



CN 107827890 B
2020.03.27

201711147876.9

(2006.01)

2017.11.17

CN 107827890 A

2018.03.23

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46

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(2006.01)

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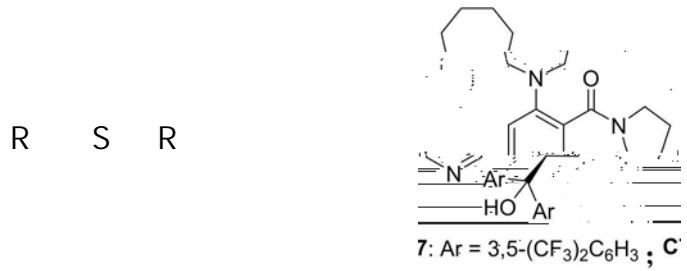
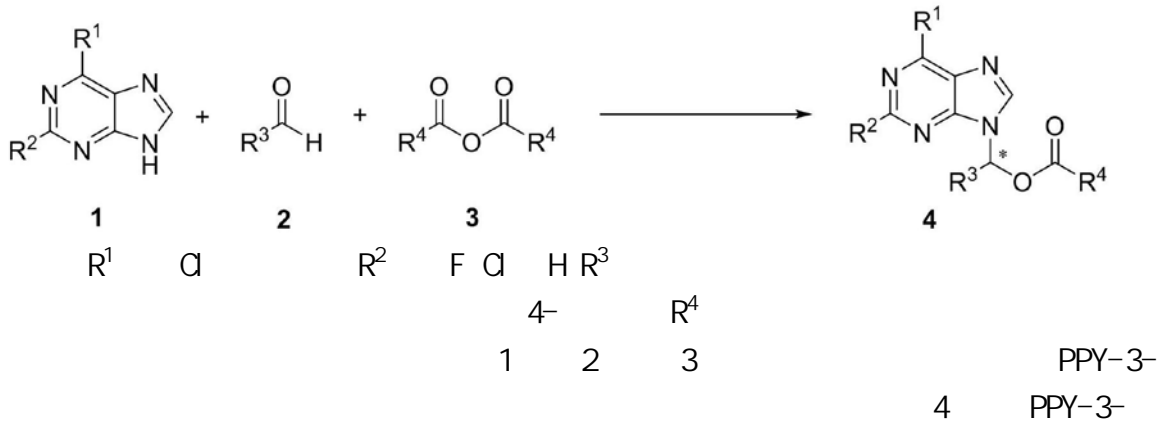
CN 104557936 A, 2015.04.29,
Artis Kinens .Development of a
Chiral DMAP Catalyst for the Dynamic
Kinetic Resolution of Azole Hemiaminal s.
J. Org. Chem .2017, 82 (2), 869-
886 .
Anne Akin .A Scalable Route for the
Regio- and Enantioselective Preparation
of a Tetrazole Prodrug: Application to
the Multi-Gram Scale Synthesis of a PCSK9
Inhibitor. Org. Process Res. Dev .2017,
21 (12), 1990-2000 .
David W Piotrowski .Regio- and
Enantioselective Synthesis of Azole
Hemiaminal Esters by Lewis Base Catalyzed
Dynamic Kinetic Resolution. J. Am Chem
Soc. .2016, 138 (14), 4818-4823

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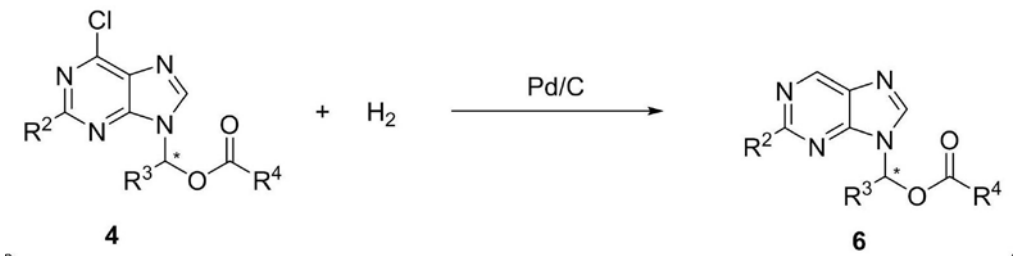
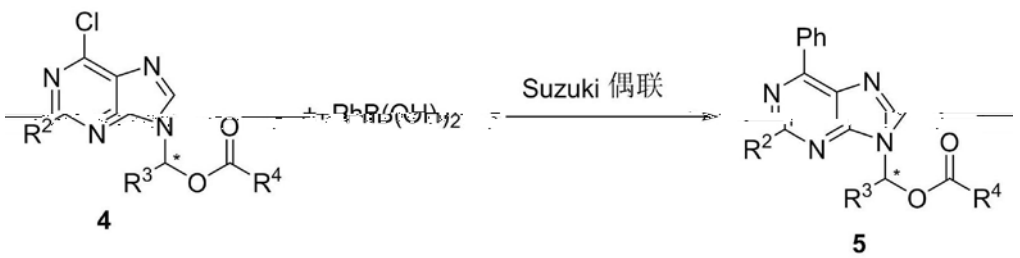
PPY 3

CN 107827890 B

1.



1 2 3 PPY-3-
 2. 1
 -10 70
 3. 1
 4 5
 6

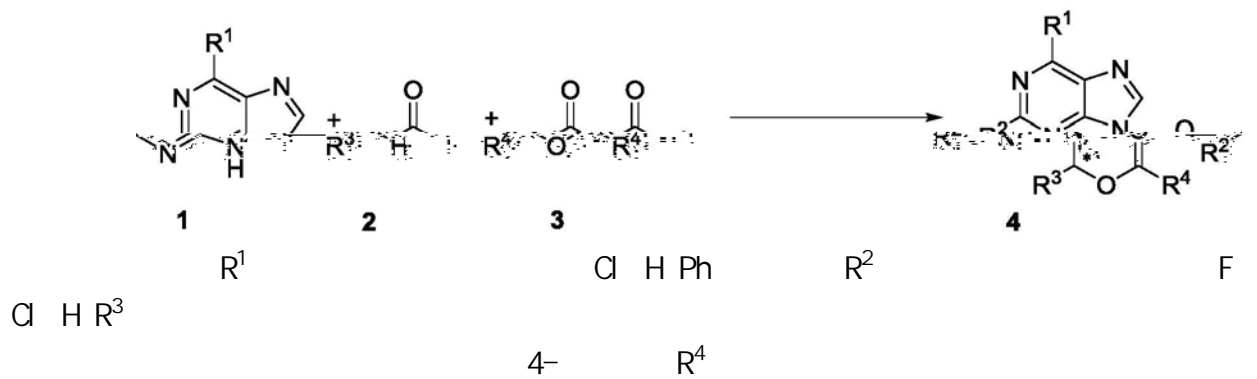


(HSV) Ganciclovir (HBV)
 (CMV) Acyclovir
 (CMV) Adefovir and Tenofovir

N7 N9
 N9

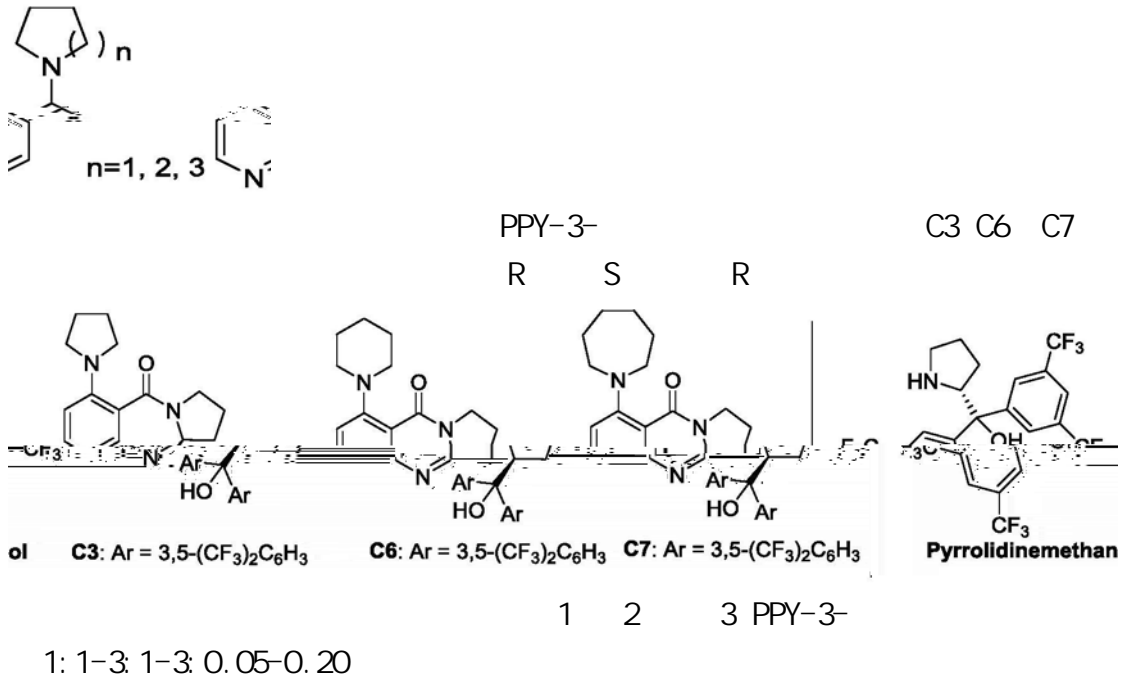
1 2 3 PPY-3-

1 2 3 4 PPY-3-



PPY 4-
 Pi peri di nopyri di ne) 4-
 azepane}

(4-Pyr r ol i di nopyri di ne) 4- (4-
 { 4-azepanepyr i di ne 1-(pyri di n-4-yl)

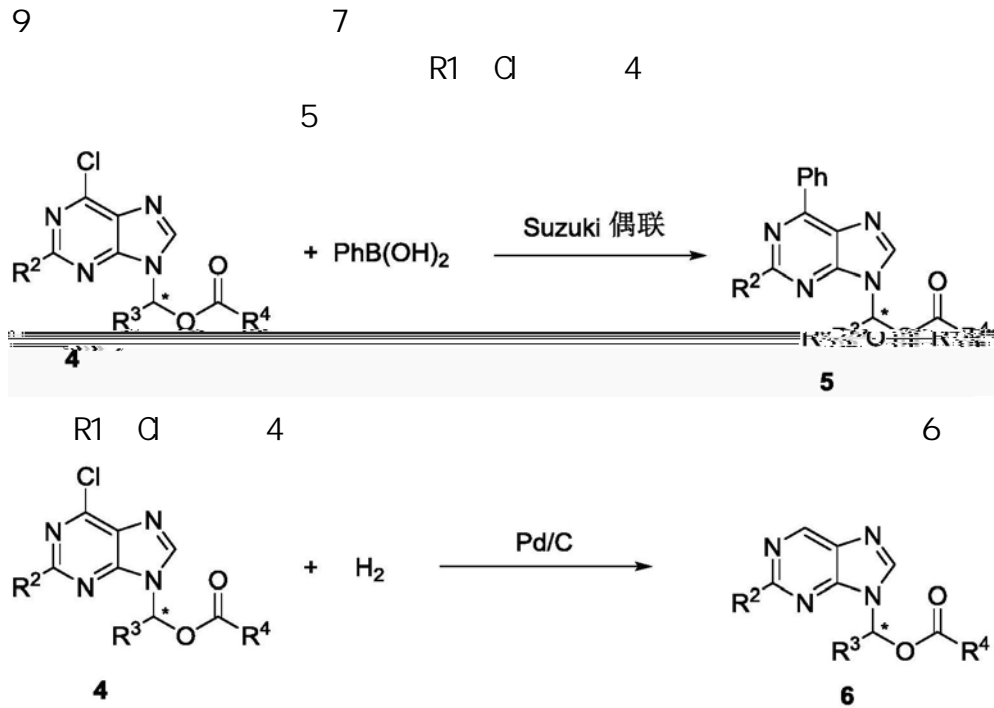


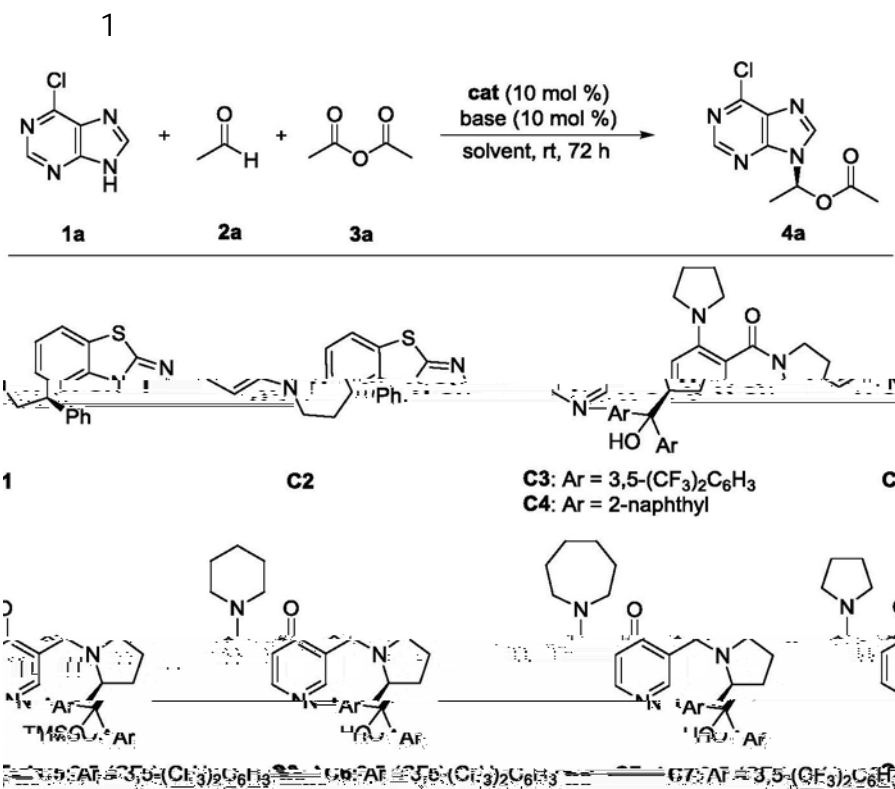
DABCO

DABCO

-10 70

65 -95





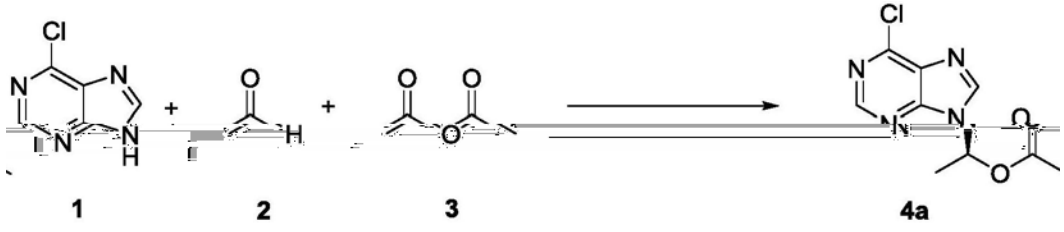
标号 ^a	催化	溶剂	碱	底物比例	产率 (%) ^b	ee (%) ^c	
1	C1	toluene	Et ₃ N	1:1.1:1.1	46	53	
2	C2	toluene	Et ₃ N	1:1.1:1.1	51	-63	
67	85	3	C3	toluene	Et ₃ N	1:1.1:1.1	
45	-42	4	C4	toluene	Et ₃ N	1:1.1:1.1	
45	23	5	C5	toluene	Et ₃ N	1:1.1:1.1	
	1:1.1:1.1	60	87	6	C6	toluene	Et ₃ N
	1:1.1:1.1	62	88	7	C7	toluene	Et ₃ N
	1:1.1:1.1	63	70	8	C7	CH ₂ Cl ₂	Et ₃ N
	1:1.1:1.1	58	84	9	C7	Et ₂ O	Et ₃ N
	1:1.1:1.1	48	42	10	C7	THF	Et ₃ N
	1:1.1:1.1	74	72	11	C7	PhF	Et ₃ N
	1:1.1:1.1	48	78	12	C7	PhCl	Et ₃ N
1	1:1.1:1.1	52	46	13	C7	toluene	Pr ₂ EtN
2	1:1.1:1.1	57	89	14	C7	toluene	DABCO
3	1:1.1:1.1	59	82	15	C7	toluene	K ₂ CO ₃
3	1:1.1:1.1	54	90	16	C7	toluene	Cs ₂ CO
3	1:1.1:1.1	61	91	17	C7	toluene	Na ₂ CO
3	1:1.1:3	69	91	18	C7	toluene	Na ₂ CO
3	1:2:3	72	90	19	C7	toluene	Na ₂ CO
3	1:3:3	88	91	20	C7	toluene	Na ₂ CO
3	1:3:3	87	91	21 ^d	C7	toluene	Na ₂ CO
3	1:3:3	85	94	22 ^e	C7	toluene	Na ₂ CO

1a (0.1 mmol), catalyst (10 nmol), and base (10 nmol) were added in a test tube, followed by adding 3a, 2a, and solvent (2 mL) at room temperature. ^b Isolated yield based on 1a. ^c Determined by chiral HPLC analysis. ^d At 50 °C. ^e 4 Å MS (60 ng) was added.

1-7) PPY (7.7 ng, 10 nmol), 3 (1 ng, 0.10 mmol), 2a (1 μL, 0.3 mmol), 3a (24 μL, 0.3 mmol), 2 mL, 60 ng, 4 Å MS, TLC, 4a 85 94 ee

1a 2a 3a

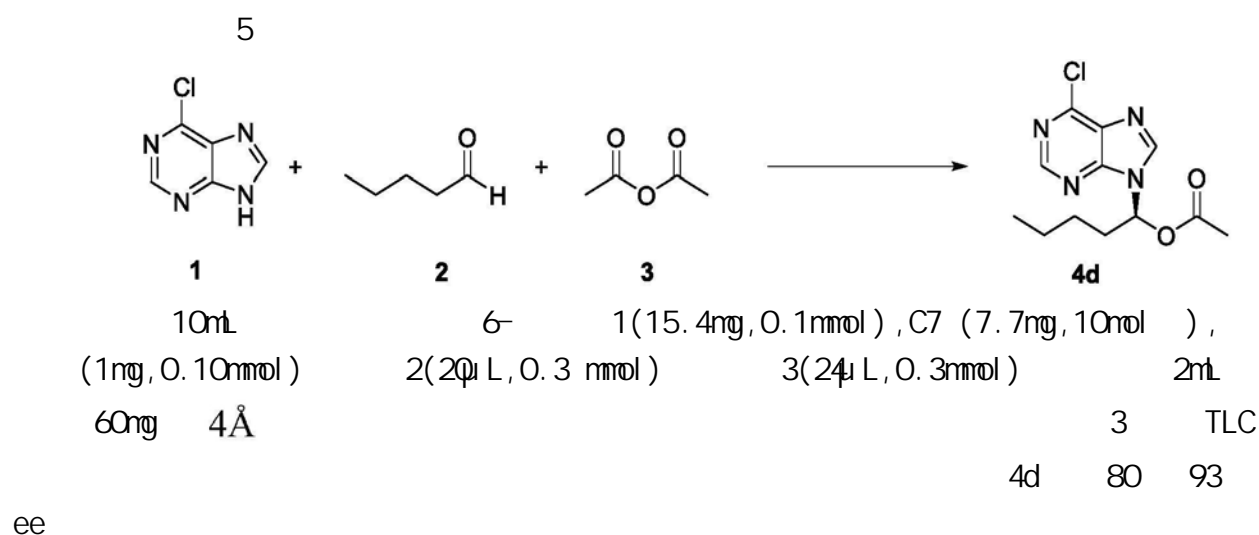
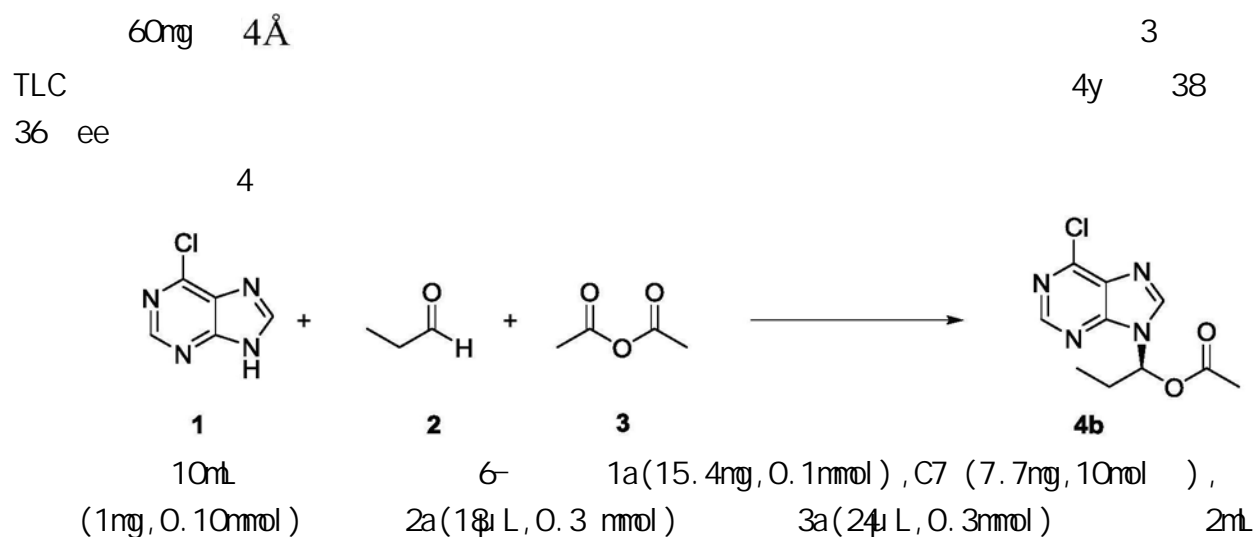
4a



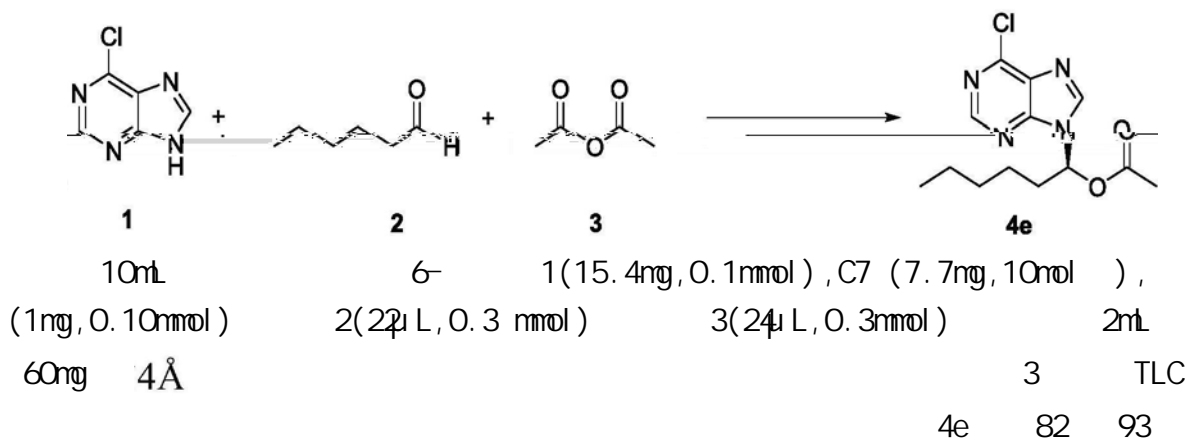
5 mmol PPY
 10 mmol PPY
 15 mmol PPY

yi el d 55 ee 82
 yi el d 80 ee 90
 yi el d 80 ee 84

s c0 0 0 f0 0 € O G Ö c0 0 0 f0 0 € O G Ö ê s

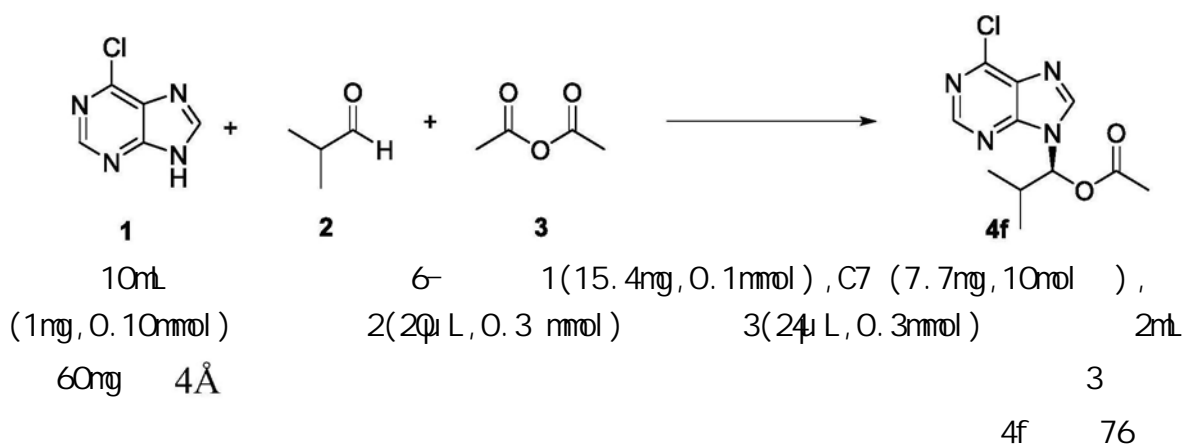


4d, 80% yield, 93% ee. $[\alpha]_D^{25} -18.2$ (c 1.06, CH₂Cl₂)
HPLC (n-hexane/2-propanol 90/10, 0.6mL/min, 256nm): 13.26min, 16.173min. ¹H NMR (600MHz, CDCl₃): 8.76(s, 1H), 8.27(s, 1H), 6.91(t, J = 7.2Hz, 1H), 2.33-2.41(m, 2H), 1.35-1.38(m, 3H), 1.18-1.23(m, 1H), 0.86(t, J = 6.0Hz, 3H). ¹³C NMR (100MHz, CDCl₃): 169.6, 152.4, 151.4, 151.2, 144.3, 131.7, 78.0, 50.5, 32.9, 26.7, 22.0, 20.7, 13.8. HRMS calcd for C₁₂H₁₅ClN₄O₂Na[M+Na]⁺ 305.0776, found 305.0784.



ee

7

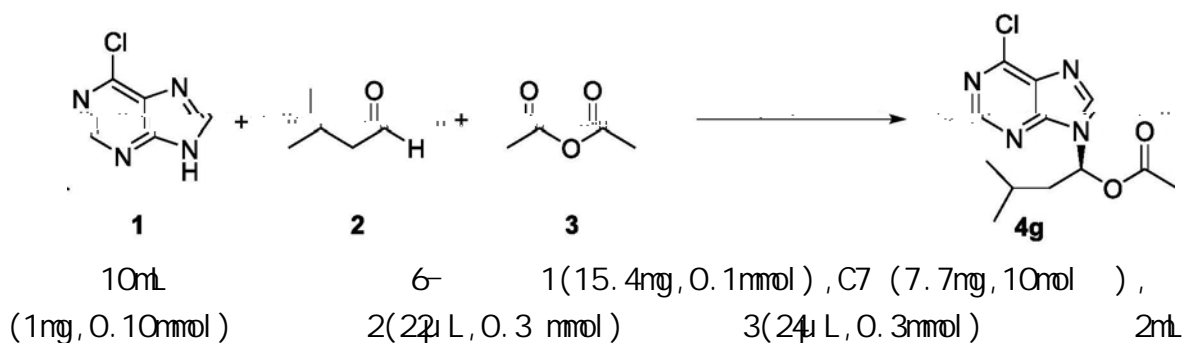


TLC

94 ee

4f, 76% yield, 94% ee. $[\alpha]_D^{25} -21.3$ (c 0.95, CH₂Cl₂) Ee
 HPLC (n-hexane/2-propanol 90/10, 0.6mL/min, : 256nm
 : 14.360min, 16.450 min.) ¹H NMR(600MHz, CDCl₃) 8.77(s, 1H), 8.23(s, 1H),
 6.60(d, J 9.0Hz, 1H), 2.82-2.88(m, 1H), 2.09(s, 3H), 1.12(d, J 6.0Hz, 3H), 0.80(d, J
 6.0Hz, 3H) ¹³C NMR(100MHz, CDCl₃): 169.5, 152.5, 151.5, 151.4, 144.1, 131.7, 82.3,
 31.9, 20.7, 18.3, 17.7 HRMS calcd for C₁₁H₁₃ClN₄O₂Na[M+Na]⁺ 291.0619, found
 291.0627.

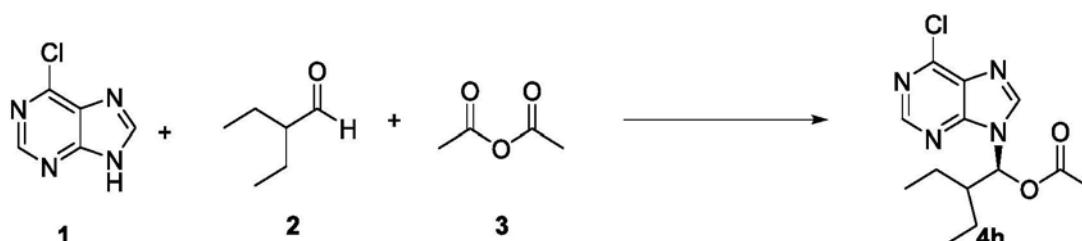
8



60mg  3
 TLC 4g 72
 91 ee

4g, 72% yield, 91% ee. $[\alpha]_D^{25} -19.9$ (c 1.15, CH₂Cl₂) Ee
 HPLC (n-hexane/2-propanol 90/10, 0.6mL/min, : 256nm
 : 12.623min, 15.463 min.) ¹H NMR(400MHz, CDCl₃) 8.78(s, 1H), 8.28(s, 1H),
 7.02(t, J 7.2Hz, 1H), 2.19-2.35(m 2H), 2.07(s, 3H), 1.48-1.55(m 1H), 0.99 (d, J
 6.8Hz, 3H), 0.94(d, J 6.8Hz, 3H) ¹³C NMR(100MHz, CDCl₃): 169.5, 152.5, 151.5, 151.4,
 144.2, 131.9, 77.7, 53.6, 41.8, 24.6, 22.3, 22.2, 20.8 HRMS calcd for C₁₂H₁₅Cl N₄O₂Na[M
 +Na]⁺305.0776, found 305.0776.

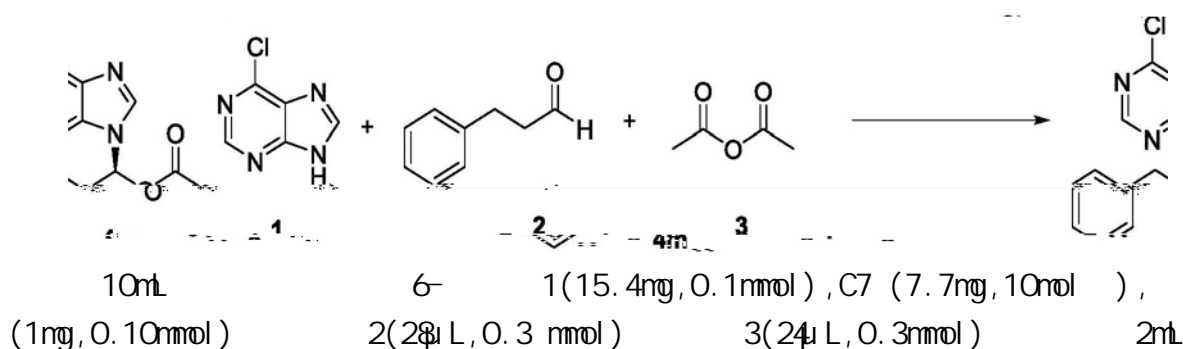
9



10mL 6- 1(15.4mg, 0.1mmol), C7 (7.7mg, 10mol),
 (1mg, 0.10mmol) 2(24μL, 0.3mmol) 3(24μL, 0.3mmol)
 2mL 60mg 4Å 3
 TLC 4h 82
 92 ee

4h, 82% yield, 92% ee. $[\alpha]_D^{25} -31.1$ (c 0.55, CH₂Cl₂) Ee
 HPLC (n-hexane/2-propanol 90/10, 0.6mL/min, : 256nm
 : 11.907min, 15.410 min.) ¹H NMR(600MHz, CDCl₃) 8.76(s, 1H), 8.23(s, 1H),
 6.81(d, J 9.6Hz, 1H), 2.49-2.56(m 1H), 2.1(s, 3H), 1.51-1.62(m 2H), 1.06-1.21(m
 2H), 0.95(t, J 7.2Hz, 3H), 0.78(t, J 7.2Hz, 3H) ¹³C NMR(100MHz, CDCl₃): 169.5,
 152.5, 151.4, 144.1, 131.6, 79.7, 42.9, 20.7, 20.7, 20.4, 10.0, 9.9 HRMS calcd for
 C₁₃H₁₇Cl N₄O₂Na[MNa]⁺ 319.0932, found 319.0936.

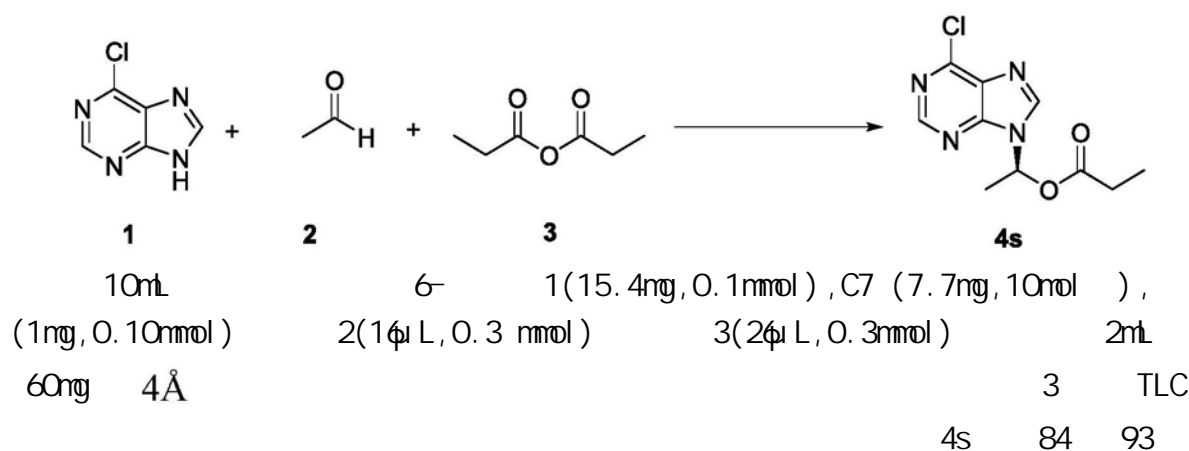
10



60mg 4Å
TLC
95 ee

4m ,83 yi el d, 95 ee. $[\alpha]_D^{25} -27.9$ (c 1.60, CH₂Cl₂) Ee
HPLC (n-hexane/2-propanol 90/10, 0.6mL/min, : 256nm
: 20.537min, 26.617 min.) ¹H NMR(600MHz, CDCl₃) 8.79(s, 1H), 8.21(s, 1H),
7.25-7.27(m 2H), 4.95-5.02(m 2H), 2.45-2.60(m 2H), 2.10-2.12(m 2H), 2.08(s, 3H)
¹³C NMR(100MHz, CDCl₃): 169.6, 152.4, 151.6, 151.3, 144.7, 138.9, 132.0, 128.8, 128.3,
126.8, 77.8, 34.1, 31.1, 20.8 HRMS calcd for C₁₆H₁₅Cl N₄O₂Na[MNa]⁺353.0781, found
353.0776.

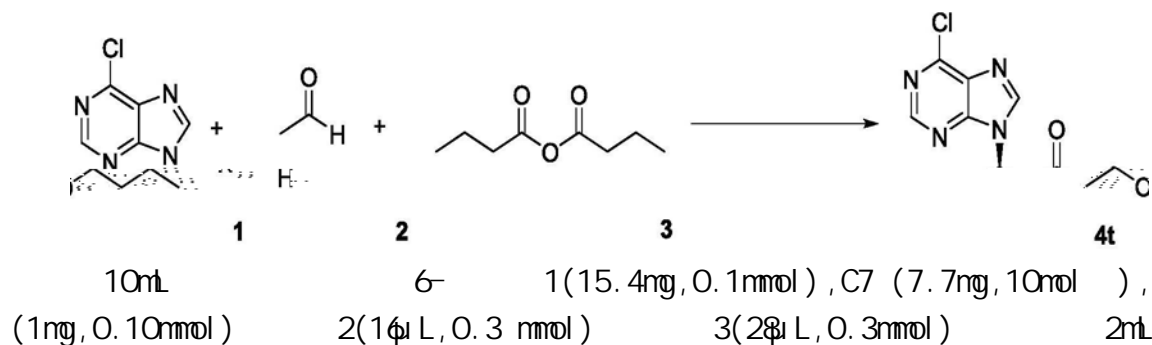
11



ee

4s ,84 yi el d, 93 ee. $[\alpha]_D^{25} -14.5$ (c 1.05, CH₂Cl₂) Ee
HPLC (n-hexane/2-propanol 90/10, 0.6mL/min, : 256nm
: 17.567min, 21.420 min.) ¹H NMR(400MHz, CDCl₃) 8.78(s, 1H), 8.31(s, 1H),
7.11(q, J 6.4Hz, 1H), 2.26-2.42(m 2H), 2.02(d, J 6.4Hz, 3H), 1.09(t, J 7.6Hz, 3H)
¹³C NMR(100MHz, CDCl₃): 173.0, 152.0, 151.0, 144.4, 131.4, 74.9, 49.6, 27.0, 19.4,
8.3 HRMS calcd for C₁₀H₁₁Cl N₄O₂Na[MNa]⁺277.0470, found 277.0463.

12



60mg 4Å

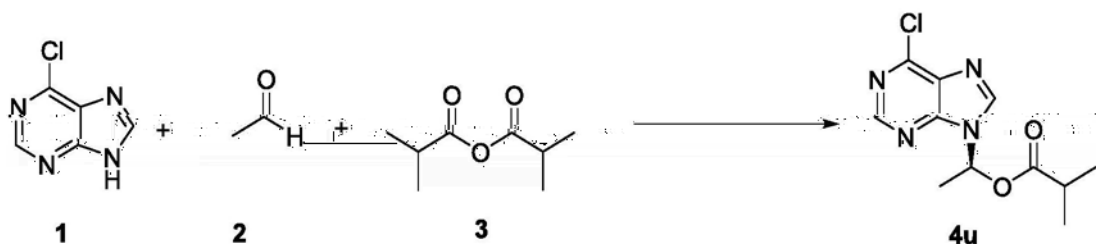
3 TLC

4t 74 92

ee

4t ,74 yi el d,92 ee. []²⁵_D -13.2(c 0.60,CH₂Cl₂) Ee
 HPLC (n-hexane/2-propanol 90/10, 0.6mL/min, : 256nm
 : 14.753min,18.790 min.) ¹H NMR(600MHz, CDCl₃) 8.78(s,1H), 8.30(s,1H),
 7.11(q, J 6.0Hz,1H), 2.25-2.35(m 2H), 2.20(d, J 6.0Hz, 3H), 1.58-1.61 (m 2H),
 .0.87(t, J 7.2Hz, 3H) ¹³C NMR(100MHz, CDCl₃): 172.1, 152.4,151.5,151.2,143.9,
 131.9,74.8,35.8,20.0,18.1,13.5 HRMS cal cd for C₁₁H₁₃Cl N₄O₂Na[MNa]⁺291.0619,
 found 291.0607.

13



10mL 6- 1(15.4mg, 0.1mmol), C7 (7.7mg, 10mol),
 (1mg, 0.10mmol) 2(1μL, 0.3 mmol) 3(2μL, 0.3mmol) 2mL
 60mg 4Å 3

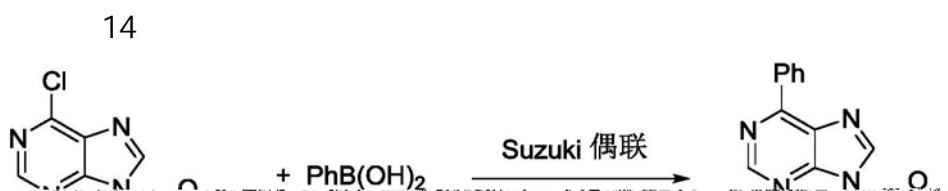
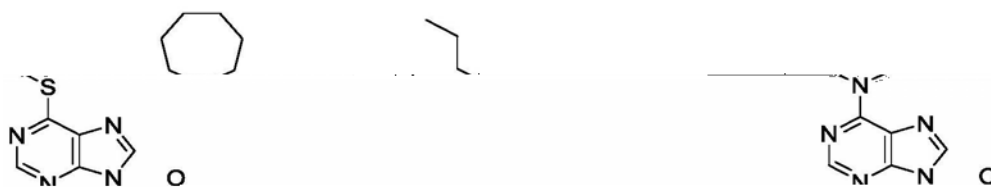
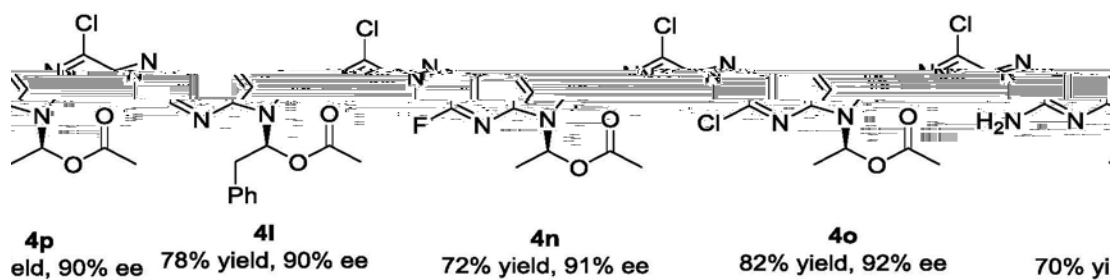
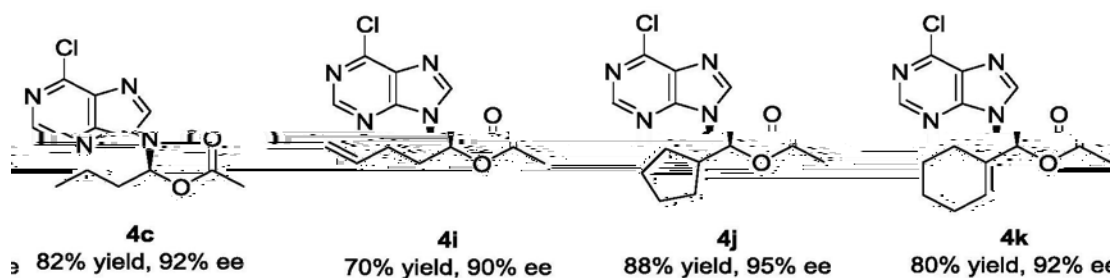
TLC

4u 71

92 ee

4u ,71 yi el d,92 ee. []²⁵_D -15.9(c 1.10,CH₂Cl₂) Ee
 HPLC (n-hexane/2-propanol 90/10, 0.6mL/min, : 256nm
 : 13.677min,21.090 min.) ¹H NMR(600MHz, CDCl₃) 8.75(s,1H), 8.29(s,1H),
 7.08(q, J 6.0Hz,1H), 2.00(d, J 6.0Hz, 3H), 1.12(d, J 6.6Hz, 3H), 1.05 (d, J
 6.6Hz, 3H) ¹³C NMR(100MHz, CDCl₃): 175.5,152.4,151.5, 151.2,143.8,131.9,74.9,
 33.8,20.0,18.7 HRMS cal cd for C₁₁H₁₃Cl N₄O₂Na[MNa]⁺291.0619,found 291.0625.

4



10mL
(34ng, 0.25mmol)

4a(43.4ng, 0.17mmol),
(18, 0.016mmol)

(30 ng, 0.25mmol)
2mL

12 TLC

5a 84 95 ee



4a

10mL

4a(62.5ng, 0.26mmol),

6a

(4.15 ng, 15 mmol)

	2mL		12
TLC		6a	82
95 ee			