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Organocatalytic Enantioselective Aza-Michael Addition of Purine Bases to α,β-Unsaturated Ketones

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Abstract: The first organocatalytic enantioselective aza-Michael addition of purine bases to α,β-unsaturated ketones has been developed, affording Michael adducts in moderate to high yields (up to 96% yield) and high to excellent enantioselectivities (up to >99% *ee*). A wide range of α,β-unsaturated ketones including aliphatic and aromatic enones are tolerated in this process, generally demonstrating good reactivity, regioselectivity and enantioselectivity. The aromatic α,β-unsaturated ketones showing quite low reactivity in the reported catalytic systems, were first successfully employed as Michael acceptors in this transformation, yielding high enantioselectivities (up to 94% *ee*). The utility of this method was also applied for the synthesis of enantioenriched non-natural nucleoside analogues with potential biological activities.

Keywords: aza-Michael addition; organocatalysis; purine bases; α,β-unsaturated ketones

An aza-Michael reaction of a nitrogen-centered source is a convenient and important way to prepare pharmacologically and synthetically useful β-amino carbonyl compounds, including β-amino acids and β-lactams.[1] Over the last decade, tremendous progress has been achieved by employing numerous attractive nitrogen nucleophiles for this important organic transformation.[2] The purine scaffold as the structural core of the nucleobases, is a ubiquitous feature in both biological systems and synthetic compounds, finding applications as biologically active drugs and fluorescent probes.[3] A great number of purine-based compounds for chemotherapy belonging to open chain acyclic sugar analogues with chiral carbons with various medicinal activities are known (Figure 1).[4] Notably, the biological effect has an enantiospecific character in all these compounds.[5] For example, (+)-(*2S,3R*)-EHNA is the most potent isomer as an inhibitor of adenosine deaminase whereas its enantiomer (−)-(*2R,3S*)-EHNA is approximately 250-fold less active.[5a] The remarkably different activities of respective enantiomers as well as the challenging issues of reactivity and regioselectivity between two (N-7−H and N-9−H) competitive tautomeric forms[6] make the development of effective methods for synthesis of these interesting chiral building blocks highly desirable.

In the past several years, however, most of those methodologies for the preparation of chiral purine bases relied on the introduction of a chiral side chain to purines.[7] In contrast, considerably less attention has been paid to the investigation of a catalytic enan-

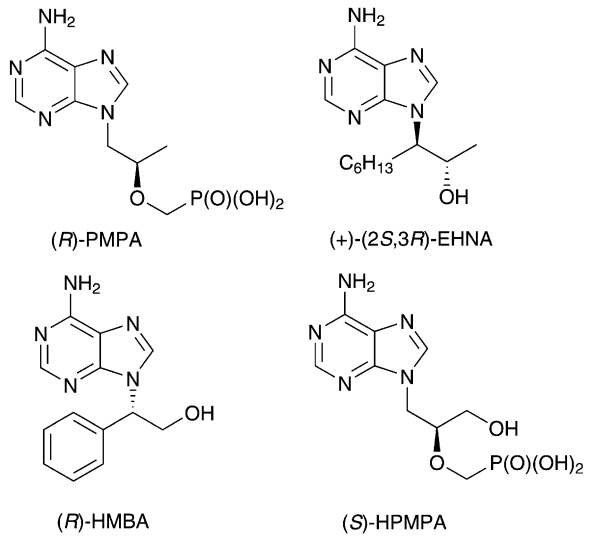
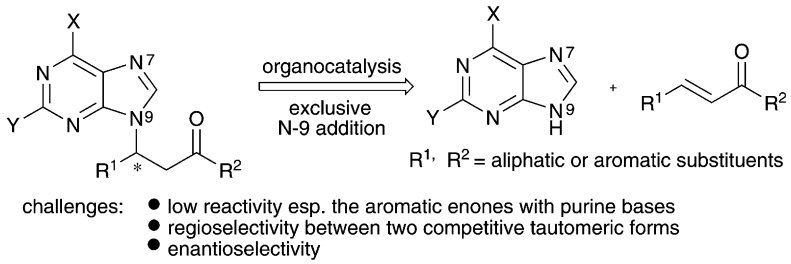


Figure 1. Structures of some typical chiral purine bases with various biological activities.



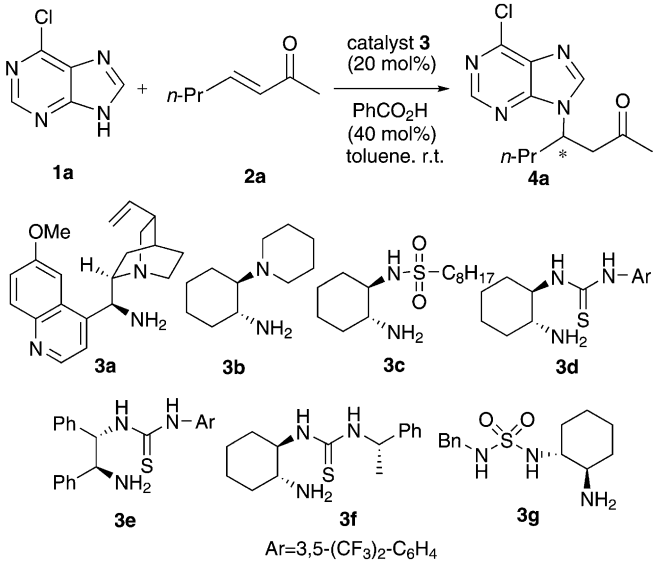
Scheme 1. Synthetic route to chiral purine bases *via* organocatalytic aza-Michael addition and three challenges of the strategy.

tioselective synthesis of these compounds with achiral starting materials *via* an asymmetric aza-Michael addition catalyzed by a chiral catalyst.[8] Jacobsen firstly reported the successful use of [(salen)Al] complexes in the conjugate addition of purine to α, β-unsaturated ketones and imides, opening a new entry to the synthesis of non-nature nucleosides.[8a] Qu demonstrated an organocatalytic method for the synthesis of optically active acyclonucleosides by employing α,β-unsaturated enals.[8b] These two methods both gave adducts with high enantioselectivities, but their application were restricted by the spectrum of α,β-unsaturated carbonyl compounds (no reactions when substrates bearing aromatic β-substituents),[8] harsh reaction conditions[8b] and not well-developed regioselectivity between two competitive tautomeric forms[8a] as well as employment of expensive organometallic complexes that were difficult to prepare.[8a] These limitations promoted us to develop a new method for the enantioselective synthesis of chiral purine bases by the aza-Michael addition (Scheme 1).

During the last decade, organocatalysis has been one of the most rapidly growing and competitive fields in asymmetric catalysis, and has developed to a third pillar beside metal catalysis and biocatalysis.[9] It offers several advantages, such as mild reaction conditions, simple operation, and easily accessible catalyst systems. We envisioned that the extension of Jacobsen's chemistry to the aza-Michael addition of purines to α,β-unsaturated ketones using suitable organocatalysts would provide an efficient asymmetric synthetic route to chiral purine bases (Scheme 1). Herein, to the best of our knowledge, we report the first organocatalytic aza-Michael addition of purine bases to a broad spectrum of α,β-unsaturated ketones ranging from aliphatic to aromatic enones for the highly enantioselective synthesis of chiral purine bases with exclusive N-9 addition regioselectivity under mild reaction conditions (up to 96% yield, up to >99% *ee*).

To begin our initial investigation, several bifunctional catalysts **3** (20 mol%) were screened to evaluate their ability to promote the aza-Michael addition of 6-chloro-9*H*-purine **1a** to 3-hepten-2-one **2a** at room temperature in toluene in the presence of benzoic acid as cocatalyst (Table 1, entries 1–7). The utilization of chloropurine in the model reaction may

Table 1. Screening of the optimal reaction conditions.[a]



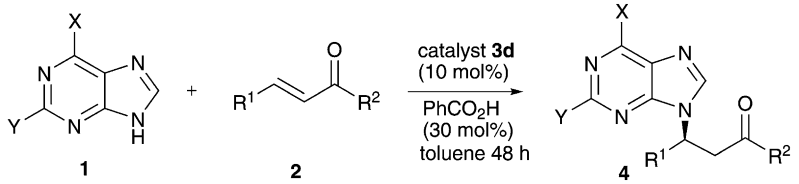
Entry	Catalyst	Time [h]	Yield[%][b]	*ee* [%][c]
1	**3a**	24	96	64 (*S*)[d]
2	**3b**	48	86	47 (*R*)[d]
3	**3c**	48	46	53 (*R*)[d]
4	**3d**	48	87	79 (*R*)[d]
5	**3e**	24	90	75 (*S*)[d]
6	**3f**	24	89	74 (*R*)[d]
7	**3g**	48	92	37 (*R*)[d]
8[e]	**3d**	48	90	92 (*R*)[d]
9[f]	**3d**	48	88	94 (*R*)[d]
10[f,g]	**3d**	48	80	96 (*R*)[d]

[a] Unless otherwise noted, reactions were carried out by using 6-chloro-9*H*-purine **1a** (0.1 mmol, 1.0 equiv.) and 3-hepten-2-one **2a** (0.15 mmol, 1.5 equiv.) in toluene (1 mL) with 20 mol% catalyst and 40 mol% $PhCO_2H$ at room temperature.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] The absolute configuration was determined by comparison with the literature.
[e] 10 mol% catalyst and 40 mol% $PhCO_2H$ were used.
[f] 10 mol% catalyst and 30 mol% $PhCO_2H$ were used.
[g] Reaction was conducted at 0 °C.

prove especially noteworthy, as relatively facile nucleophilic substitution of chloride enables the preparation of various derivatives.[6] To our delight, the reaction proceeded smoothly to provide the desired adduct **4a** in moderate to good yields (46–96%) with moderate enantioselectivities (Table 1, entries 1–4, 47–79% *ee*). A promising result was obtained with the chiral thiourea–primary amine **3d**, affording 87% yield and 79% *ee* (Table 1, entry 4). On this basis, several commonly used bifunctional chiral thiourea–primary amines were investigated. However, disappointing results without any improvement were obtained albeit with somewhat better yields (Table 1, entries 5–7). Therefore, catalyst **3d** was chosen as the best catalyst. Further reaction optimization focused on the catalyst and additive loadings. Gratifyingly, when the amount of catalyst **3d** was decreased to 10 mol%, a great improvement in enantioselectivity was implemented (entry 8, 92% *ee*). Further changing the loadings of benzoic acid from 10 mol% to 60 mol% showed that the enantioselectivity could increase to the apex when 30 mol% of $PhCO_2H$ was added (Table 1, entry 9, 88% yield, 94% *ee*; TS-1 in the Supporting Information). Lowering the temperature to 0 °C, the reaction gave the desired product with excellent enantioselectivity and good yield (entry 10, 80% yield, 96% *ee*).

With the established optimal reaction conditions in hand, the scope of the asymmetric transformation was examined by employing a variety of α,β-unsaturated ketones and purine bases. The process proved to be a general strategy for enantioselective aza-Michael addition with significant structural variations. Exclusive formation of the N-9 regioisomers was observed in all cases. As revealed in Table 2, all α,β-unsaturated aliphatic ketones gave the aza-Michael adducts in high yields and excellent enantioselectivities both at room temperature and at 0 °C (Table 2, entries 1–9, 70–91% yield, 91–97% *ee*). Generally, better *ee* values were realized when reactions were carried out at 0 °C albeit with lower yields. Increasing the length of the side chains had a limited effect on both yield and enantioselectivity. Notably, when an aromatic β-substituted enone showing no reactivity in the literature was used,[8] the reaction gave a satisfactory enantioselectivity and moderate yield (entry 10, 52–67% yield, 88–89% *ee*). To the best of our knowledge, this is the first successful example showing that the asymmetric aza-Michael reaction of aromatic β-substituted α,β-unsaturated ketones to purine bases could proceed easily with high enantioselectivity. Other purine bases

Table 2. Substrate scope for organocatalytic aza-Michael of α, β-unsaturated aliphatic ketones **2** with purine bases **1**.[a]



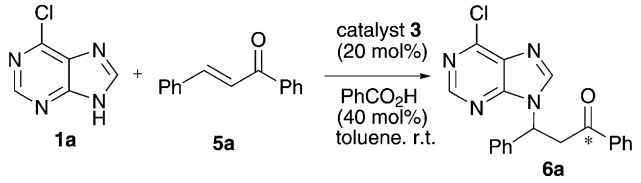
Entry	X	Y	R^1	R^2	Product	Yield [%][b,d]	*ee* [%][c,d]
1	Cl	H	Me	Me	**4b**	85 (79)	93 (96)
2	Cl	H	*n*-Pr	Me	**4a**	88 (80)	94 (96)
3	Cl	H	*i*-Pr	Me	**4c**	84 (77)	92 (96)
4	Cl	H	*n*-Bu	Me	**4d**	87 (76)	95 (97)
5	Cl	H	*n*-pentyl	Me	**4e**	86 (79)	91 (93)
6	Cl	H	*n*-hexyl	Me	**4f**	89 (85)	94 (95)
7	Cl	H	$BnOCH_2$	Me	**4g**	91 (83)	96 (96)
8	Cl	H	Me	Et	**4h**	82 (73)	95 (97)
9	Cl	H	Me	*n*Bu	**4i**	83 (70)	94 (96)
10	Cl	H	Ph	Me	**4j**	67 (52)	88 (89)
11	OBn	H	*n*-Pr	Me	**4k**	84 (73)	93 (93)
12	SMe	H	*n*-Pr	Me	**4l**	92 (83)	95 (93)
13	NHBoc	H	*n*-Pr	Me	**4m**	69 (52)	>99 (98)
14	Br	H	*n*-Pr	Me	**4n**	89 (78)	96 (97)
15	Cl	Cl	*n*-Pr	Me	**4o**	96 (90)	80 (82)
16	H	H	*n*-Pr	Me	**4p**	82 (76)	92 (90)

[a] Unless otherwise noted, reactions were carried out by using purine bases **1** (0.1 mmol, 1.0 equiv.) and enones **2** (0.15 mmol, 1.5 equiv.) in toluene (1 mL) with 10 mol% catalyst **3d** and 30 mol% $PhCO_2H$ for 48 h at room temperature.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] The value in parentheses indicates the yields and *ee* when reactions were carried out at 0 °C.

also displayed good to excellent reactivities and enantioselectivities in the aza-Michael addition to enones (Table 2, entries 11–16, 52–96% yield, 80–>99% *ee*). Lowering the temperature to 0 °C did not show any great improvement in enantioselectivity. It is noteworthy that the N-Boc-protected purine underwent the aza-Michael addition with 3-hepten-2-one smoothly at room temperature, thus providing the product **4m** with greater than 99% *ee* (Table 2, entry 13). Unfortunately, in the case of 2,6-dichloro-9*H*-purine, the enantioselectivity decreased as compared with the 6-monosubstituted purine bases (Table 2, entry 15). Surprisingly, the exclusive N-9 substituted product was observed when purine was employed with high yield and enantioselectivity (Table 2, entry 16, 92% *ee*).[8a]

Although recent progress on the asymmetric aza-Michael reaction of purine bases has been remarkable, one challenge that the reaction is highly substrate-dependent continues to limit the application of this transformation. Only α,β-unsaturated aliphatic carbonyl compounds could be employed as good substrates, giving good yields and high enantioselectivities while α,β-unsaturated aromatic aldehydes or ketones afforded only traces of the Michael adducts.[8] It is also noteworthy that some chiral purine bases with aromatic substituents, for example, (*R*)-HMBA, were found to exhibit more potent inhibition of adenosine deaminase than the corresponding enantiomer (Figure 1).[5c] In order to further demonstrate the generality and use of our organocatalyzed aza-Michael reaction between purine bases and α,β-unsaturated enones, other enones such as α,β-unsaturated aromatic enones were chosen as substrates in the developed reaction. With all these considerations, we turned our attention to the possibility of employing *trans*-chalcone **5a** in an aza-Michael reaction with 6-chloro-9*H*-purine **1a** catalyzed by the chiral amines **3** (Table 3). Gratifyingly, the desired aza-Michael reaction occurred, affording moderate yields and enantioselectivities (Table 3, entries 1–4, 38–49% yield, 26–59% *ee*). The catalyst **3d** which was the optimal catalyst for aza-Michael addition of aliphatic enones, however, gave only 38% yield and 46% *ee* (entry 2). Poor regioselectivity was obtained when catalyst **3e** was used, although a much better *ee* was afforded (entry 3, 59% *ee*).[10] So quinine-derived chiral primary amine **3a** giving exclusively the N-9 adduct, was chosen for further optimization of the reaction. Then the catalyst loading and acidic additives as co-catalysts were investigated. When the catalyst loading was decreased to 10 mol%, fortunately, a significant improvement in enantioselectivity was seen (TS-2 in the Supporting Information, 64% *ee*). After testing several acidic additives able to enhance both reactivity and selectivity, Boc-L-proline as a chiral acid was employed with the best results in terms of stereoselectivity (Table 3, entry 5, 70% *ee*). Further investigation of the additive loading revealed that the enantioselectivity climbed to the summit when 30 mol% Boc-L-proline was added (Table 3, entry 8, 77% *ee*, TS-2 in the Supporting Information). On lowering the temperature to 0 °C, a great improvement in enantioselectivity was observed albeit with lower yield (Table 3, entry 9, 52% yield, 87% *ee*).

Table 3. Screening of the optimal reaction conditions.[a]

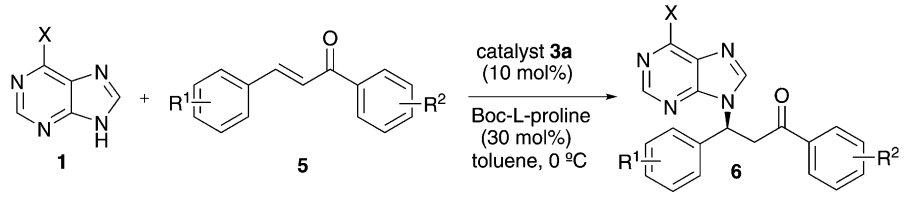


Entry	Catalyst	Time [h]	Yield [%][b]	*ee* [%][c]
1	**3a**	72	49	52 (*S*)[d]
2	**3d**	96	38	46 (*R*)[d]
3	**3e**	96	42	59 (*S*)[d]
4	**3f**	96	39	26 (*R*)[d]
5[e,f]	**3a**	72	53	70 (*S*)[d]
6[e,g]	**3a**	72	49	67 (*S*)[d]
7[e,h]	**3a**	72	53	73 (*S*)[d]
8[e,i]	**3a**	72	59	77 (*S*)[d]
9[e,i,j]	**3a**	72	52	87 (*S*)[d]

[a] Unless otherwise noted, reactions were carried out by using 6-chloro-9*H*-purine **1a** (0.1 mmol, 1.0 equiv.) and chalcone **5a** (0.15 mmol, 1.5 equiv.) in toluene (1 mL) with 20 mol% catalyst and 40 mol% $PhCO_2H$ at room temperature.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] The absolute configuration was determined by comparison with the literature.
[e] 10 mol% catalyst was used.
[f] 40 mol% Boc-L-proline was used.
[g] 10 mol% Boc-L-proline was used.
[h] 20 mol% Boc-L-proline was used.
[i] 30 mol% Boc-L-proline was used.
[j] Reaction was conducted at 0 °C.

Subsequent study probed the generality of the aza-Michael addition focusing upon variation of chalcones (**5**) and purine bases (**1**). Table 4 shows that a wide range of aromatic α,β-unsaturated enones with electron-donating and electron-withdrawing groups were compatible under the optimized reaction conditions, affording high to excellent enantioselectivities and moderate yields (Table 4, entries 1–8, 46–58% yield, 80–93% *ee*). The substitution pattern of R^1 at the *ortho*, *meta* or *para* position was observed to have no significant effect on the enantioselectivity (entries 4–6). Purine bases containing electron-donating or electron-withdrawing substituents at C-6 were also readily tolerated, thus giving exclusively N-9 adducts in good yields and high enantioselectivities (entries 9–12, 51–63% yield, 83–94% *ee*). Despite moderate yields in

Table 4. Substrate scope for organocatalytic aza-Michael of α, β-unsaturated aromatic ketones **5** with purine bases **1**.[a]



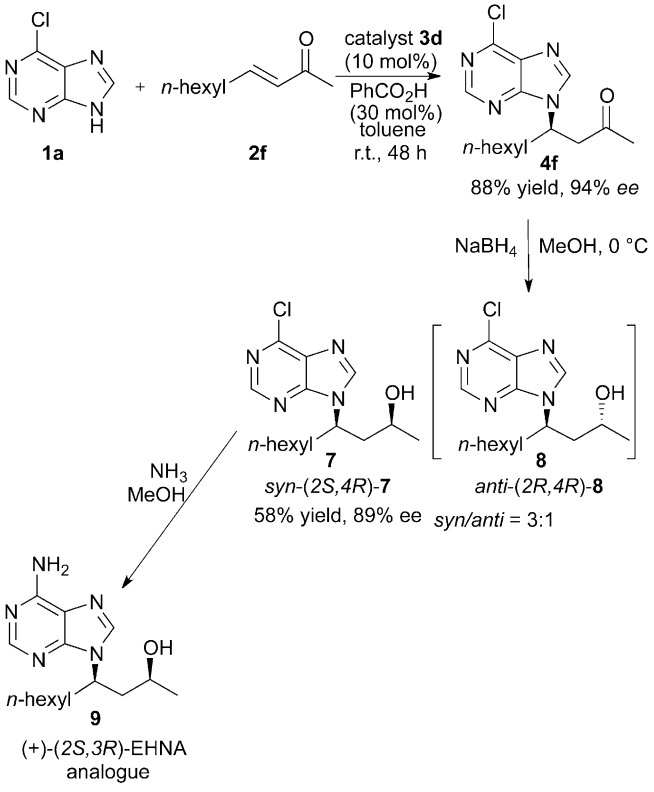
Entry	X	R^1	R^2	Product	Yield [%][b]	*ee* [%][c]
1	Cl	H	H	**6a**	52	87
2	Cl	4-Me	H	**6b**	49	83
3	Cl	4-F	H	**6c**	53	83
4	Cl	4-Cl	H	**6d**	55	80
5	Cl	2-Cl	H	**6e**	46	81
6	Cl	3-Cl	H	**6f**	50	82
7	Cl	H	4-Cl	**6g**	58	93
8	Cl	H	4-OMe	**6h**	52	85
9	OBn	H	H	**6i**	60	94
10	SMe	H	H	**6j**	63	88
11	NHBoc	H	H	**6k**	51	85
12	Br	H	H	**6l**	59	83

[a] Unless otherwise noted, reactions were carried out by using purine bases **1** (0.1 mmol, 1.0 equiv.) and enones **5** (0.15 mmol, 1.5 equiv.) in toluene (1 mL) with 10 mol% catalyst **3a** and 30 mol% Boc-L-proline for 72 h at 0 °C.
[b] Isolated yields.
[c] Determined by HPLC analysis.

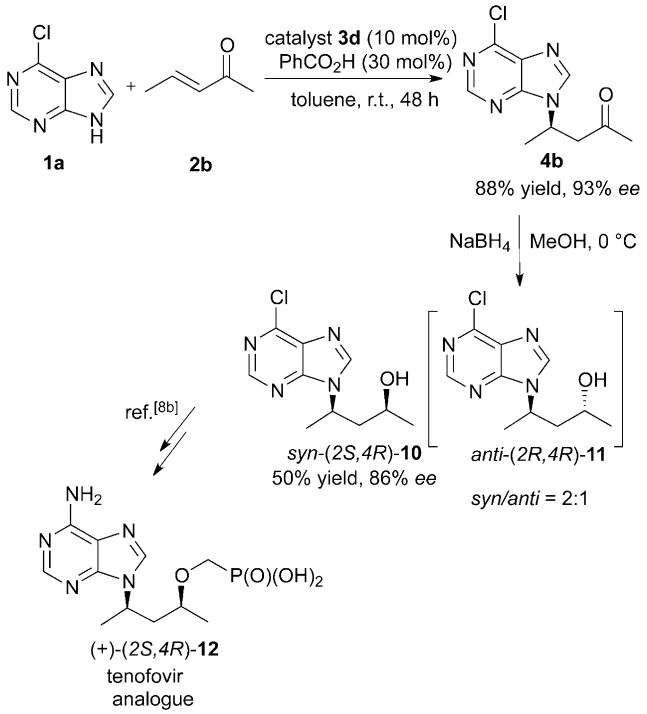
the presence of this catalyst system, to the best of our knowledge, it is the first successful example of the enantioselective aza-Michael reaction of purine bases to aromatic α,β-unsaturated enones, which provides a new direct method to design other chiral purine inhibitors with enhanced inhibitory properties.

With the successful strategy as described above, the transformations of the target adducts into non-natural nucleoside molecules that are similar to (+)-(2*S*,3*R*)-EHNA and (*R*)-PMPA were performed. Aza-Michael addition of **1a** to **2f** under the optimized conditions provided **4f** in 88% yield and 94% *ee*. Reduction of **4f** by $NaBH_4$ gave *syn*-(2*S*,4*R*)-**7** (58% yield, 89% *ee*) and *anti*-(2*R*,4*R*)-**8**. Finally ammonification of **7** led to the (+)-(2*S*,3*R*)-EHNA analogue **9** (Scheme 2). Addition of **1a** and **2b** gave the adduct **4b** in 88% yield and 93% *ee* which was readily reduced by $NaBH_4$, affording *syn*-(2*S*,4*R*)-**10** (50% yield, 86% *ee*) and *anti*-(2*R*,4*R*)-**11**. The sequential esterification and ammonification afforded the desired (*R*)-PMPA analogue **12** (Scheme 3). This is the unprecedently most successful strategy for the highly enantioselective synthesis of these chiral non-natural nucleoside analogues employing achiral α,β-unsaturated ketones.

The assignment of the absolute configuration of the diastereomeric pairs (**7**, **8** and **10**, **11**) was achieved by the Trost model,[11] which is based on the chemical shift differences in the NMR spectra between the two diastereomers. Taking compounds **10** and **11**, for instance, after chromatographic separation, **10** and **11** were respectively esterified with (*S*)-methoxyphenylacetic acid [(*S*)-MPA] to furnish **12** and **13**. The abso-



Scheme 2. Synthesis of the (+)-(2*S*,3*R*)-EHNA analogue **9**.



Scheme 3. Synthesis of the (*R*)-PMPA analogue **12**.

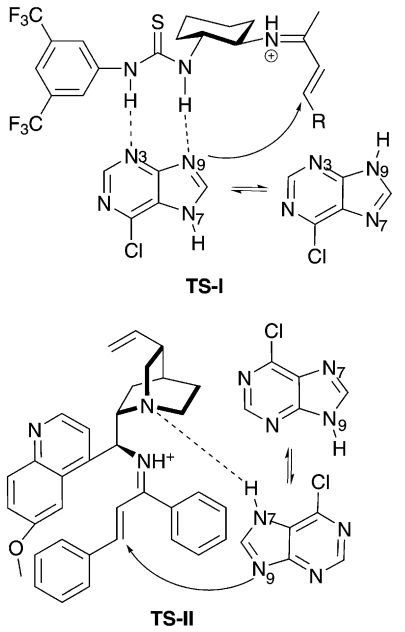
lute configuration of **12**, **13** and hence *syn*-**10**, *anti*-**11** were deduced from the ^{1}H NMR spectrum of the (*S*)-MPA esters (Scheme 4, Table 5). The signals of the substituents under the shielding cone are moved upfield.[12] Accordingly, the combination of structural analysis and chiral HPLC led to the conclusion that the aza-Michael adducts reduced by $NaBH_4$ gave the chiral alcohol *syn*-(2*S*,4*R*)-**10** and *anti*-(2*R*,4*R*)-**11**.

To account for the stereochemical outcomes of the aza-Michael addition, two plausible transition state models are proposed in Scheme 5. (i) When the chiral bifunctional thiourea–primary amine **3d** was used (Scheme 5, **TS-I**), the primary amine of the catalyst

Table 5. Chemical shift data of the diastereomeric pair of **12** and **13**.[a]

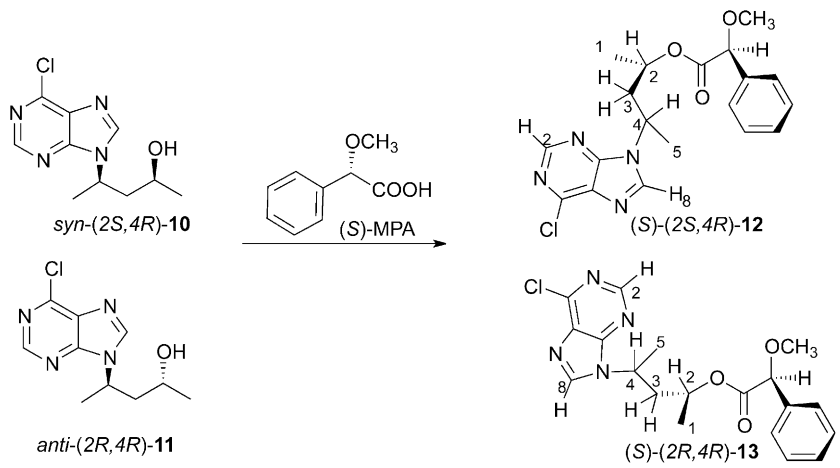
Entry	Group	δ (**12**)[b]	δ (**13**)[b]	$\Delta\delta$[b]
1	1-CH_3	1.28	1.12	0.16
2	5-CH_3	1.37	1.60	0.23
3	3-CH_2(H1)	2.06-2.14	2.14-2.20	0.08
4	3-CH_2(H2)	2.20-2.29	2.32-2.44	0.12
5	4-CH	5.05	5.06	0.01
6	8*H*-(adenine)	7.68	8.09	0.41
7	2*H*-(adenine)	8.70	8.75	0.05

[a] ^{1}H NMR (400 MHz, $CDCl_3$).
[b] δ in ppm.



Scheme 5. Proposed transition-states I and II.

3d yielded the ketiminium cation with enone **2**. Meanwhile, the exclusive N-9 regioselectivity indicated that



Scheme 4. Determination of absolute configuration of *syn*-(2*S*,4*R*)-**10** and *anti*-(2*R*,4*R*)-**11**.

the N-9 and N-3 position in the tautomeric form (N-7) of purine formed hydrogen bonds with the thiourea moiety to orient the purine to attack the ketiminium cation (Table 2, entry 16). (ii) When the chiral bifunctional thiourea–primary amine **3a** was used for the reaction of chalcone (Scheme 5, **TS-II**), the ketiminium cation formed between **3a** and chalcone **5a** might adopt a *trans* conformation. Meanwhile, a hydrogen bond could be formed from the bridgehead nitrogen of **3a** and the NH group of the tautomeric form (N-7) of purine to produce concerted communication.

In conclusion, the unprecedented asymmetric organocatalytic aza-Michael addition of purine bases to α,β-unsaturated ketones has been developed, affording Michael adducts in moderate to high yields (up to 96% yield) and high to excellent enantioselectivities (up to >99% *ee*). A wide range of α,β-unsaturated enones ranging from aliphatic to aromatic enones were both tolerated to this process, generally demonstrating good reactivity, regioselectivity and enantioselectivity. The aromatic α,β-unsaturated ketones including aromatic β-substituted enones were first successfully employed as Michael acceptors in this aza-Michael process. This methodology offers several advantages, such as mild reaction condition, no need to use toxic and expensive organometallic complexes and easily accessible catalyst system. Meanwhile, this first successful protocol for highly enantioselective synthesis of chiral acyclonucleosides analogues from achiral α,β-unsaturated ketones provides a new access to optical active non-natural nucleosides. Further studies into expanding the application of this approach to synthesize more promising candidates for acyclonucleosides as well as the biological evaluation of these compounds are currently underway.

Experimental Section

General Procedure for Aza-Michael Addition of Purine Bases to α,β-Unsaturated Aliphatic Ketones

To a sample vial equipped with a magnetic stirring bar was added catalyst **3d** (0.01 mmol, 10 mol%), $PhCO_2H$ (0.03 mmol, 30 mol%) and toluene (1.0 mL), and the solution was stirred for 5 min at the room temperature or at 0 °C. After addition of aliphatic enone **2** (0.15 mmol), the mixture was stirred for another 10 min. Then purine base **1** (0.1 mmol) was added at the desired temperature. The reaction was monitored by TLC and the resulting residue was purified by flash column chromatography on silica (eluent: 5% methanol in ethyl acetate) to afford the desired product **4**.

Compound (*R*)-4a: *ee* = 96% (at 0 °C); $[\alpha]_D^{24}$: 3.5 (*c* 0.5 in chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (s, 1H), 8.17 (s, 1H), 4.96 (m, 1H), 3.54 (dd, *J* = 18.5, 8.6 Hz, 1H), 3.06 (dd, *J* = 18.4, 4.3 Hz, 1H), 2.29–2.21 (m, 1H), 2.11 (s, 3H), 1.89 (m, 1H), 1.23–1.18 (m, 1H), 1.07 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 204.95, 151.42, 151.14, 146.02, 132.27, 53.49, 46.75, 35.31, 30.24, 19.43, 13.35; HR-MS: *m/z* = 267.1005, calcd. for $C_{12}H_{15}ClN_4O$ $[M+H]^+$: 267.1007; HPLC (Chiralpack AD, 2-propanol/hexane = 6/94, flow rate 1.2 mL min^{-1}, λ = 254 nm): t_{major} = 16.521 min, t_{minor} = 25.731 min.

General Procedure for Aza-Michael Addition of Purine Bases to α,β-Unsaturated Aromatic Ketones

To a sample vial equipped with a magnetic stirring bar was added catalyst **3a** (0.01 mmol, 10 mol%), Boc-L-proline (0.03 mmol, 30 mol%) and toluene (1.0 mL), and the solution was stirred for 5 min at 0 °C. After addition of aromatic enone **5** (0.15 mmol), the mixture was stirred for another 10 min. Then purine base **1** (0.1 mmol) was then added at 0 °C. The reaction was monitored by TLC after 72 h and the resulting residue was purified by flash column chromatography on silica (eluent: 5% methanol in dichloromethane) to afford the desired product **6**.

Compound (*S*)-6a: *ee* = 87%; $[\alpha]_D^{25}$: 8.3 (*c* 0.2 in chloroform). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.72 (s, 1H), 8.25 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.59 (m, 1H), 7.54–7.43 (m, 4H), 7.37 (m, 3H), 6.40 (dd, *J* = 8.7, 5.1 Hz, 1H), 4.78 (dd, *J* = 18.0, 9.1 Hz, 1H), 3.93 (dd, *J* = 18.1, 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.58, 151.70, 151.24, 145.42, 137.95, 135.90, 133.93, 132.23, 129.29, 128.96, 128.86, 128.13, 127.13, 56.92, 41.93; HR-MS: *m/z* = 363.1010, calcd. for $C_{20}H_{15}ClN_4O$ $[M+H]^+$: 363.1007; HPLC (Chiralpack AD, 2-propanol/hexane = 10/90, flow rate 1.2 mL min^{-1}, λ = 254 nm): t_{major} = 31.993 min, t_{minor} = 26.491 min.

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