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Asymmetric Transfer Hydrogenation of *rac*-α-(Purin-9-yl)cyclopentones via Dynamic Kinetic Resolution for the Construction of Carbocyclic Nucleosides

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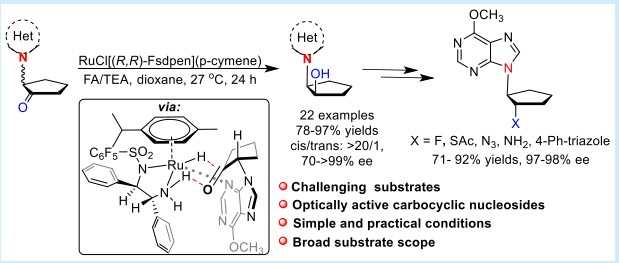
Supporting Information

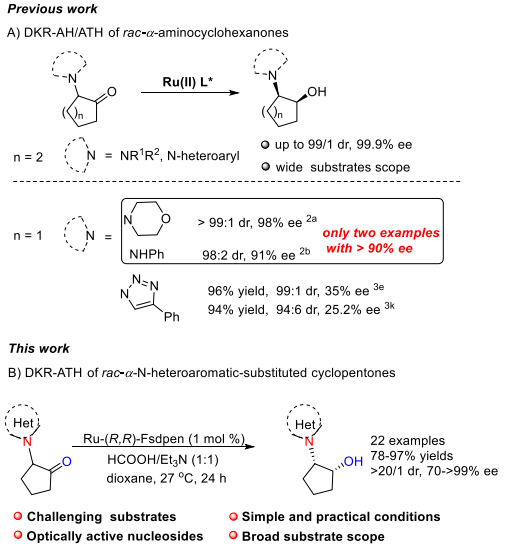
ABSTRACT: An asymmetric transfer hydrogenation via dynamic kinetic resolution of a broad range of *rac*-α-(purin-9-yl)cyclopentones was first developed. A series of *cis*-β-(purin-9-yl)cyclopentanols were obtained with up to 97% yield, >20/1 dr, and >99% ee. This also provides an efficient synthetic route to a variety of chiral carbocyclic nucleosides.



Chiral aminocycloalkanols have attracted considerable interest because of their important pharmaceutical drug frameworks and their roles as ligands in asymmetric synthesis.[1] Various methods for enantio- and diastereoselective preparations of these compounds, including ring opening of *meso*-epoxides or aziridines via asymmetric desymmetrization and acylation of *rac*-β-aminocycloalkanols via kinetic resolution, have been reported.[1b] Recently, dynamic kinetic resolution (DKR) through asymmetric hydrogenation (AH)[2] and asymmetric transfer hydrogenation (ATH)[3] of *rac*-α-aminocycloalkanones provided one of the most efficient approaches to obtain chiral β-aminocycloalkanols. DKR coupled with Ru-catalyzed hydrogenation processes has been demonstrated to effectively convert *rac*-α-aminocyclohexanones to chiral β-aminocyclohexanols (Scheme 1A).[2a,b,3e,k] However, to the best of our knowledge, successful AH/ATH of *rac*-α-aminocyclopentones has been rare (only two examples with >90% ee), and this may be attributed to the relatively rigid cyclopentone skeletons which decrease the rate of racemization.[4] Hence, the AH/ATH of such substrates to furnish chiral β-aminocyclopentanols is desirable but remains elusive.

More recently, we developed the AH of α-purine nucleobase-substituted α,β-unsaturated esters using a chiral Rh-(*R*)-Synphos catalyst,[5] and it was found that purine base possibly coordinated to the Rh center to facilitate stereoinduction. This induction mode was distinct from the conventional edge/face CH (sp^3)/π attraction between the η^6-arene ligand and the carbonyl aryl substituent in ketone ATH[6] or the conventional nonbonded repulsion to control steroselectivities. Inspired by this work, we envisioned that *rac*-α-(purin-9-yl)cyclopentones could be ideal substrates for ATH to synthesize chiral β-(purin-9-yl)cyclopentanols. Moreover,

Scheme 1. DKR-AH/ATH of *rac*-α-Aminocycloalkanones



these compounds have been reported to exhibit outstanding biological activities[7] (Figure 1). For example, abacavir and entecavir have been approved by the FDA for the treatment of HIV and HBV infections, respectively.[8] Therefore, the development of efficient synthetic routes to construct various chiral carbocyclic nucleoside analogs is desirable. Continuing from our previous works on nucleosides,[9] herein we report the

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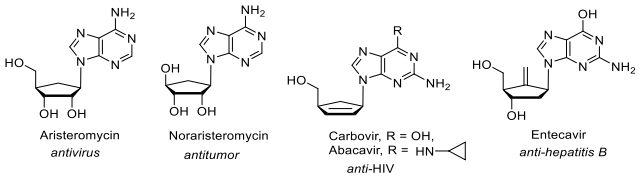
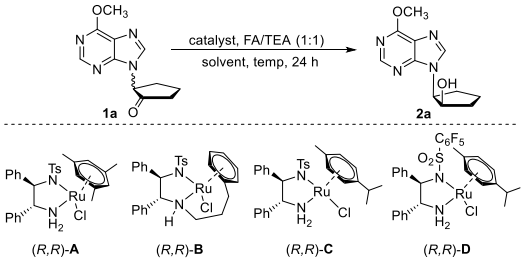


Figure 1. Representative biologically active chiral carbocyclic nucleosides.

first highly enantioselective ATH of a broad range of *rac*-α-(purin-9-yl)cyclopentones, which could provide an easy access to a variety of chiral carbocyclic nucleosides in excellent yields and stereoselectivities (Scheme 1B).

In our studies, we utilized 2-(6-methoxy-9*H*-purin-9-yl)-cyclopentan-1-one **1a** as a model substrate to optimize the reaction conditions (Table 1). Among the typically efficient

Table 1. Screening of Reaction Conditions[a,b]



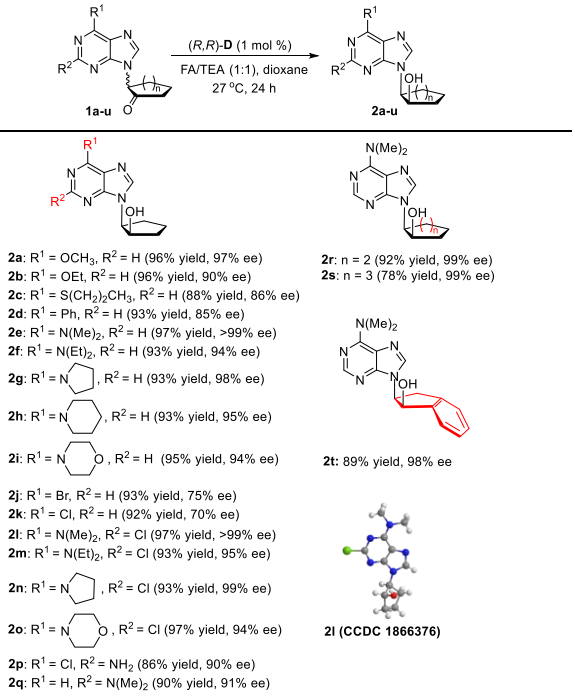
entry	cat. (mol %)	solvent	temp (°C)	yield[c] (%)	ee[d] (%)
1	(*R*,*R*)-**A** (2)	dioxane	27	93	52
2	(*R*,*R*)-**B** (2)	dioxane	27	95	38
3	(*R*,*R*)-**C** (2)	dioxane	27	35	79
4	(*R*,*R*)-**D** (2)	dioxane	27	98	96
5	(*R*,*R*)-**D** (2)	$CHCl_3$	27	90	94
6	(*R*,*R*)-**D** (2)	EtOAc	27	91	94
7	(*R*,*R*)-**D** (2)	DCM	27	93	82
8	(*R*,*R*)-**D** (2)	THF	27	32	89
9	(*R*,*R*)-**D** (2)	CH_3OH	27	92	36
10	(*R*,*R*)-**D** (2)	CH_3CN	27	95	65
11[e]	(*R*,*R*)-**D** (2)	dioxane	27	96	82
12[f]	(*R*,*R*)-**D** (2)	dioxane	27	90	90
13	(*R*,*R*)-**D** (1)	dioxane	27	96	97
14	(*R*,*R*)-**D** (0.5)	dioxane	27	81	97

[a]Unless otherwise noted, reaction conditions: *rac*-α-(purin-9-yl)-cyclopentone **1a** (0.1 mmol), respective mol % of catalyst and 70 μL of FA/TEA (1:1) in solvent (1.0 mL) for 24 h. [b]>20:1 dr. [c]Isolated yields. [d]Determined by chiral HPLC analysis. [e]FA/TEA (2.5:1) was used. [f]FA/TEA (0.2:1) was used. FA = formic acid. TEA = triethylamine.

catalysts for ATH, several chiral 1,2-diamine-based Ru(II) catalysts were first examined at 27 °C using formic acid (FA)/triethylamine (1:1) as the hydrogen source in dioxane (entries 1−4). When (*R*,*R*)-**A** and (*R*,*R*)-**B** were used as catalysts, high reduction yields were achieved, albeit with low ee (93−95% yields, 38−52% ee, entries 1 and 2). A low yield was obtained from reduction with Noyori's catalyst (*R*,*R*)-**C** (35% yield, entry 3). When Ru-(*R*,*R*) FsDPEN ((*R*,*R*)-**D**) was used as catalyst, the corresponding product **2a** was obtained with a high yield of up to 98% and 96% ee (entry 4). Thus, the best catalyst (*R*,*R*)-**D** was selected to further optimize solvents. However, dioxane turned out to already be the best solvent (entries 5−10). Therefore, dioxane was used in subsequent studies. With varying ratios of FA/TEA, results were not further improved (entries 11 and 12). Finally, the catalyst loading was examined (entries 13 and 14). To our delight, a catalyst loading of 1 mol % was sufficient to produce high yield of up to 96% without loss of ee (entry 13). Decreasing the catalyst loading to 0.5 mol % resulted in a lower yield without affecting ee value (81% yield, 97% ee, entry 14).

Under the optimal reaction conditions, the scope of reaction was investigated, and the results are presented in Scheme 2. In

Scheme 2. Substrate Scope of *rac*-α-(Purin-9-yl)cycloalkanones[a−d]



[a]Unless otherwise noted, the reaction was performed with **1a−t** (0.1 mmol), (*R*,*R*)-**D** (1 mol %), and 70 μL of FA/TEA (1:1) in dioxane (1.0 mL) at 27 °C for 24 h. [b]>20:1 dr. [c]Isolated yields. [d]The ee values were determined by HPLC using chiral columns.

general, the reactions worked considerably well, generating chiral β-(purin-9-yl)cyclopentanols with excellent yields and enantioselectivities. The absolute configuration of product **2l** was determined to be (1*R*,2*S*) by single-crystal X-ray diffraction analysis. Substrates with an increasingly bulky group at the C6 of purine, such as OMe, OEt, $S(CH_2)_2CH_3$, and Ph, were evaluated and their reductions proceeded in excellent yields and good ee's (**2a-d**, 88−96% yields, 85−97% ee). Notably, ee values decreased with increasing steric hindrance at the C6 of purine. Substrates **1e−i** bearing different amine groups, such as dimethylamino, diethylamino, pyrrolidino, piperidino, and morpholino groups, at the C6 position of the purine skeleton were also examined. Interestingly, the introduction of different amine substituents to the purine skeleton appeared to have little effect on the reaction (**2e−i**, 93−97% yields, 94 → 99% ee). This may be because the electron-donating effects of the substituents are stronger than their steric hindrance. Subsequently, subtrates **1j,k** bearing a Br atom or a Cl atom at C6 of the purine skeleton were studied. Although the reactions proceeded with excellent yields (**2j,k**, 92−93% yields), the ee values obviously

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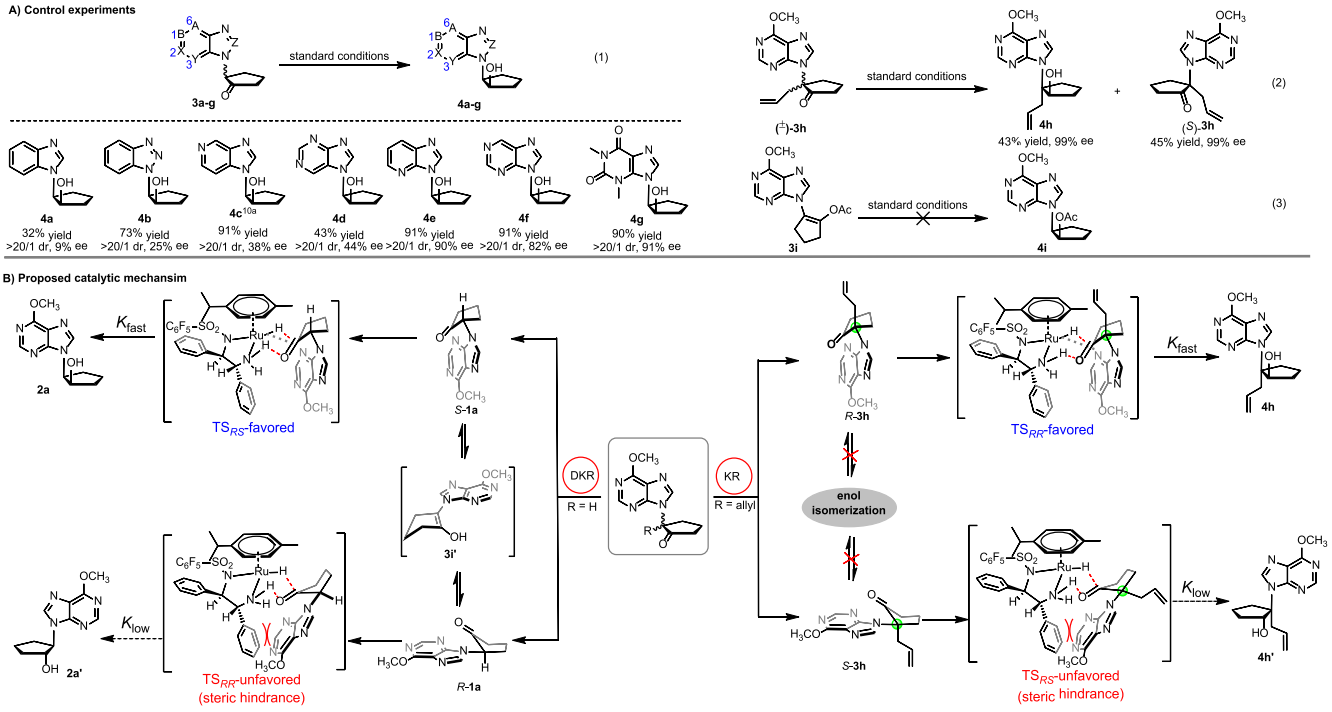
Scheme 3. Experimental Mechanistic Studies



decreased (70−75% ee). On the other hand, the reductions of α-(purin-9-yl)cyclopentones **1l−o** bearing different amine groups at the C2 position and Cl at the C6 of purine proceeded very well (**2l−o**, 93−97% yields, 94 → 99% ee). Substrates **1p−q** bearing a Cl atom or an H atom at the C6, or a NH_2 or a $N(CH_3)_2$ at the C2 of purine also underwent reduction well, delivering the desired products **2p−q** with 86−90% yields and 90−91% ee. Varying the size of carbocyclic ring had no effect on enantioselectivities (**2r,s**, 99% ee). In addition, the benzo-fused cyclopentone **1t** was also reduced satisfactorily (**2t**, 89% yield, 98% ee).

To better understand the origins of enantioselectivity, a series of control experiments were conducted (Scheme 3A). When benzimidazole was used as the N-heteroaromatic substituent, both a low yield and enantioselectivity were observed, although an excellent diastereoselectivity was still obtained (**4a**, 32% yield, > 20/1 dr, 9% ee). When cyclopentones **3b−d** with different N-heteroaromatic substituents such as *N*-benzotriazole, an N-heteroaromatic group bearing an N atom at the 1-position, and an N-heteroaromatic group bearing nitrogen atoms at the 2- and 6-positions were reduced, low enantioselectivities were observed (**4b−d**, 25−44% ee); however, a 91% yield was obtained in the case of α-heteroaromatic-substituted cyclopentone **3c**. Remarkably, when cyclopentone **3e** having an α-N-heteroaromatic group bearing an N atom at the 3 position, was reduced, the enantioselectivity was significantly increased. Moreover, the ATH of *rac*-α-(purin-9-yl)cyclopentone **3f** also proceeded well, producing the desired product with excellent yield and satisfactory enantioselectivity (**4f**, 91% yield, 82% ee). These results (**4a−d**, 9−44% ee vs **4e−f**, 82−90% ee) indicate that the enantioselectivities of the ATH can be influenced by the N atom at the 3 position of the heteroaromatic group. Interestingly, the α-(xanthin-9-yl)-substituted cyclopentone **3g** was also efficiently reduced to the desired product **4g** with 90% yield and 91% ee, which further corroborated that the N atom at the 3 position of the heteroaromatic group played an important role in the enantioselectivities of the ATH. Presumably, the purine base may coordinate the ruthenium (Ru) center of the catalyst (*R,R*)-**D**; thus the enantioselectivities of the ATH was significantly influenced by the interaction between the purine group and Ru atom. In addition, when *rac*-α-(purin-9-yl)cyclopentone **3h** containing a quaternary stereocenter at the α position was employed as the substrate, a classical kinetic resolution occurred. The corresponding product **4h** was produced in 43% yield and an excellent ee of 99%, with the starting material (*S*)-**3h** being recovered with 45% yield and 99% ee (S factor is 1057).[10b] When enol acetate **3i** was used as the substrate, the reaction did not proceed. These results demonstrate that the C═O group is hydrogenated through the classic six-membered transition state, rather than through an enol intermediate.

In light of the above results and literature precedents,[11] we propose the mechanism for Ru-FsDPEN-catalyzed DKR-ATH, as shown in Scheme 3B. Based on Noyori's metal−ligand bifunctional mechanism, the catalyst (*R,R*)-**D** can be easily converted to the amine hydrido Ru complex in the presence of Et_3N and HCOOH. The complex subsequently forms a 6-membered pericyclic transition state (TS_{RS}) with *S*-**1a**, which is stabilized by hydrogen bonds formed between the NH unit and the carbonyl oxygen atom. Meanwhile, the purine base also coordinated to the Ru atom to facilitate reactivity and stereoinduction. The hydridic Ru−H and protic N−H of Ru complex are then simultaneously transferred to the C═O bond of *S*-**1a** to generate product **2a**. As *R*-**1a** is not efficiently reduced due to the unfavorable transition state (TS_{RR}), it tautomerizes to *S*-**1a** through enol intermediate **3i** in the presence of Et_3N. When **3h** bearing a quaternary stereocenter is used, racemization of *R*-**3h** cannot take place; as a result, the reaction follows a kinetic resolution process.

The introduction of fluorine, sulfur, N_3, or amino groups into the sugar moieties of nucleosides can modulate or

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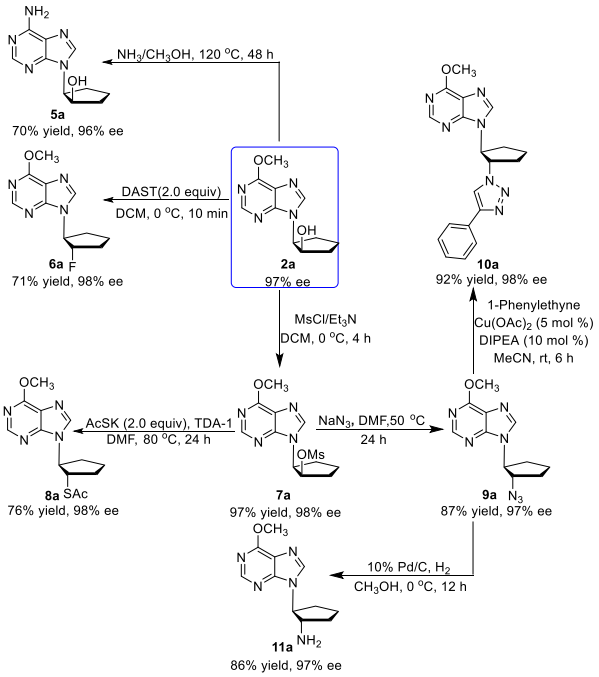
improve biological activities.[12] Consequently, a series of transformations of compound **2a** were carried out (Scheme 4). In the presence of NH_3/CH_3OH, adenine nucleoside **5a**

Scheme 4. Product 2a Elaboration



was synthesized with 70% yield and 96% ee. Treatment of **2a** with DAST (diethylaminosulfurtrifluoride) resulted in 2′-F-modified carbocyclic nucleoside **6a** in 71% yield and 98% ee. Mesylation of 2′-OH of substrate **2a** resulted in a complete conversion with excellent retention of ee (**7a**, 97% yield, 98% ee). A sulfur atom was introduced into the carbocycle of **7a** through nucleophilic substitution using AcSK, and the chiral thionucleoside derivative **8a** was obtained in 76% yield and 98% ee. The N_3 group was also subsequently introduced into **7a** using NaN_3, and the 2′-N_3-modified nucleoside **9a** was obtained with 87% yield and 97% ee. Furthermore, a click reaction of the enantioenriched **9a** and phenylacetylene was conducted in the presence of $Cu(OAc)_2$, and the 2′-triazole-modified nucleoside **10a** was obtained in 92% yield and 98% ee. Finally, **9a** was also efficiently reduced to afford primary amine **11a** in 86% yield and 97% ee.

In summary, we have successfully developed the asymmetric transfer hydrogenation via dynamic kinetic resolution of *rac*-*α*-(purin-9-yl)cyclopentones. Various optically active *cis*-*β*-(purin-9-yl)cyclopentols were obtained with excellent yields and ee's. The purine base was found to possibly coordinate the ruthenium (Ru) center of the catalyst to facilitate its reactivity and stereoinduction. This reaction can provide an efficient synthetic route for a variety of chiral carbocyclic nucleosides analogues.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00451.

Experimental procedures and compound characterization data (PDF)

Accession Codes

CCDC 1866376 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(10) (a) The ee of product was determined by its trimethylsilyl ether. (b) $s = \ln[(1 - C)(1 - ee^1)]/\ln[(1 - C)(1 + ee^2)]$; $C = ee^1/(ee^1 + ee^2)$, where ee^1 = ee of the recovered substrate and ee^2 = ee of the product).
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