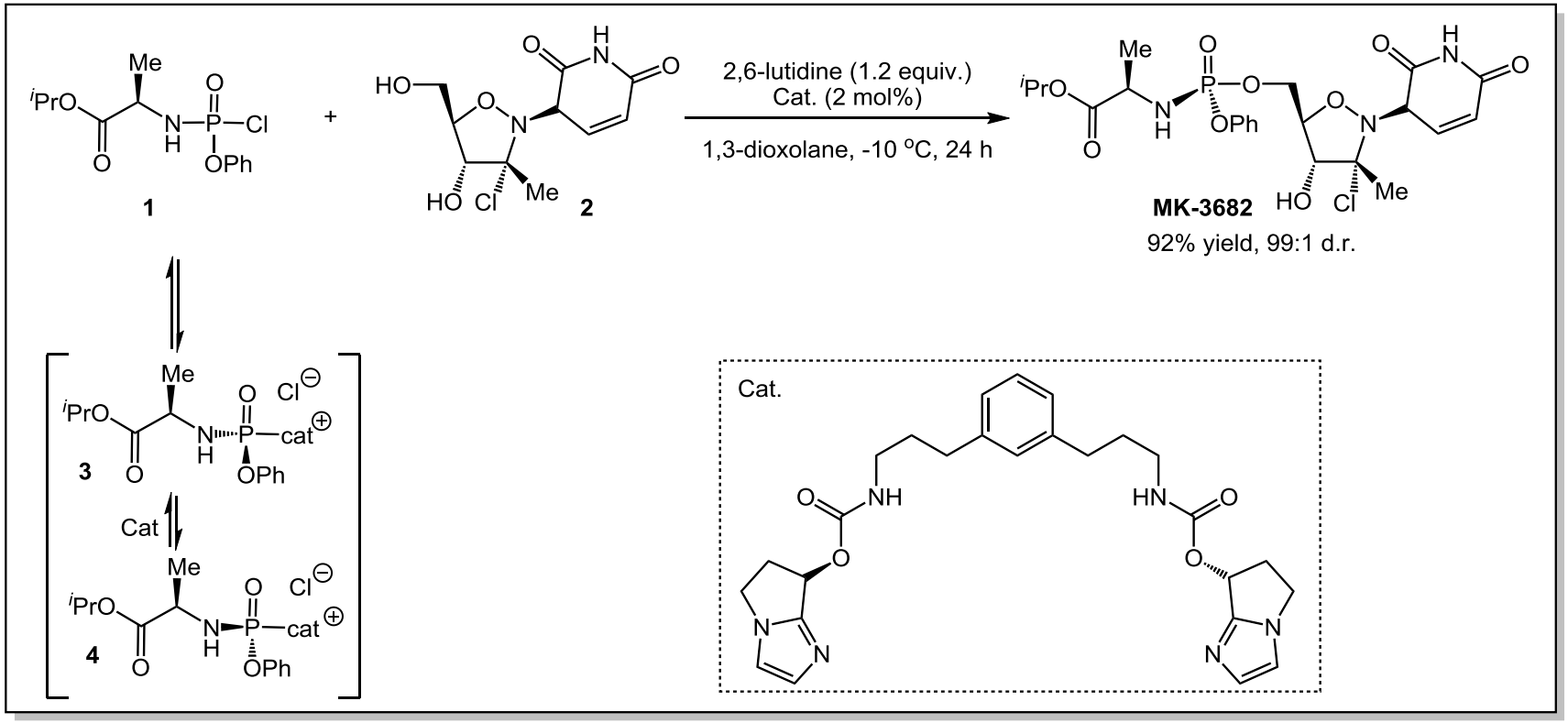
Wang, M.; Zhang. W.; et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 20814-20819.

Synthesis of P-stereogenic Phosphoramides



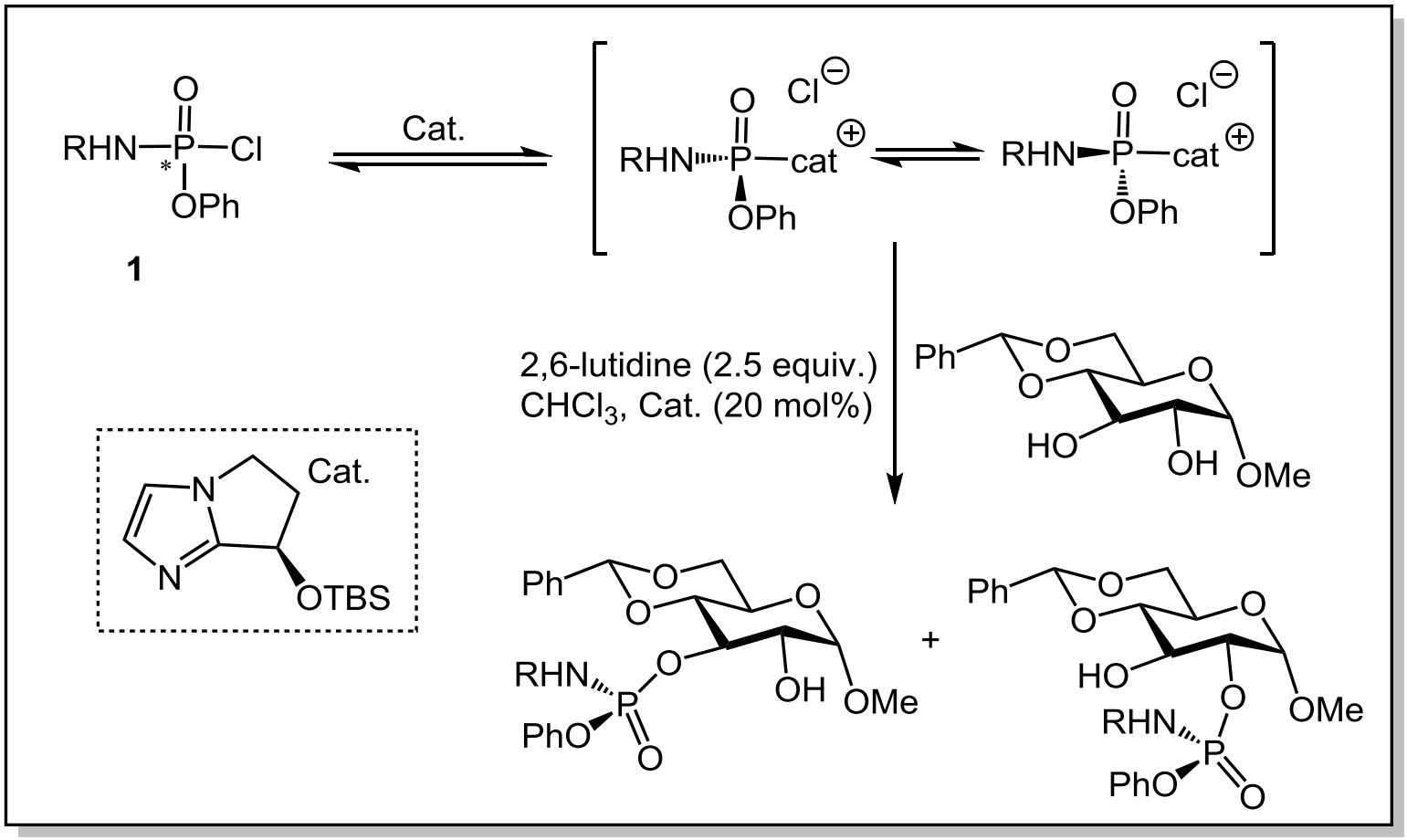
Liu, S.; Zhang. W.; et al. *Tetrahedron:Asymmetry* **2012**, *23*, 329-332.

Synthesis of MK-3682 via DYKAT



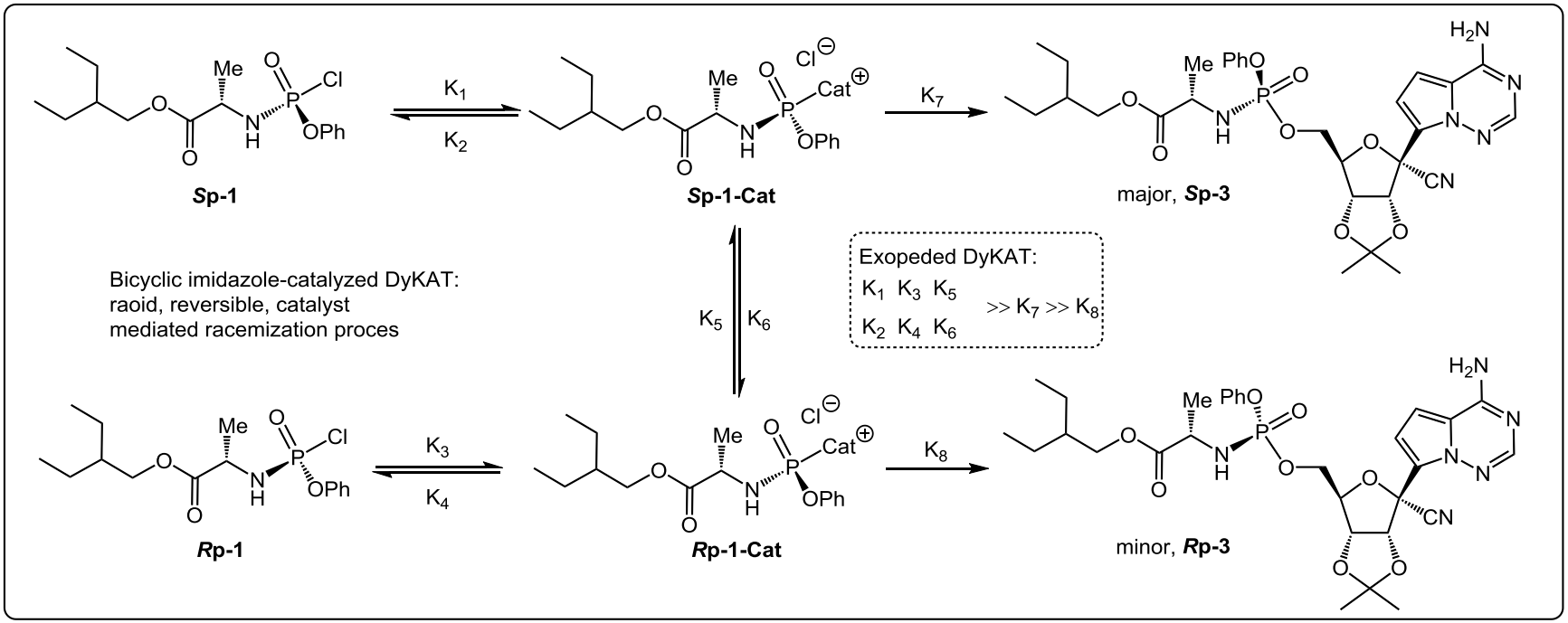
DiRocco, D. A.; et al. *Science* **2017**, *356*, 426-430.

Synthesis of P-stereogenic Phosphoramides



Tang, W.; et al. *Adv. Synth. Catal.* **2019**, *361*, 3729-3732.

Synthesis of Remdesivir via DYKAT



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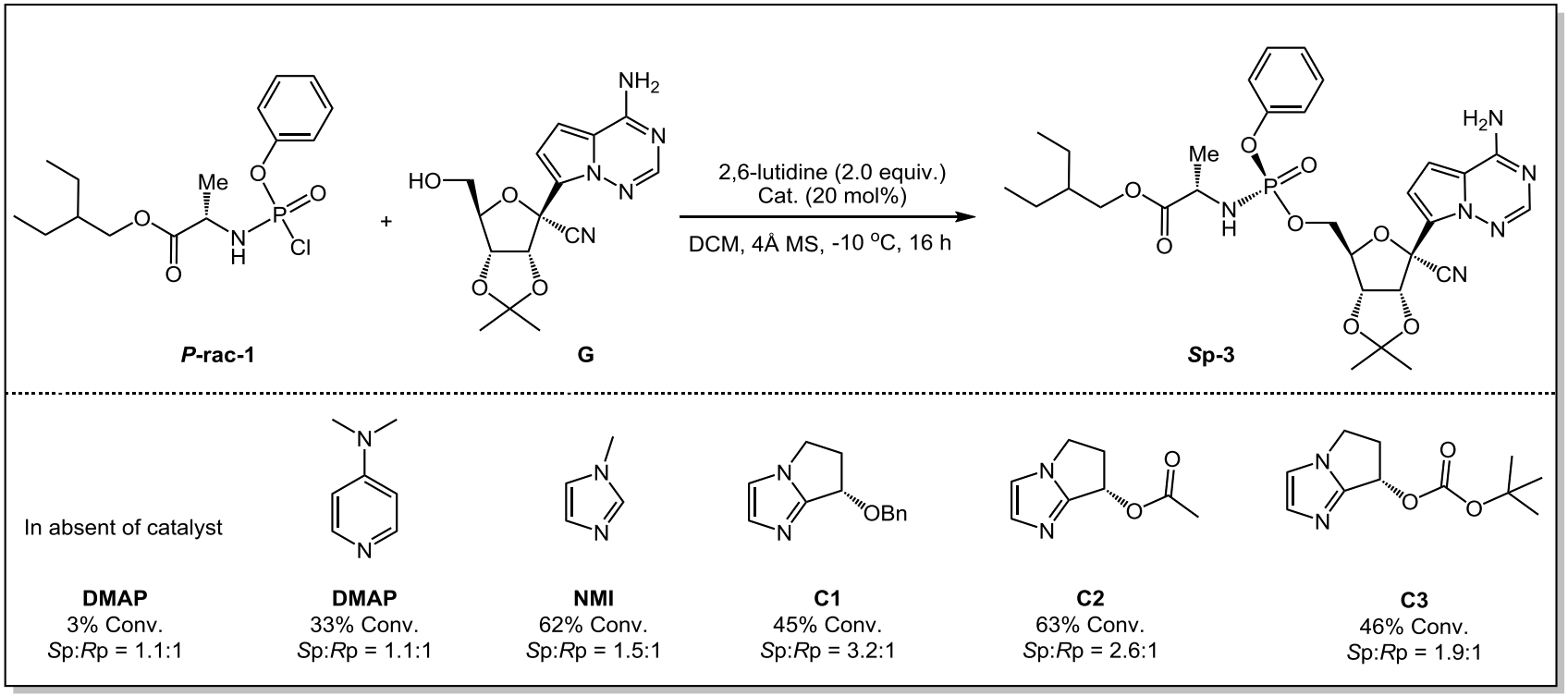
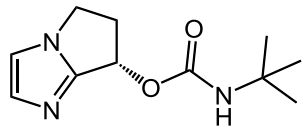
Optimization of the Reaction Conditions

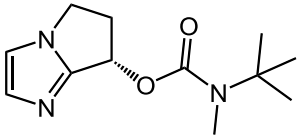


Reaction conditions: ***P*-rac-1** (104.3 mg, 0.30 mmol, 1.5 equiv), **G** (66.3 mg, 0.20 mmol, 1.0 equiv), 2,6-lutidine (46.6 mL, 0.40 mmol, 2.0 equiv), 4Å MS (80 mg), DCM (2 mL). Determined by ^{31}P NMR analysis. Determined by ^{31}P NMR analysis using $P(O)(OMe)_3$ as the internal standard.

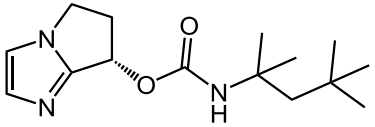
Optimization of the Reaction Conditions



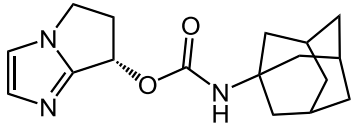
C4
91% Conv.
Sp:*Rp* = 9.3:1



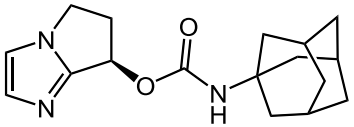
C5
47% Conv.
Sp:*Rp* = 6.2:1



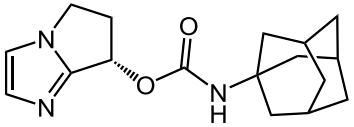
C6
83% Conv.
Sp:*Rp* = 7.4:1



C7
91% Conv.
Sp:*Rp* = 11.2:1



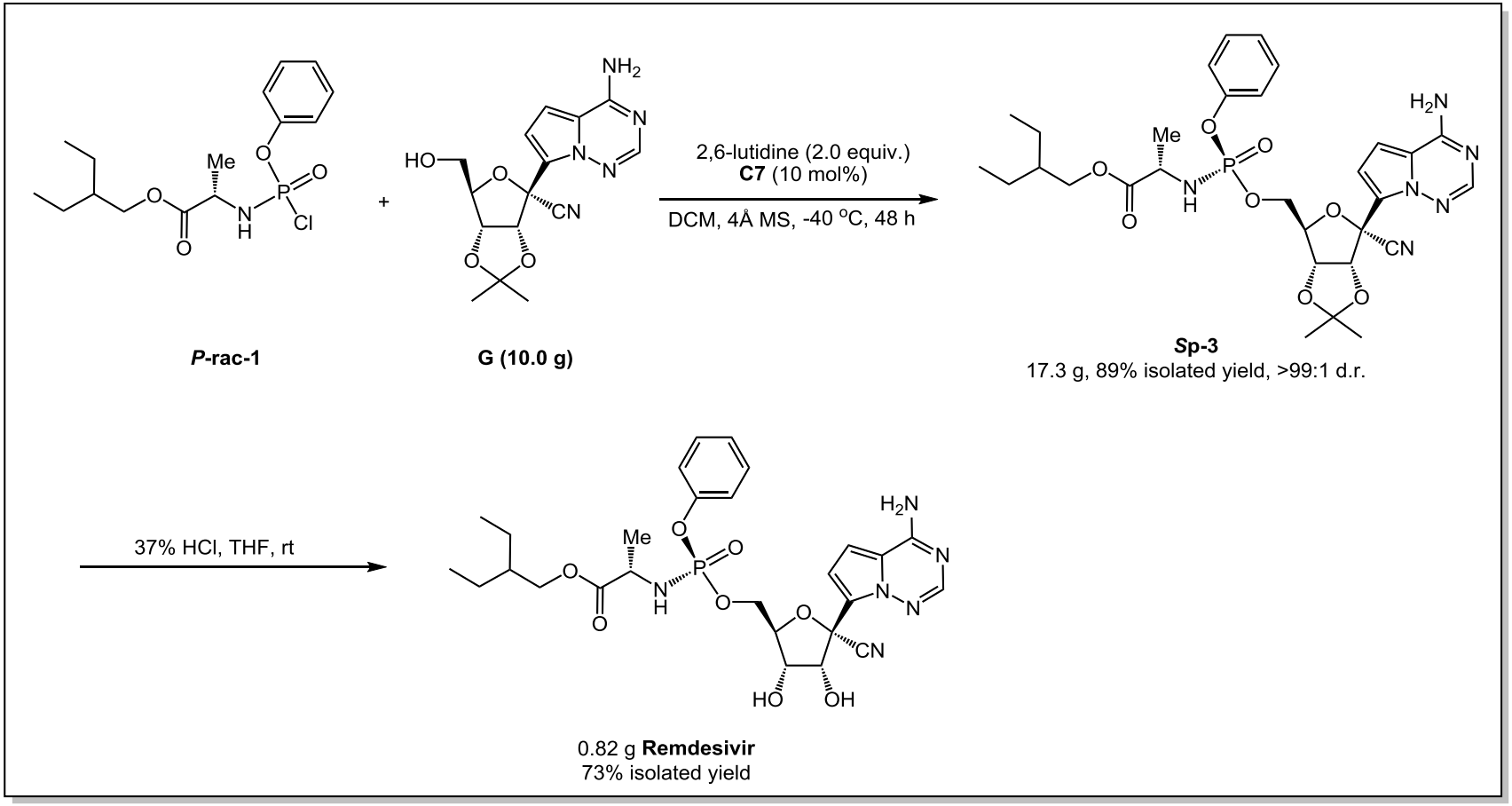
(*R*)-C7
81% Conv.
Sp:*Rp* = 4.3:1



20 mol% **C7**, -10 °C , 16 h, 77% Conv., *Sp*:*Rp* = 7.8:1 (no base)
20 mol% **C7**, -30 °C , 16 h, 96% Conv., *Sp*:*Rp* = 16.6:1
20 mol% **C7**, -40 °C , 36 h, 96% Conv., *Sp*:*Rp* = 21.8:1
10 mol% **C7**, -30 °C , 36 h, 95% Conv., *Sp*:*Rp* = 16.4:1
5 mol% **C7**, -30 °C , 48 h, 94% Conv., *Sp*:*Rp* = 16.4:1
10 mol% C7, -40 °C , 48 h, 95% Conv., *Sp*:*Rp* = 21.6:1

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

Gram-scale Synthesis of Remdesivir



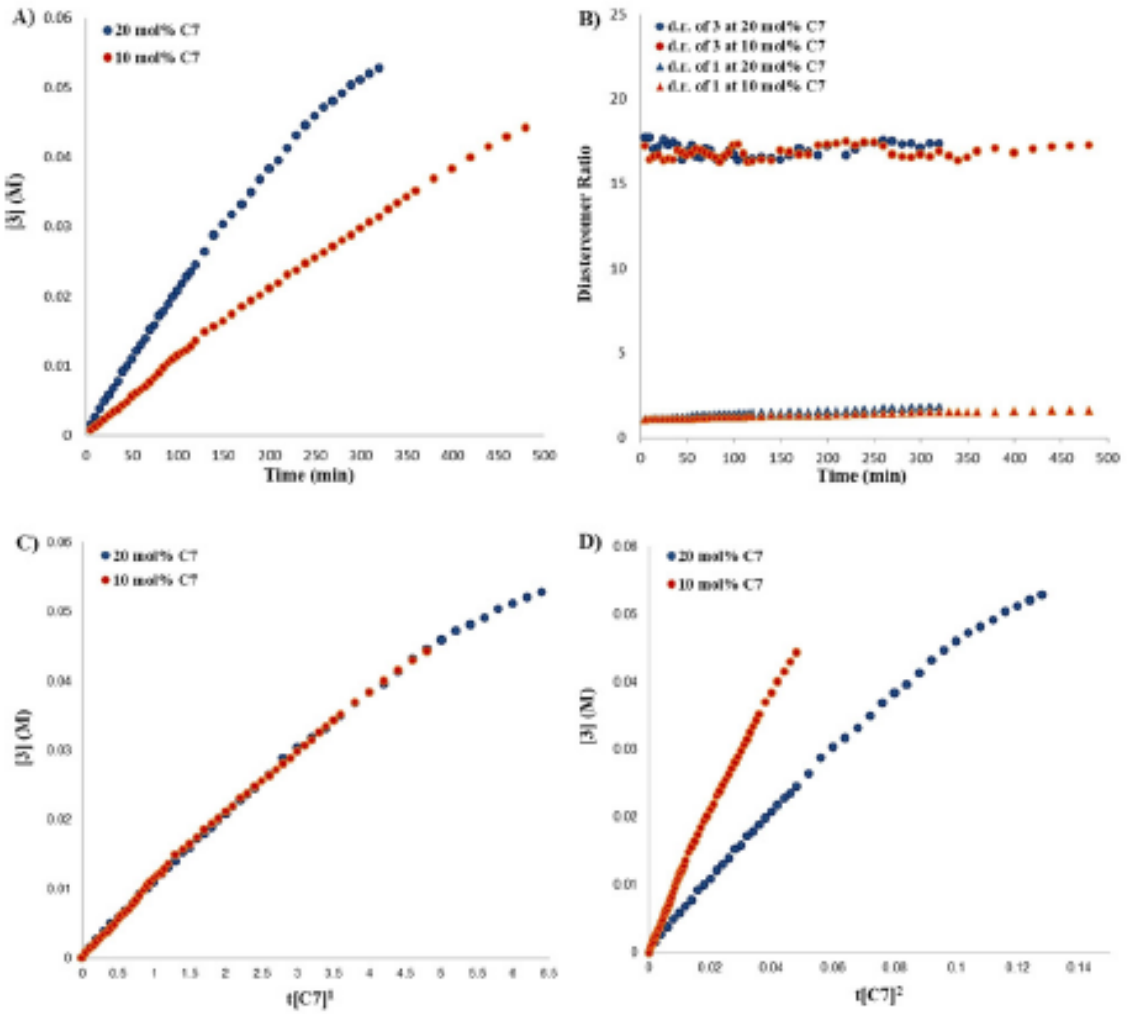
***P*-rac-1**

G (10.0 g)

***Sp*-3**
17.3 g, 89% isolated yield, >99:1 d.r.

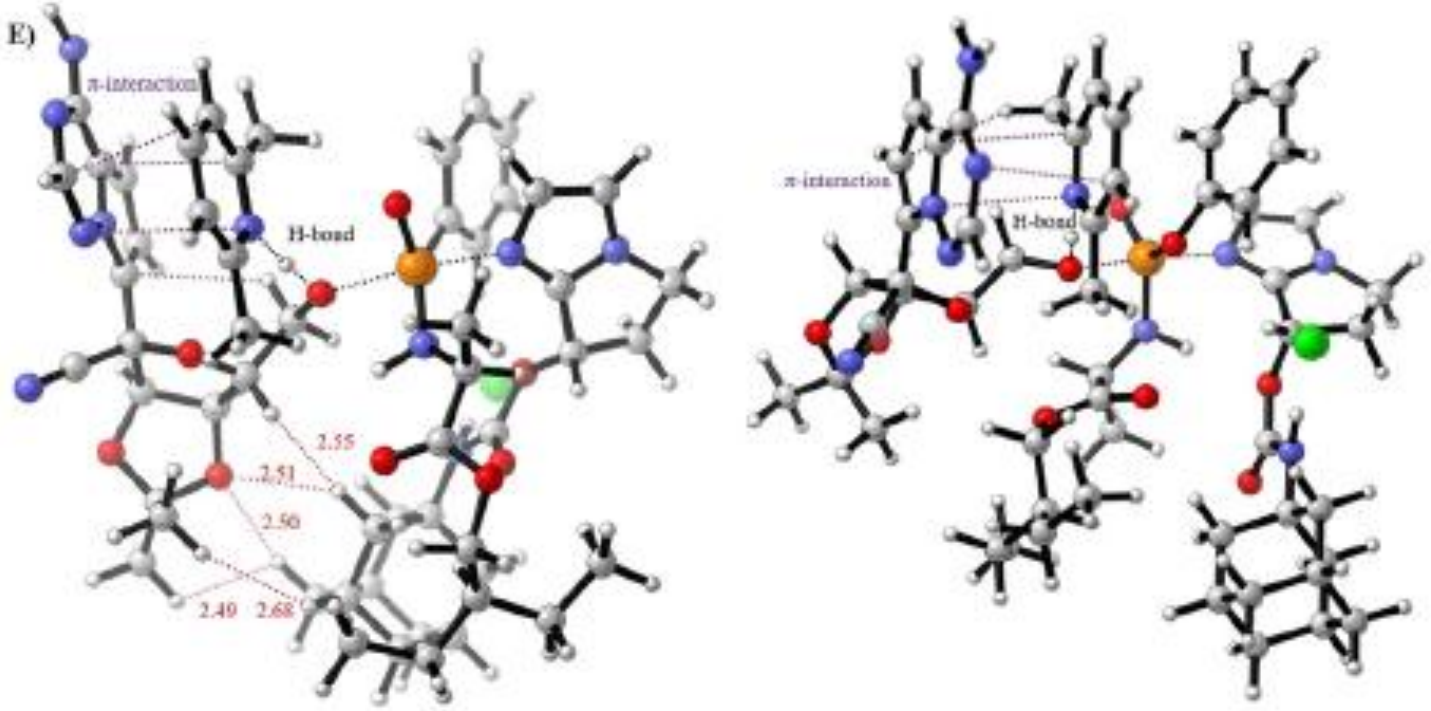
0.82 g **Remdesivir**
73% isolated yield

Mechanistic Study



The two plots of **[3]** against t[cat]^n showed an overlay of n = 1, indicating that reaction is first-order with respect to [**C7**].

Mechanistic Study



$\Delta\Delta G^{\ddagger}$ = 0.0 kcal/mol for S_P-3

$\Delta\Delta G^{\ddagger}$ = 3.5 kcal/mol for R_P-3

The First Paragraph

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. 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. Recent clinical trial results have shown that it can effectively shorten the recovery period

The First Paragraph

of hospitalized patients and reduce the risk of death by 62% in patients with severe cases of the disease, 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. 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.

The Last Paragraph

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 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.

Representative Examples

Unlike the progress achieved in the catalytic asymmetric synthesis of carbon centers, stereogenic phosphorus groups are still challenging to construct.

A mismatched relationship was observed by changing the configuration of the enantiopure C7, suggesting chiral recognition between the chiral catalyst and the substrate.

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