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Synthesis of Azacyclic Nucleoside Analogues via Asymmetric [3 + 2] Cycloaddition of 9-(2-Tosylvinyl)-9*H*-purines

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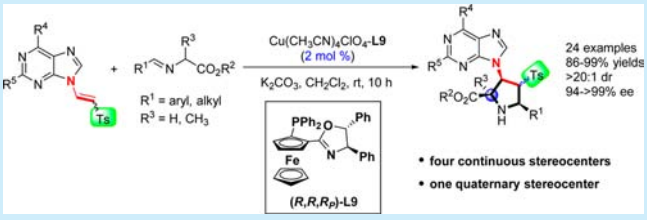
Supporting Information

ABSTRACT: With 9-(2-tosylvinyl)-9*H*-purines as the dipolarophiles, a series of chiral azacyclic nucleosides with four continuous stereocenters were obtained in 86−99% yields, >20:1 dr, and 94 → 99% ee via the Cu(I)-catalyzed asymmetric [3 + 2] cycloaddition. Both (*E*)- and (*Z*)-9-(2-tosylvinyl)-9*H*-purines were suitable dipolarophiles, enriching the structure diversity of azacyclic nucleosides. Furthermore, when α-methyl imino ester was explored, the corresponding azacyclic nucleoside with a chiral quaternary stereocenter could also be afforded with excellent results.



Chiral cyclic nucleosides have displayed significant antivirus and anticancer activities, making modification of the ribose moiety an advanced research hotspot.[1] Modification of the ribose moiety was mainly focused on the following: (1) introducing different substituent groups or a quaternary stereocenter to the ribose moiety;[2] (2) employing a structurally similar oxathiolanyl, cyclopentyl, or pyrrolidine ring to replace the furan ring.[3] As illustrated in Figure 1, AZT, an antiretroviral medication for the

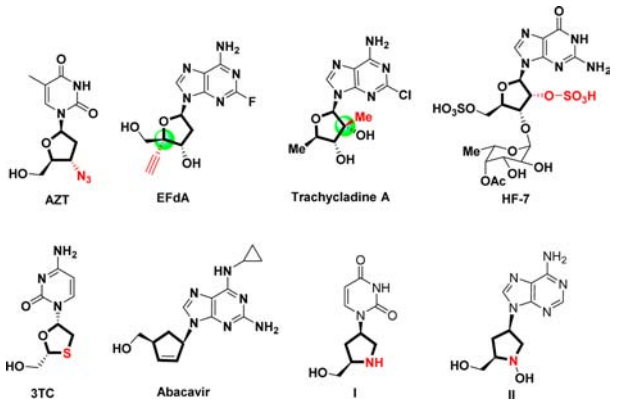
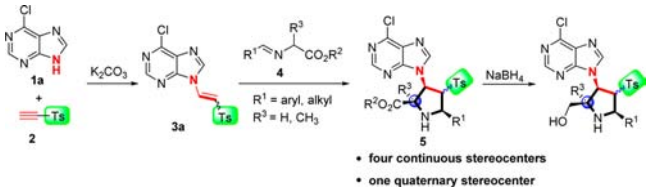


Figure 1. Selected chiral cyclic nucleosides with biological activities.

treatment of HIV/AIDS, incorporated an azide group in the deoxyribose ring;[4] EFdA, Trachycladine A, and HF-7, including an alkynyl group, a sulfate group, or a quaternary carbon center, also showed outstanding biological activities.[5] Meanwhile, 3TC and Abacavir, an oxathiolanyl or cyclopentyl ring incorporated in the nucleosides, have been approved by the FDA (Food and Drug Administration) to treat HIV infections;[6] azacyclic nucleosides **I** and **II** could inhibit the growth of BHK (Baby hamster kidney) cells and exhibit anti-HIV-1_{TEKI} activity, respectively.[7] Although much effort has been devoted to modification of the ribose moiety,[8] the structure diversity of azacyclic nucleosides is still very limited.[9] Therefore, finding an efficient route for the synthesis of azacyclic nucleosides with different substituent groups on the pyrrolidine ring would be highly desirable.

Here, we propose that the dipolarophile 9-(2-tosylvinyl)-9*H*-purine **3a** could be afforded via the addition of 6-chloro-9*H*-purine **1a** to Ts-substituted alkyne **2**. Through asymmetric [3 + 2] cycloaddition of dipolarophile **3a** with azomethine ylides **4**,[10] the chiral azacyclic nucleoside analogues **5** could be obtained with four continuous stereocenters and one quaternary stereocenter, which could be easily reduced to an azacyclic nucleoside with different substituent groups (Scheme 1).

Scheme 1. Our Strategy for the Synthesis of Azacyclic Nucleoside Analogues



Initially, 9-(2-tosylvinyl)-9*H*-purine **3a** was obtained in a mixture of *E*/*Z* isomers when the addition reaction was carried out in CH_3CN for 4 h (Table S1, entry 1). By prolonging the reaction time from 4 to 30 h, the *Z*-**3a** was transformed to *E*-**3a** totally (entry 2). Meanwhile, by changing the reaction solvent to DMF, only *E*-**3a** could be afforded (entry 3). Comparatively, when the reaction was performed in CH_2Cl_2, the *Z*-**3a** isomer was

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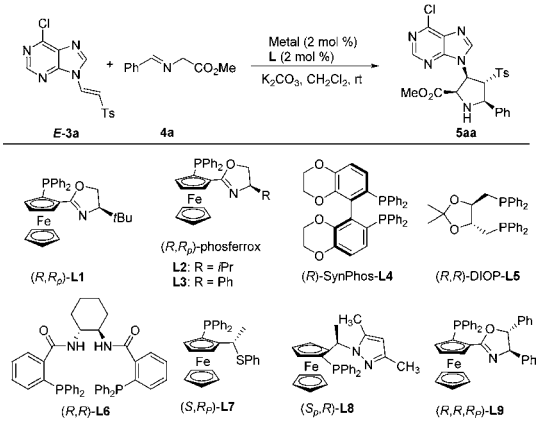
generated in the dominant form after 6 h. However, the *Z*-**3a** isomer could be transformed to *E*-**3a** when the reaction time was prolonged (entries 4−5).

With (*E*)-9-(2-tosylvinyl)-9*H*-purine **3a** in hand, the asymmetric [3 + 2] cycloaddition of *E*-**3a** to *N*-benzylidene glycine methyl ester **4a** was investigated (Table 1). First, in the presence of (R, R_P)-phosferrox **L1**, several central metals including Cu(I), Cu(II), and Ag(I) salts were screened (entries 1−5). Cu-$(CH_3CN)_4ClO_4$ was superior compared to other central metals, delivering the chiral azacyclic nucleoside analogue **5aa** in 86% yield, >20:1 dr, and 95% ee (entry 3). Then, 1,2-*P*,*N*-ferrocene ligands **L2**−**L3** with different steric hindrance were examined, and no better results were obtained (entries 6−7). When other types of ligands including (*R*)-SynPhos **L4**, (*R*,*R*)-DIOP **L5**, and (*R*,*R*)-Trost ligand **L6** were tried, the cycloaddition reaction did not occur (entries 8−10). Subsequently, several ferrocenyl ligands **L7**−**L9** were investigated carefully (entries 11−13). **L9**, a phenyl group at the 5-position of the oxazoline ring, could achieve the highest enantioselective (>99% ee, entry 13). After utilizing different solvents including $ClCH_2CH_2Cl$ (DCE), dioxane, THF, and CH_3CN, CH_2Cl_2 was still the better solvent (entries 13−17). Meanwhile, when the reaction was performed at 1 mol % catalyst loading, the diastereo- and enantioselectivity could still be maintained, although with a lower yield (entry 18). By reducing the amount of α-iminoester **4a**, the yield of **5aa** decreased significantly (entries 19−20). When the reaction was performed under air, the cycloadduct **5aa** was obtained in 43% yield, >20:1 dr, and 91% ee (entry 21). Thus, the optimal reaction conditions include 2 mol % $Cu(CH_3CN)_4ClO_4$−**L9** in CH_2Cl_2 at rt for 10 h (entry 13).

With the optimized reaction conditions in hand, the α-iminoesters **4a**−**4m**, azomethine ylide precursors, were subjected to the asymmetric [3 + 2] cycloaddition reactions (Table 2). By changing the ester group of α-iminoesters, the corresponding chiral azacyclic nucleoside analogues **5ab** and **5ac** could still be obtained in excellent selectivities (97−99% ee, entries 2−3). Then, the steric hindrance of the substituted group on the aromatic ring was explored, and the cycloadducts could be afforded in excellent yields as well as diastereo- and

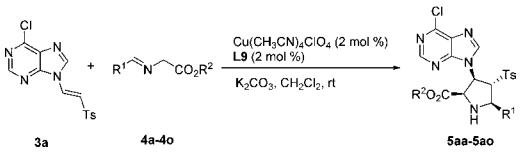
Table 1. Optimization of Reaction Conditions[a]



entry	metal	L	solvent	yield (%)[b]	endo: exo[c]	ee (%)[d] (endo)
1	CuCl	**L1**	CH_2Cl_2	N.R.		
2	[Cu(OTf)]•1/2Tol	**L1**	CH_2Cl_2	N.R.		
3	$Cu(CH_3CN)_4ClO_4$	**L1**	CH_2Cl_2	86	>20:1	95
4	$Cu(OTf)_2$	**L1**	CH_2Cl_2	85	>20:1	91
5	AgOAc	**L1**	CH_2Cl_2	89	>20:1	90
6	$Cu(CH_3CN)_4ClO_4$	**L2**	CH_2Cl_2	72	>20:1	90
7	$Cu(CH_3CN)_4ClO_4$	**L3**	CH_2Cl_2	73	>20:1	75
8	$Cu(CH_3CN)_4ClO_4$	**L4**	CH_2Cl_2	N.R.		
9	$Cu(CH_3CN)_4ClO_4$	**L5**	CH_2Cl_2	N.R.		
10	$Cu(CH_3CN)_4ClO_4$	**L6**	CH_2Cl_2	N.R.		
11	$Cu(CH_3CN)_4ClO_4$	**L7**	CH_2Cl_2	N.R.		
12	$Cu(CH_3CN)_4ClO_4$	**L8**	CH_2Cl_2	58	>20:1	67
13	$Cu(CH_3CN)_4ClO_4$	**L9**	CH_2Cl_2	90	>20:1	>99
14	$Cu(CH_3CN)_4ClO_4$	**L9**	DCE	75	>20:1	95
15	$Cu(CH_3CN)_4ClO_4$	**L9**	dioxane	N.R.		
16	$Cu(CH_3CN)_4ClO_4$	**L9**	THF	28	>20:1	91
17	$Cu(CH_3CN)_4ClO_4$	**L9**	CH_3CN	35	>20:1	81
18[e]	$Cu(CH_3CN)_4ClO_4$	**L9**	CH_2Cl_2	42	>20:1	>99
19[f]	$Cu(CH_3CN)_4ClO_4$	**L9**	CH_2Cl_2	55	>20:1	98
20[g]	$Cu(CH_3CN)_4ClO_4$	**L9**	CH_2Cl_2	trace		
21[h]	$Cu(CH_3CN)_4ClO_4$	**L9**	CH_2Cl_2	43	>20:1	91

[a]Unless otherwise noted, the reaction conditions are as follows: metal/**L** (1:1, 2 mol %), **3a** (0.05 mmol), **4a** (0.25 mmol), and K_2CO_3 (20 mol %) in solvent (0.7 mL) under N_2 at rt for 10 h. [b]Isolated yield. [c]Determined by the ^1H NMR spectra of the crude products. [d]Determined by chiral HPLC analysis. [e]Catalyst loading: 1 mol %. [f]**4a** (0.15 mmol) was used. [g]**4a** (0.075 mmol) was used. [h]Under air.

Table 2. Substrate Scope of Azomethine Ylides[a]



entry	R^1	R^2	product	yield (%)[b]	endo: exo[c]	ee (%)[d] (endo)
1	Ph	Me	**5aa**	90	>20:1	>99
2	Ph	Et	**5ab**	98	>20:1	99
3	Ph	*t*Bu	**5ac**	93	>20:1	97
4	2-ClC_6H_4	Me	**5ad**	98	>20:1	99
5	3-ClC_6H_4	Me	**5ae**	95	>20:1	98
6	4-ClC_6H_4	Me	**5af**	90	>20:1	>99
7	4-BrC_6H_4	Me	**5ag**	99	>20:1	>99
8	4-FC_6H_4	Me	**5ah**	98	>20:1	>99
9	4-$CF_3C_6H_4$	Me	**5ai**	99	>20:1	99
10	4-$CH_3C_6H_4$	Me	**5aj**	95	>20:1	98
11	4-$CH_3OC_6H_4$	Me	**5ak**	90	>20:1	99
12		Me	**5al**	89	>20:1	99
13		Me	**5am**	90	>20:1	97
14		Me	**5an**	N.R.		
15		Me	**5ao**	N.R.		

[a]Reaction conditions: $Cu(CH_3CN)_4ClO_4$−**L9** (1:1, 2 mol %), **3a** (0.05 mmol), **4a**−**4m** (0.25 mmol), and K_2CO_3 (20 mol %) in CH_2Cl_2 (0.7 mL) under N_2 at rt for 10 h. [b]Isolated yield. [c]Determined by the ^1H NMR spectra of the crude products. [d]Determined by chiral HPLC analysis. N.R. = No Reaction.

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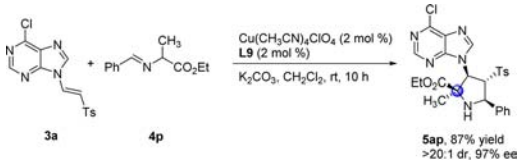
enantioselectivities (entries 4−6). Subsequently, several α-iminoesters with different electron-withdrawing groups on the phenyl ring were investigated, and the desired cycloadducts were generated in 98−99% yields, >20:1 dr, and 99 → 99% ee (entries 7−9). Furthermore, when α-iminoesters with electron-donating groups on the phenyl ring were examined, excellent results could still be achieved (entries 10−11, 90−95% yields, > 20:1 dr, 98−99% ee). Meanwhile, 2-naphthaldehyde-derived α-iminoester **4l** also was a suitable substrate, undergoing the cycloaddition well (entry 13). In the case of 2-thienyl α-iminoester **4m**, the desired azacyclic product **5am** was afforded in 90% yield, >20:1 dr, and 97% ee (entry 13). In addition, cyclohexyl and *tert*-butyl aldehyde-derived α-iminoesters **4n**−**4o** were also examined. Unfortunately, the asymmetric [3 + 2] cycloaddition reactions did not occur (entries 14−15).

Encouraged by the excellent results obtained using α-iminoesters, we then examined the asymmetric [3 + 2] cycloaddition with α-methyl imino ester **4p** (Scheme 2). In the

Scheme 2. Synthesis of Chiral Azacyclic Nucleoside Analogue 5an with a Quaternary Stereocenter



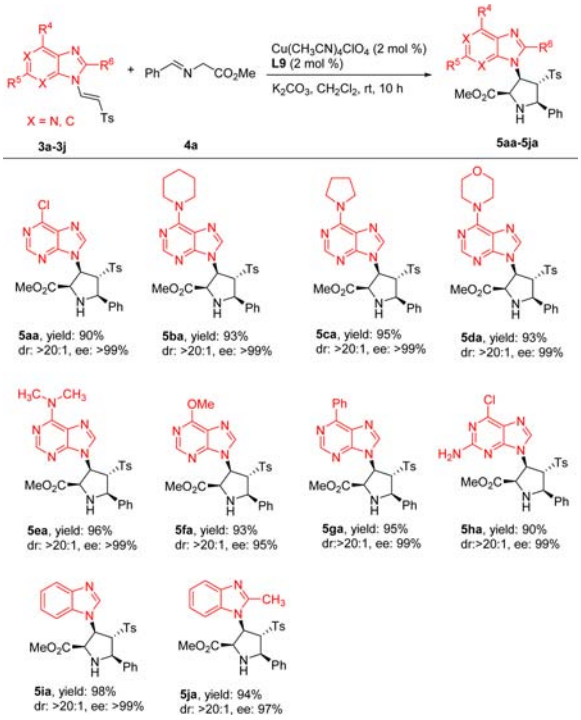
presence of 2 mol % of Cu(I)−**L9**, the cycloaddition of α-methyl imino ester **4p** to 9-(2-tosylvinyl)-9*H*-purine **3a** proceeded well, affording the corresponding chiral azacyclic nucleoside analogue **5ap** with a chiral quaternary stereocenter in 87% yield, >20:1 dr, and 97% ee.

Subsequently, the substrate scope of the dipolarophiles was investigated (Scheme 3). A series of 9-(2-tosylvinyl)-9*H*-purines with different substituents at the C6 or C2 position were synthesized. As for the dipolarophiles **3b**−**3e** with amino substituents at the C6 position of purine, the [3 + 2] cycloaddition reactions proceeded well, delivering the desired azacyclic nucleoside analogues **5ba**−**5ea** in 93−96% yields, >20:1 dr, and 90 → 99% ee. With 6-methoxyl purine derived dipolarophile **3f** as the reactant, the corresponding cycloadduct **5fa** was obtained in excellent yield. In the case of 6-phenyl-purine derived dipolarophile **3g**, the corresponding azacyclic product **5ga** was given in 95% yield, >20:1 dr, and 99% ee. Then, the [3 + 2] cycloaddition of 9-(2-tosylvinyl)-9*H*-purine **3h** with the amino group at the C2 position was performed, affording the desired adduct **5ha** in 90% yield, >20:1 dr, and 99% ee. Furthermore, benzoimidazole derived dipolarophiles **3i** and **3j** also were suitable reactants, giving the cycloadducts **5ia** and **5ja** with excellent results (97 → 99% ee).

To our delight, when *Z*-**3a** was used as the dipolarophile, the corresponding [3 + 2] cycloaddition proceeded well under air, affording the desired adduct **6aa** in 86% yield, >20:1 dr, and 94% ee (Scheme 4), which enriched the structure diversity of azacyclic nucleosides.

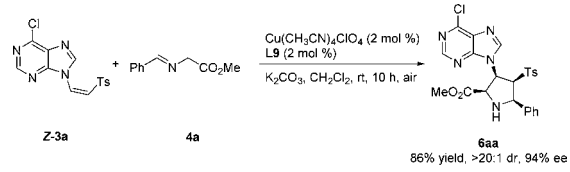
To further evaluate the prospect of the methodology in synthesis, a gram-scale synthesis of chiral azacyclic nucleoside analogue **5aa** was performed. As shown in Scheme 5, by treatment of 2 mmol of 9-(2-tosylvinyl)-9*H*-purine **3a** in the Cu(I)−**L9** catalytic system, chiral azacyclic nucleoside analogue **5aa** was afforded in 93% yield (0.95 g) with >20:1 dr and 97% ee.

Scheme 3. Substrate Scope of the Dipolarophiles[a]

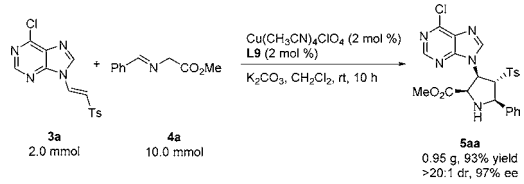


[a]Reaction conditions: $Cu(CH_3CN)_4ClO_4$−**L9** (1:1, 2 mol %), **3a**−**3j** (0.05 mmol), **4a** (0.25 mmol), and K_2CO_3 (20 mol %) in CH_2Cl_2 (0.7 mL) under N_2 at rt for 10 h. And the yields were referred to isolated yields. The dr values were determined by the ^1H NMR analysis of the crude products, and the ee values were determined by chiral HPLC analysis.

Scheme 4. Asymmetric [3 + 2] Cycloaddition of *Z*-9-(2-Tosylvinyl)-9*H*-purine 3a



Scheme 5. Gram-Scaled Asymmetric Synthesis of 5aa



The absolute configuration of the chiral azacyclic nucleoside analogue **5aa** was unambiguously determined to be (2*R*,3*R*,4*R*,5*R*) by single crystal X-ray diffraction analysis of the tosyl group protected azacyclic nucleoside analogue **7aa** (Scheme 6).[11] In the presence of $NaBH_4$, the hydrogenation of the product **5aa** proceeded well, affording the desired chiral azacyclic nucleoside **8aa** in excellent yield (Scheme 6).

In conclusion, we have developed an efficient method for the synthesis of chiral azacyclic nucleoside analogues via asymmetric [3 + 2] cycloaddition of 9-(2-tosylvinyl)-9*H*-purines with azomethine ylides. With 2 mol % of Cu(I)−**L9** as the catalyst, a variety of chiral azacyclic nucleosides with four continuous

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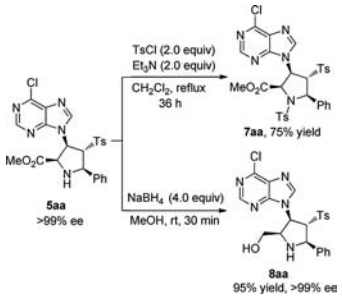
Scheme 6. Derivatization of 5aa



stereocenters were obtained in 86−99% yields, >20:1 dr, and 94 → 99% ee. Both (*E*)- and (*Z*)-9-(2-tosylvinyl)-9*H*-purines were suitable dipolarophiles, enriching the structure diversity of azacyclic nucleosides. Furthermore, when α-methyl imino ester was investigated, the desired azacyclic nucleoside with a chiral quaternary stereocenter could also be afforded with excellent results. Moreover, a chiral azacyclic nucleoside could be easily obtained from the cycloadduct via a simple reduction reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00108.

Experimental procedures, synthesis method of starting materials, and compound characterization data (PDF)
X-ray data for compound **7aa** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) See Supporting Information for detail CCDC 1445750 (**7aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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