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Enantioselective Synthesis of 4-Heterosubstituted Cyclopentenones

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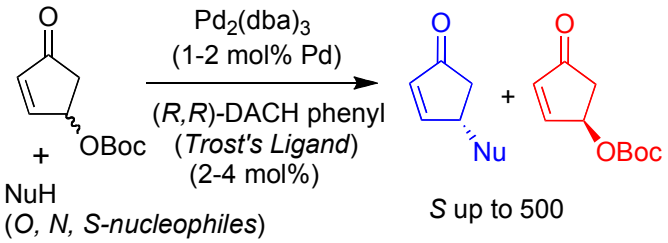
In Memoriam Robert E. Gawley[#]

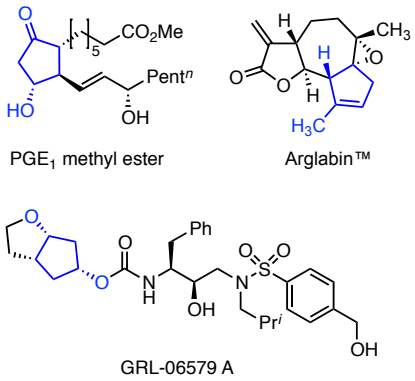


Racemic 4-hydroxycyclopentenone, readily derived from furfuryl alcohol, can be transformed via its *O*-Boc derivative to 4-acyloxy, 4-aryloxy-, 4-amino-, or 4-thio-substituted cyclopentenones with high enantioselectivity by palladium-catalyzed kinetic resolution via nucleophilic allylic substitutions. Applying this methodology, a short formal synthesis of *ent*-noraristeromycin was readily accomplished.

Enantiopure 4-hydroxycyclopentenone (**2**) has been recognized as a most versatile chiral intermediate,[1] having been used as a key synthon for the synthesis of natural products and

pharmaceutical drugs. Prominent examples are found in the synthesis of prostaglandin PGE_1 methyl ester,[2a] the HIV protease inhibitor GRL-06579[2b] or the farnesyltransferase inhibitor Arglabin™.[2c]

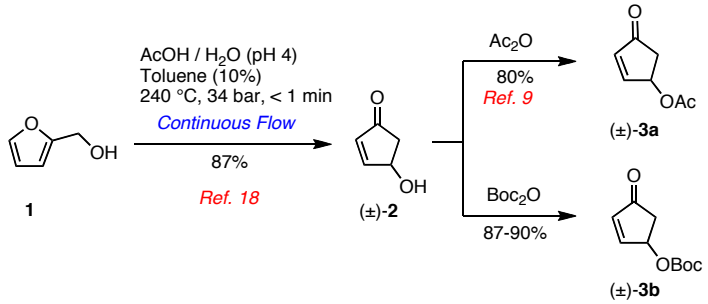
Figure 1. 4-Hydroxycyclopentenone as synthon in the synthesis of drugs.



Consequently, a considerable number of synthetic approaches towards racemic[3] and enantiopure **2** and derivatives thereof utilizing the chiral pool[4], chiral reagents[5] or catalysts[6] have been developed. A majority of these transformations involve selective changing the oxidation state of the corresponding 1,3-*cis*-diol[7] or 1,3-diketone.[8]

The direct deracemization of (±)-**2** or its *O*-acyl derivative was achieved by enzymatic resolution with lipases[9] or penicillin G acylase.[10] Kinetic resolution of (±)-**2** had also been achieved by catalytic asymmetric isomerization[11] or hydrogenation.[12] Surprisingly in light of the well-established methodology for asymmetric nucleophilic substitutions of cyclic and acyclic allylic alcohols, as well as their esters, by chiral palladium catalysts (Tsuji-Trost reaction),[13,14,15,16] this approach was not investigated with (±)-**2**. Arguably, the most direct access to racemic (±)-**2** is the transformation of furfuryl alcohol (**1**) under aqueous acidic conditions,[17] a process that could recently be greatly improved moving from batch to flow conditions in microreactors (Scheme 1).[18] We report here the easily prepared *O*-Boc derivative (±)-**3b** as an excellent substrate for resolving (±)-**2** by regioselectively introducing oxygen, nitrogen, and sulfur nucleophiles with high asymmetric induction.

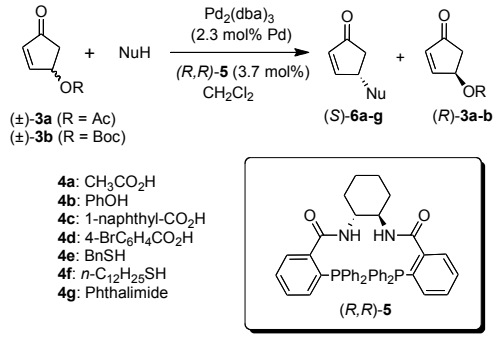
Scheme 1. Facile and high-yielding synthesis of starting materials (±)-**3** from furfuryl alcohol **1**.



We started our investigation by converting (±)-**2** to its corresponding acetate (±)-**3a**, which was subjected to palladium catalyzed allylations with various nucleophiles using Trost's ligand (*R*,*R*)-**5**. However, under various conditions tried, (±)-**3a** turned out to be a sluggish substrate for the title transformation, resulting in low selectivities which was accompanied by decomposition of the starting material at extended reaction times (Table 1, entries 1, 2). Obviously, the allyl acetate moiety in (±)-**3a** is deactivated by the conjugated carbonyl group, making a more activated derivative necessary. Gratifyingly, turning to the *O*-Boc derivative (±)-**3b**, the allyl palladium complex formation occurred readily even at –78 °C, allowing the introduction of various *O*-, *S*- and *N*-nucleophiles. Initially, the nucleophiles were used in stoichiometric quantities with the aim to achieve a dynamic kinetic resolution, which had been proven possible for hydroxybutenolide and related substrates.[14,15,16,20] However, for (±)-**3b** as substrate, the reaction only took place in a kinetic resolution mode because the reaction did not proceed to completion even when the nucleophiles (acetate and phthalimide) were present in excess, and moreover, the products were obtained with low optical purities in such cases. On the other hand, good to excellent enantioselectivities were obtained when the amount of the nucleophiles was decreased to 0.5 equiv or less (Table 1). Carboxylic acids (entries 3, 5, 7) and phenol (entry 4) proved to be suitable nucleophiles, giving generally selectivity factors of > 30 in the kinetic resolution at room temperature within 1 hour reaction time. For 1-naphthoic acid (entry 6), a scale-up to 5 mmol of the substrate (±)-**3b** with concurrent lowering of the temperature to –20 °C allowed the

isolation of both recovered starting material (*R*)-**3b** and product **6c** in enantiopure forms (> 99% ee) with almost perfect yield.

Table 1. Palladium-catalyzed allylic substitutions of **3**.[a]



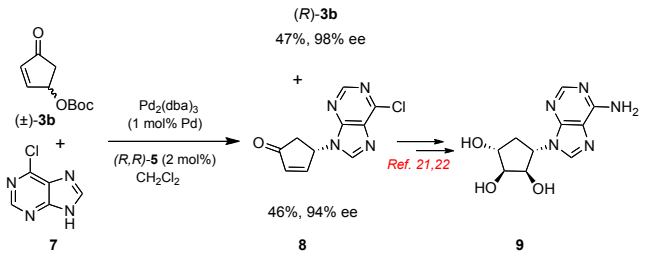
entry	**3**	**4**	t (h)	T (°C)	**3** yield (%)	**3** %ee	**6** yield (%)	**6** % ee	S[b]
1	**3a**	**4b**	18	25	23	26	12	91	24
2	**3a**	**4c**	4	0	50	25	30	77	11
3	**3b**	**4a**	1	0	46	96	35 (**3a**)	90	31
4	**3b**	**4b**	2	0	34	99	34	93	44
5	**3b**	**4c**	1	0	31	90	46	90	44
6	**3b**	**4c**[c]	4	–20	43	>99	45	>99	501
7	**3b**	**4d**	1	0	44	95	41	91	41
8	**3b**	**4e**	17	–78	33	>99	42	93	56
9	**3b**	**4f**	17	–78	38	92	39	93	50
10	**3b**	**4g**	18	rt	31	>99	50[d]	96[d]	194
11	**3b**	**4g**[c]	16	rt	42	>99	48[e]	95[e]	113

[a] (±)-**3** (0.5 mmol), **4** (0.24 mmol), $Pd_2(dba)_3$ (1.2 mol%, 2.3 mol% Pd based on the nucleophile), (*R,R*)-**5** (3.7 mol% based on the nucleophile) in dichloromethane (2 mL). Absolute configurations of **6a** and **6d** were obtained by comparison of specific rotation values with literature (see experimental part) as well as by X-ray crystallography (**6g**, see supporting information). [b] Selectivity factor.[19] [c]5 mmol scale, $Pd_2(dba)_3$ (0.5 mol%; 1 mol% Pd based on the nucleophile), (*R,R*)-**5** (2 mol% based on the nucleophile).[d]36%, 99% ee after single recrystallization from ethanol. [e]43%, 97% ee after single recrystallization from ethanol.

Likewise, sulfur nucleophiles (entries 8,9) were also successfully employed, however, due to their greater reactivity we found that the reactions are best carried out at –78 °C to give **6e** and **6f** with selectivity factors around 50. This successful use of thiols as nucleophiles in a palladium-catalyzed allylic substitution represents new examples of the very rare reactions of this type.[13,20] Finally, phthalimide allowed the enantioselective introduction of a nitrogen nucleophile into the cyclopentenone moiety (entries 10, 11), being especially relevant for the synthesis of carbocyclic nucleosides.

Indeed, starting from (±)-**3b** a short formal synthesis of the enantiomer of the antiviral and antitumor drug noraristeromycin was readily accomplished. The key intermediate **8**, previously synthesized from from desymmetrized *cis*-4-cyclopentene-1,3-diol,[21,22] can be obtained in one step from (±)-**3b** and 6-chloropurine (**7**) in 46% yield (92% yield based on **7**) and in 94% ee, which can be raised to 98% ee (39% yield) by a single recrystallization. In addition, (*R*)-**3b** was also recovered in 47% yield and 98% ee.

Scheme 2. Formal synthesis of (*ent*)-noraristeromycin **9.**



In summary, we have demonstrated a successful kinetic resolution of (±)-**3** via Pd-catalyzed asymmetric allylic substitution. Excellent enantioselectivities of both substitution products and recovered starting materials were obtained even at low catalyst loading (1–2 mol% Pd, 2–4 mol% (*R,R*)-**5** based on the nucleophile). The scope of participating nucleophiles is very broad - phenols, carboxylic acids, thiols

and nitrogen-containing heterocycles. This method should provide a potentially useful access to a variety of optically active 4-substituted-2-cyclopentenone derivatives.

Experimental Section

General Information. All reagents of which the preparation is not described were obtained from commercial suppliers and used without further purification. 4-Hydroxy-2-cyclopentenone (±)-**2**, 4-acetoxy-2-cyclopentenone (±)-**3**, and the (*R,R*)-**5** were prepared according to published procedures.[9,18,23] CH_2Cl_2 and THF were obtained from a solvent purification system. CH_2Cl_2 was degassed by three freeze-pump-thaw cycles. Hexanes and EtOAc were distilled before use. Chemical shifts are reported in ppm from $CHCl_3$ (7.26 ppm) as internal standard on the δ scale. ^{13}C chemical shifts are reported in ppm from $CHCl_3$ (77 ppm) as internal standard on the δ scale. The ^{13}C signals assignment were assisted by DEPT 90 and DEPT 135 experiments. The optical rotation was determined on a polarimeter at 589 nm wavelength (sodium-d-line) in a 0.5 dm measuring cell of ca. 1 mL volume.

General procedure for Pd-catalyzed kinetic resolution. To a solution of (±)-**3b** (0.50 mmol) and the nucleophile (0.24 mmol) in dry, degassed CH_2Cl_2 (2 mL) under nitrogen at the specified temperature was added the catalyst solution, which was separately prepared by stirring $Pd_2(dba)_3$ (2.6 mg, 0.0028 mmol, 2.3 mol% Pd based on **4**) and (*R,R*)-**5** (6.1 mg, 0.0088 mmol, 3.7 mol% based on **4**) in dry, degassed CH_2Cl_2 (1 mL) under nitrogen until the initially purple solution turned yellow-brown (2–3 min). The progress of the reaction was monitored by TLC. Once the reaction was complete, the reaction mixture was directly loaded onto a silica gel column and the product eluted by an appropriate PE:EtOAc mixture.

General procedure for Pd-catalyzed kinetic resolution on larger scale. To a solution of (±)-**3b** (5 mmol) and the nucleophile (2.4 mmol) in dry, degassed CH_2Cl_2 (20 mL) under nitrogen at the specified temperature was added the catalyst solution, which was separately prepared by stirring $Pd_2(dba)_3$ (11

mg, 0.012 mmol, 1 mol% Pd based on **4**) and (*R*,*R*)-**5** (33 mg, 0.048 mmol, 2 mol% based on **4**) in dry, degassed CH_2Cl_2 (10 mL) under nitrogen until the initially purple solution turned yellow-brown (2–3 min). The reaction mixture was monitored by TLC. Once the reaction was complete, the solvent was evaporated and the crude product was purified by column chromatography with PE:EtOAc as eluent mixture.

4-(*tert*-Butoxycarbonyloxy)-2-cyclopentenone (±)-3b. To a solution of 4-hydroxy-2-cyclopentenone (±)-**2** (0.500 g, 5 mmol) and Boc_2O (1.167 g, 6 mmol) in THF (5 mL), triethylamine (0.84 mL, 6 mmol) and DMAP (10 mg) were added. After stirring at room temperature for 30 min, the solvent was removed and the residue purified by column chromatography to give the product as a white solid (0.865 g, 87%). M.p. 38–39 °C. R_f = 0.33 (PE/EtOAc 90:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9H), 2.41 (dd, 1H, *J* = 18.7, 2.3 Hz), 2.84 (dd, 1H, *J* = 18.7, 6.4 Hz), 5.72 (dtd, 1H, *J* = 6.1, 2.3, 1.3 Hz), 6.34 (dd, 1H, *J* = 5.7, 1.3 Hz), 7.60 (dd, 1H, *J* = 5.7, 2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8, 41.0, 74.2, 83.3, 137.2, 152.7, 158.6, 204.6. IR (solid): ν_{max}(cm^{-1}) = 1731, 1716. HRMS (EI-quadrupole): *m/z* calcd for $C_{10}H_{14}O_4$: 198.0892 [$M^{\cdot+}$]; found: 198.0896.

Recovered starting material from kinetic resolution: (*R*)-4-(*tert*-Butoxycarbonyloxy)-2-cyclopentenone (*R*)-**3b.** 99% ee (t_R major, minor = 12.9, 14.2 min, Chiralcel OJ-H, 4.6×250 mm, 10 µm, heptane:*i*-PrOH 99:1, 1.0 mL/min). $[\alpha]^{22}_D$ = +85.0 (c = 1.60, $CHCl_3$).

(*S*)-4-Acetoxycyclopent-2-enone 3a. Colorless oil (Table 1, entry 3: 35%, 50 mg, 1 mmol of starting material (±)-**3b** applied). 90% ee (t_R major, minor = 28.7, 18.1 min, Chiralcel AS-H 4.6×250 mm 10 µm, heptane:*i*-PrOH 90:10, 1.0 mL/min). R_f = 0.22 (PE/EtOAc 80:20). $[\alpha]^{23}_D$ = –103.9 (c = 1.22, $CHCl_3$) ($[\alpha]^{20}_D$ = –111 (c = 0.51, $CHCl_3$))[24]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3H), 2.32 (dd, 1H, *J* = 18.7, 2.2 Hz), 2.83 (dd, 1H, *J* = 18.8, 6.4 Hz), 5.85 (dtd, 1H, *J* = 6.1, 2.3, 1.4 Hz), 6.33 (dd, 1H, *J* = 5.7, 1.3 Hz), 7.57 (dd, 1H, *J* = 5.7, 2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 41.1, 72.0, 137.1,

159.0, 170.5, 204.9. IR (film): $\nu_{max}(cm^{-1})$ = 1717; HRMS (EI-quadrupole): *m/z* calcd for $C_7H_8O_3$: 140.0473 [$M^{\cdot+}$]; found: 140.0476.

(*S*)-4-Phenoxycyclopent-2-enone 6b. Colorless oil (Table 1, entry 4: 34%, 28 mg). 93% ee (t_R major, minor = 13.5, 12.4 min, Phenomenex Lux Cellulose-1 4.6×250 mm 5 µm, heptane:*i*-PrOH 90:10, 1.0 mL/min). R_f = 0.20 (PE/EtOAc 90:10). $[\alpha]^{22}_D$ = –7.2 (c = 1.36, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (dd, 1H, *J* = 18.4, 2.1 Hz), 2.90 (dd, 1H, *J* = 18.4, 6.0 Hz), 5.47 (dtd, 1H, *J* = 5.8, 2.2, 1.3 Hz), 6.38 (dd, 1H, *J* = 5.7, 1.2 Hz), 6.93 (dd, 2H, *J* = 8.7 Hz), 7.01 (t, 1H, *J* = 7.4 Hz), 7.33 (dd, 2H, *J* = 8.6, 7.5 Hz), 7.72 (dd, 1H, *J* = 5.7, 2.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.9, 75.1, 115.3, 121.8, 129.8, 136.6, 157.3, 159.7, 205.1. IR (film): $\nu_{max}(cm^{-1})$ = 1720. HRMS (EI-quadrupole): *m/z* calcd for $C_{11}H_{10}O_2$: 174.0681 [$M^{\cdot+}$]; found: 174.0677.

(*S*)-4-(1-Naphthoyl)oxycyclopent-2-enone 6c. White solid (Table 1, entry 6: 45%, 566 mg). M.p. 60–62 °C. >99% ee (t_R major, minor = 14.7, 16.9 min, Phenomenex Lux Cellulose-1 4.6×250 mm 5 µm, heptane:*i*-PrOH 90:10, 1.0 mL/min). R_f = 0.44 (PE/EtOAc 80:20). $[\alpha]^{22}_D$ = –143.7 (c = 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.56 (dd, 1H, *J* = 18.8, 2.2 Hz), 3.01 (dd, 1H, *J* = 18.8, 6.4 Hz), 6.20 (tdd, 1H, *J* = 4.6, 3.6, 1.8 Hz), 6.42 (dd, 1H, *J* = 5.7, 1.3 Hz), 7.47–7.57 (m, 2H), 7.64 (ddd, 1H, *J* = 8.6, 6.9, 1.5 Hz), 7.76 (dd, 1H, *J* = 5.7, 2.4 Hz), 7.90 (dd, 1H, *J* = 8.1, 1.4 Hz), 8.05 (d, 1H, *J* = 2.0 Hz), 8.20 (dd, 1H, *J* = 7.3, 1.3 Hz), 8.94 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.3, 72.5, 124.5, 125.6, 125.9, 126.5, 128.1, 128.8, 130.7, 131.4, 133.9, 134.1, 137.3, 159.1, 166.8, 205.0. IR (film): $\nu_{max}(cm^{-1})$ = 1712. HRMS (EI-quadrupole): *m/z* calcd for $C_{16}H_{12}O_3$: 252.0786 [$M^{\cdot+}$]; found: 252.0784.

(*S*)-4-(4-Bromobenzoyl)oxycyclopent-2-enone 6d. White solid (Table 1, entry 7: 41%, 58 mg). M.p. 92–93 °C (lit. m.p. 89 °C)[25] 91% ee (t_R major, minor = 13.8, 15.3 min, Phenomenex Lux Cellulose-1 4.6×250 mm 5 µm, heptane:*i*-PrOH 70:30, 0.5 mL/min). R_f = 0.20 (PE/EtOAc 90:10). $[\alpha]^{22}_D$ = –166.0 (c = 1.46, $CHCl_3$) ($[\alpha]^D$ = –167.7 (c = 0.43, $CHCl_3$))[25]. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48 (dd, 1H, *J* = 18.8, 2.2 Hz), 2.95 (dd , 1H, *J* = 18.8, 6.4 Hz), 6.10 (dtd, 1H, *J* = 6.1, 2.2, 1.2 Hz), 6.41 (dd, 1H, *J* = 5.7,

1.2 Hz), 7.60 (d, 2H, *J* = 8.6 Hz), 7.68 (dd, 1H, *J* = 5.7, 2.4 Hz), 7.89 (d, 2H, *J* = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.1, 72.7, 128.2, 128.8, 131.3, 132.0, 137.4, 158.7, 165.3, 204.7. IR (solid): $\nu_{max}(cm^{-1})$ = 1704. HRMS (EI-quadrupole): *m/z* calcd for $C_{12}H_9BrO_3$: 279.9733 [$M^{\cdot+}$]. found: 279.9740.

(*S*)-4-(Benzylthio)cyclopent-2-enone 6e. Colorless oil (Table 1, entry 8: 42%, 42 mg). 93% ee (t_R major, minor = 16.0, 14.8 min, Chiralcel OJ-H 4.6×250 mm 10 μm, heptane:*i*-PrOH 85:15, 1.0 mL/min). R_f = 0.15 (PE/EtOAc 90:10). $[\alpha]^{26}_D$ = –163.2 (c = 1.13, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (dd, 1H, *J* = 19.2, 2.1 Hz), 2.73 (dd, 1H, *J* = 19.2, 6.5 Hz), 3.74–3.84 (m, 2H), 3.91 (tdd, 1H, *J* = 6.5, 2.6, 2.0 Hz), 6.19 (dd, 1H, *J* = 5.6, 1.8 Hz), 7.24–7.37 (m, 5H), 7.46 (dd, 1H, *J* = 5.6, 2.6, Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ= 35.7, 42.7, 43.3, 127.5, 128.8, 128.9, 134.6, 137.6, 163.4, 207.3. IR (film): $\nu_{max}(cm^{-1})$ = 1715. HRMS (EI-quadropol): *m/z* calcd for $C_{12}H_{12}OS$: 204.0609 [$M^{\cdot+}$]; found: 204.0606.

(*S*)-4-(Dodecylthio)cyclopent-2-enone 6f. Colorless oil (Table 1, entry 9: 39%, 54 mg). 93% ee (t_R major, minor = 18.47, 15.60 min, Chiralcel AS-H 4.6×250 mm 10 μm, heptane:*i*-PrOH 85:15, 1.0 mL/min). R_f = 0.18 (PE/EtOAc 90:10). $[\alpha]^{22}_D$ = –193.8 (c = 1.56, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 6.7 Hz), 1.25 (m, 16H), 1.36 (m, 2H), 1.58 (m, 2H), 2.37 (dd, 1H, *J* = 19.2, 2.1 Hz), 2.51 (dd, 2H, *J* = 7.7, 7.1 Hz), 2.84 (dd, 1H, *J* = 19.2, 6.6 Hz), 4.01 (tdd, 1H, *J* = 6.5, 2.5, 2.0 Hz), 6.22 (dd, 1H, *J* = 5.6, 1.8 Hz), 7.57 (dd, 1H, *J* = 5.6, 2.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 22.7, 29.0, 29.2, 29.5, 29.6, 29.7, 29.7, 29.7, 32.0, 42.8, 43.5, 134.3, 163.9, 207.6. IR (KBr): $\nu_{max}(cm^{-1})$ = 2923, 2853, 1720. HRMS (EI-quadrupole): *m/z* calcd for $C_{17}H_{30}OS$: 282.2017 [$M^{\cdot+}$]; found: 282.2021.

(*S*)-4-Phthalimidocyclopent-2-enone 6g. Long white needles (Table 1, entry 10: 50%, 56 mg). M.p. 156–159 °C (dec.). 96% ee (t_R major, minor = 27.2, 30.2 min, Phenomenex Lux Cellulose-1 4.6×250 mm 5 μm, heptane:*i*-PrOH 90:10, 1.0 mL/min). R_f = 0.15 (PE/EtOAc 80:20). $[\alpha]^{23}_D$ = –230.8 (c = 1.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75 (dd, 1H, *J* = 18.3, 3.5 Hz), 2.85 (dd, 1H, *J* = 18.2, 6.8 Hz), 5.54 (tdd, 1H, *J* = 6.8, 3.5, 2.3 Hz), 6.44 (dd, 1H, *J* = 5.7, 2.2 Hz), 7.52 (dd, 1H, *J* = 5.7, 2.4 Hz),

7.72–7.78 (m, 2H), 7.82–7.89 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.6, 49.7, 123.6, 131.7, 134.4, 136.2, 159.6, 167.6, 205.2. IR (solid): ν_{max}(cm^{-1}) = 1777, 1700. HRMS (EI-quadrupole): *m/z* calcd for $C_{13}H_9NO_3$: 227.0582 [$M^{\cdot+}$]; found: 227.0583.

(*S*)-4-(6-chloro-9H-purin-9-yl)cyclopent-2-enone 8. To a solution of **(±)-3b** (991 mg, 5 mmol) and 6-chloropurine (**7**) (371 mg, 2.4 mmol) in dry, degassed dichloromethane (20 mL) under nitrogen at 0 °C the catalyst solution was added. It was separately prepared by stirring $Pd_2(dba)_3$ (11 mg, 0.012 mmol, 1 mol% Pd based on **7**) and (*R*,*R*)-**5** (33 mg, 0.048 mmol, 2 mol% Pd based on **7**) in dry, degassed dichloromethane (10 mL) under nitrogen until the initially purple solution turned yellow-brown (2–3 min). After 24 h stirring at 0 °C the solvent was evaporated. The crude product was purified by column chromatography with PE:EtOAc (10:1) for recovering starting material **3b** (47% yield, 466 mg, 98% ee) and EtOAc for product as eluent mixture. **8** was obtained as a white solid (46% yield, 536 mg, 94% ee) which gave colourless crystals after recrystallization (39% yield, 463 mg, 98% ee). M.p. 131–133 °C (135.5–136 °C)[21]. 98% ee (t_R major, minor = 24.43, 20.55 min, Chiralcel AS-H 4.6×250 mm 10 μm, heptane:*i*-PrOH 50:50, 0.5 mL/min). R_f = 0.25 (EtOAc). $[\alpha]^{22}_D$ = –114.5 (c = 0.98, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.69 (dd, 1H, *J* = 18.8, 2.8 Hz), 3.18 (dd, 1H, *J* = 18.8, 7.2 Hz), 6.01 (ddd, 1H, *J* = 7.2, 4.8, 2.5 Hz), 6.65 (dd, 1H, *J* = 5.7, 2.0 Hz), 7.69 (dd, 1H, *J* = 5.7, 2.5 Hz), 8.08 (s, 1H), 8.76 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.7, 54.5, 131.9, 138.4, 142.8, 151.4, 151.6, 152.3, 157.0**,** 203.5. IR (solid): ν_{max}(cm^{-1}) = 1720. HRMS (ESI-TOF): *m/z* calcd for $C_{10}H_7ClN_4O$: 235.0381 [M+H]$^+$; found: 235.0384. The experimental data are in accordance with literature.[21]

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SUPPORTING INFORMATION PARAGRAPH. Full experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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