Asymmetric Synthesis

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Enantioselective and Regiodivergent Addition of Purines to Terminal Allenes: Synthesis of Abacavir

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Abstract: *The rhodium-catalyzed atom-economic asymmetric N-selective intermolecular addition of purine derivatives to terminal allenes is reported. Branched allylic purines were obtained in high yields, regioselectivity and outstanding enantioselectivity utilizing a Rh/Josiphos catalyst. Conversely, linear selective allylation of purines could be realized in good to excellent regio- and E/Z-selectivity with a Pd/dppf catalyst system. Furthermore, the new methodology was applied to a straightforward asymmetric synthesis of carbocyclic nucleoside abacavir.*

During the last decades, carbocyclic nucleosides have received considerable attention due to their enormous biological activity and their use as therapeutic agents for treatment of HIV,[1] hepatitis[2] and cancer[3] (Figure 1). As congeners of naturally occurring nucleosides, carbanucleosides act as nucleoside reverse transcriptase inhibitors and reveal an increased stability against phosphorylases and phosphotransferases.[4] Previous synthetic pathways employ the formation of suitable cyclopentyl precursors to which the nucleobase is coupled either via allylic substitution[5] or Mitsunobu reaction.[6] Other strategic approaches such as complete elaboration of the purine heterocycle from cyclopentylamines, prevail in literature.[7] Construction of the carbocycle is typically derived from ring-closing metathesis[8] or cycloaddition reactions[9] with subsequent resolution.[10] Methodologies such as the allylic substitution and Mitsunobu reaction generate stoichiometric amounts of waste and are therefore unfavorable, whilst enzymatic resolution requires accurate reaction procedures and is intrinsically yield-limited.

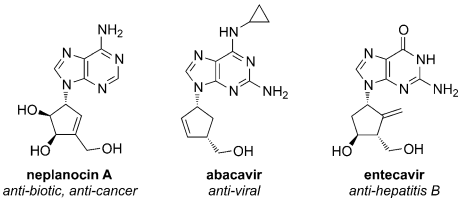
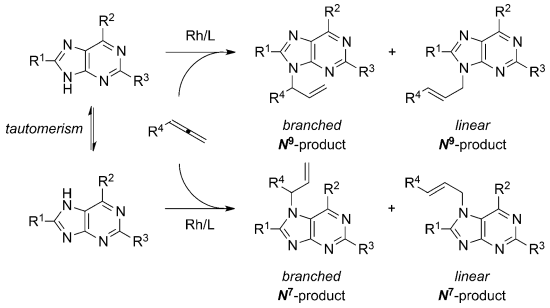


Figure 1. Selected bioactive carbanucleosides.

Arising viral resistances require additional chemical diversity and combination therapies, making derivatization of the carbocyclic scaffold as well as the purine bases highly desirable. Hence, many approaches towards carbanucleoside synthesis have been reported.[11] Nevertheless, the direct coupling of purines in a chemo-, regio- and enantioselective manner is still underdeveloped.[12]

Due to prior reports on the rhodium-catalyzed atom-economic coupling of pronucleophiles to allenes and alkynes,[13,14] as an atom-economic alternative to the Tsujii–Trost allylation, we were encouraged to apply a similar methodology towards more complex purine-type nucleophiles. Due to tautomerism, several regioselectivity issues have to be taken into account. Linear and branched products as well as the corresponding N^9/N^7 substituted products may arise during the hydroamination process (Scheme 1). To control the selectivity, methodologies based on the use of metal salts,[15] Vorbrüggen conditions[16] and transition-metal-catalyzed reactions[17] are known, but scope and conditions are limiting. Additionally, purines show a persistent insolubility and poor nucleophilicity in organic solvents, making the reaction very challenging.



Scheme 1. Possible differentiation of the two tautomeric purine species by the rhodium catalyst predominantly leading to desired branched N^9-product.

Initial reactivity assays showed that the rhodium(I)/dppp (**L1**) system is a suitable catalyst. Extensive reaction condition screening revealed that a mixture of THF/DMSO as solvent and microwave reactor irradiation for 2 hours at 130 °C is necessary to give the desired compound **3a** in excellent yield and selectivity (Table 1, entry 1). N^9-substituted branched products were formed exclusively and only traces of N^7-product **4a** could be observed. In order to elaborate on an enantioselective approach, several chiral ligand classes were probed and to our delight, Josiphos 003-1 (**L2**) furnished the desired product in good enantioselectiv-

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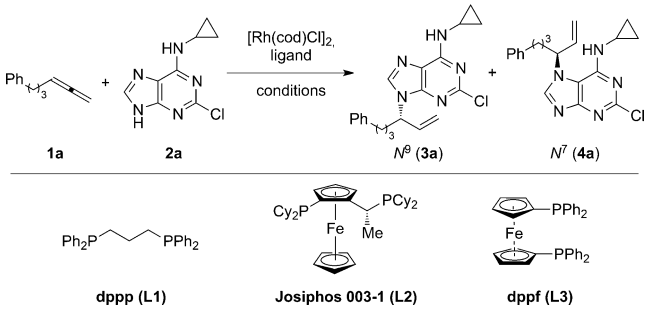
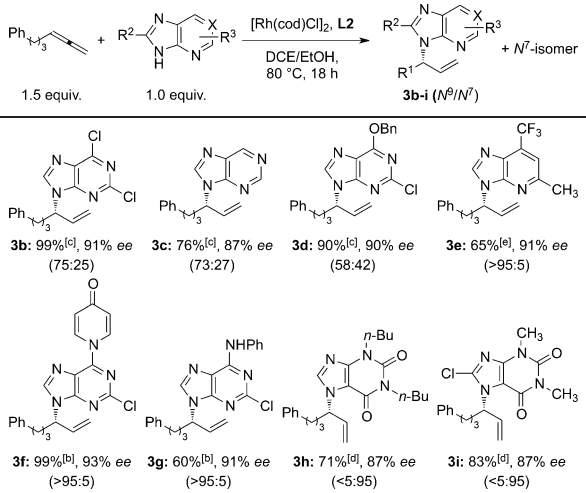
Table 1: Rhodium-catalyzed regio- and enantioselective addition of purine derivative **2a** to phenylhexadiene.



Entry	Ligand	Cond.[a]	Ratio[b] **B**:**L**	Ratio[b] **3a**:**4a**	Yield[c] [%]	*ee*[d] [%]
1	**L1**	A	>95:5	>95:5	98	*rac*
2	**L2**	A	>95:5	>95:5	54	91
3	**L2**	B	>95:5	>95:5	97	94

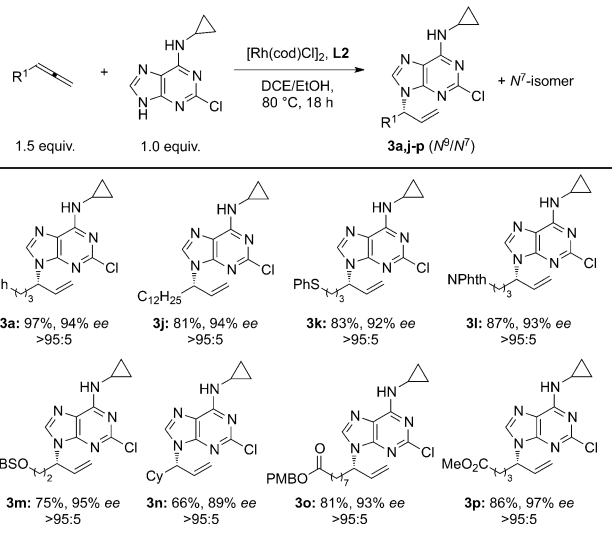
[a] Reaction conditions A: $[Rh(cod)Cl]_2$ (2.0 mol%), **L2** (6.0 mol%), **1a** (1.2 equiv), DMSO/THF (0.4 M, 1:1), 130°C, 2 h, MW; conditions B: $[Rh(cod)Cl]_2$ (2.0 mol%), **L2** (6.0 mol%), **1a** (1.5 equiv), DCE/EtOH (0.4 M, 2:1), 80°C, 18 h. [b] Regioselectivity determined by crude ^{1}H-NMR. [c] Yield of isolated product based on **2a**. [d] *ee* determined by chiral HPLC. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, DCE = 1,2-dichloroethane.

Table 2: Scope of purines towards branched allylated compounds.[a–g]



[a] All reactions were performed with $[Rh(cod)Cl]_2$ (2.0 mol%), **L2** (6.0 mol%), DCE/EtOH (0.4 M, 2:1), 80°C, 18 h. [b] Yield of isolated N^9-product. [c] Yield of the regioisomeric mixture of N^9- and N^7-products. [d] Yield of isolated N^7-product. [e] Yield of isolated N^3-product. [f] Regioselectivity determined by ^{1}H-NMR of the crude reaction mixture. [g] Assignment of the products to either the N^9- or N^7-product occurred by ^{1}H-NMR, HMBC and NOE experiments of the isolated compounds. [h] *ee* determined by chiral HPLC. [i] For the *ee* value of the corresponding N^7-product see the Supporting Information. Bn = benzyl, Bu = butyl.

Table 3: Scope of allenes towards branched allylated compounds.[a–e]



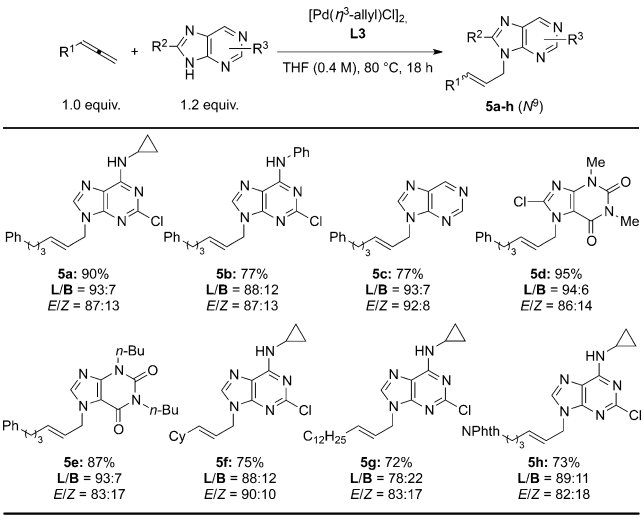
[a] All reactions were performed with $[Rh(cod)Cl]_2$ (2.0 mol%), **L2** (6.0 mol%), DCE/EtOH (0.4 M, 2:1), 80°C, 18 h. [b] Yield of isolated N^9-product. [c] Regioselectivity determined by ^{1}H-NMR of the crude reaction mixture. [d] Assignment of the products to either the N^9- or N^7-product occurred by ^{1}H-NMR, HMBC and NOE experiments of the isolated compounds. [e] *ee* determined by chiral HPLC. Phth = phthaloyl, TBS = *tert*-butyldimethyl silyl, PMB = *para*-methoxybenzyl.

ity (entry 2), although only moderate yields were obtained. Increasing the allene/purine ratio to 1.5:1 enhanced the yield. In order to increase the practicability of the reaction, we shifted from microwave reactor conditions to conventional heating conditions. Further screening revealed that performing the reaction with the ferrocene-based Josiphos 003-1 ligand (**L2**) allowed to lower the reaction temperature to 80°C and 18 hours to provide the clean hydroamination product in 97% yield with an excellent regioselectivity (branched only), N^9 to N^7 position selectivity and an excellent enantiomeric excess of 94% (Table 1, entry 3).

With the optimized conditions in hand, we investigated the scope of different purine derivatives (Table 2) and allenes (Table 3). Purine nucleophiles including functionalities in 2- and 6-position provided exclusively branched allylic products **3b**–**i** in high yield and selectivity. As expected, sterically and electronically indifferent substrates were obtained in modest N^9/N^7-selectivity (**3b**–**c**), while a benzylated oxygen function in 6-position almost shifted selectivity towards N^7-product. Trifluoromethylated deaza-purine provided lowered yields but exclusive N^3-selectivity (**3e**). The pyridone-substituted purine provided the corresponding product **3f** in 99% yield with 93% *ee*. N^1- and N^3-disubstituted xanthine derivatives showed N^7-substituted products **3h**–**i** exclusively with only slightly reduced enantiomeric excess. Next, an assorted variety of allenes containing various functional groups was investigated.[18] As shown in Table 3 allenes equipped with a thioether, an ester, an *N*-phthalimide and an unprotected hydroxy function reacted smoothly and provided the desired allylation product in high yields and excellent enantioselectivity (Table 3, **3a**, **j**–**p**).

According to previous observations,[19] switching the catalyst to a Pd/dppf system led to linear achiral compounds with high selectivities in good to excellent yields (Table 4, **5a**–**h**). This provides quick access to acyclic side chain nucleotides, which have shown similar high anti-viral activity as carbanucleosides.[20] Most derived compounds were solids

Table 4: Scope of the catalytic addition of purine derivatives to terminal allenes towards achiral linear allylated compounds.[a–e]

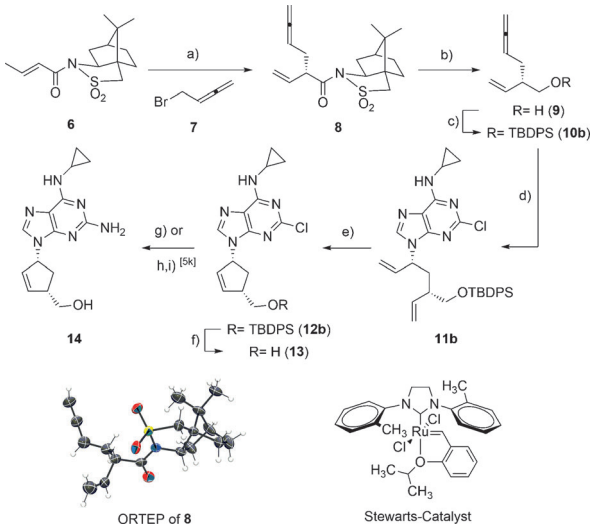


[a] All reactions were performed with $[Pd(\eta^3\text{-allyl})Cl]_2$ (2.5 mol%), **L3** (10.0 mol%), THF (0.4 M), 80 °C, 18 h. [b] Yield of isolated linear allylated N^9-product. [c] Ratio of linear and branched products were determined by ^{1}H-NMR of the crude reaction mixture. [d] *E*/*Z* ratio was determined by ^{1}H-NMR of the isolated products. [e] Assignment of the products to either the N^9- or N^7-product occurred by ^{1}H-NMR, HMBC and NOE experiments of the isolated compounds.

and could therefore be purified by precipitation or recrystallization from the reaction mixture.

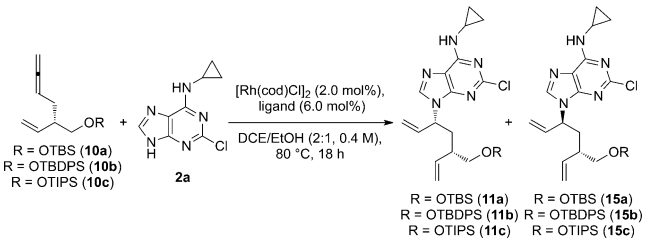
As carbocyclic nucleosides are of great interest in modern medicinal chemistry,[21] the application of our new methodology towards the total synthesis of the HIV drug abacavir (**13**) was explored. Towards this end, the chiral allene building block derived from Oppolzer-sultam (**6**) via deconjugative enolate alkylation with bromoallene electrophile (**7**), was subsequently reduced to provide the chiral allene building block (**9**) in high yield (Scheme 2). An X-ray crystal structure analysis of sultam **8** confirmed the absolute configuration. First coupling experiments of hydroxy-allene **9** with purine **2a** showed no conversion to the desired product under several investigated conditions.

Therefore, the hydroxy function was protected as various silyl-ethers (**10a–c**). Coupling of TBS-allene (**10a**) employing the achiral reaction conditions satisfyingly provided the desired N^9-products (*syn* and *anti*) in 62% yield with a substrate induced d.r. of 76:24 (Table 5, entry 1) in favor of the *syn*-diastereomer. By utilizing the privileged chiral ligand (**L2**), the d.r. could be increased to 93:7. The best substrate was found to be the TBDPS-protected allene, which provided yields of 82% with a d.r. >95:5. In order to get access to the opposite diastereomer, the reaction was run with Josiphos 003-2 (*ent*-**L2**), which led to a significant decrease in yield and a d.r. of 12:88 in favor of the *anti* diastereomer (entry 4), nevertheless proving a powerful catalyst control of diastereoselectivity. Even a bulky TIPS-group was tolerated, providing almost exclusively *syn*-N^9-product, with necessarily higher catalyst loading to compensate for the lower reactivity due to steric hindrance of the substrate (entry 5).



Scheme 2. Synthesis of abacavir. Reagents and conditions: a) **7** (2.0 equiv), LiHMDS (1.05 equiv), HMPA, THF, 0 °C then room temperature, 2 h, 88% (d.r. 94:6); b) $LiAlH_4$, Et_2O, 0 °C then room temperature, 2.5 h, 92%; c) TBDPSCl (1.5 equiv), imidazole (2.0 equiv), DMAP (20 mol%), 0 °C then room temperature, 18 h, 99%; d) **2a**, $[Rh(cod)Cl]_2$ (2 mol%), **L2** (6 mol%), DCE/EtOH (2:1, 0.4 M), 80 °C, 18 h, 82% (N^9-product, d.r. 96:4); e) Stewart's catalyst (10 mol%), DCE, 60 °C, 18 h, 80%; f) TBAF (1.1 equiv), THF, 0 °C to room temperature, 18 h, 97%; g) NH_4OH (28%). CuI (20 mol%), EtOH, 150 °C, 40 h, 63%; h) 4-Methoxybenzylamine, DMSO, 150 °C, 16 h, 90%; i) TFA, reflux, 72 h, 73%. TBDPS = *tert*-butyldiphenylsilyl, DMAP = 4-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride, TFA = trifluoroacetic acid.

Table 5: Optimization of the rhodium-catalyzed coupling of chiral allene fragments **10a–c** with **2a**.[a–e]



Entry	R	Ligand	Yield [%][a]	d.r.[b]
1[c]	TBS	**L1**	62	76:24
2	TBS	**L2**	61	93:7
3	TBDPS	**L2**	82	>95:5 (96:4)
4[d]	TBDPS	J003-2 (*ent*-**L2**)	46	12:88
5[e]	TIPS	**L2**	81	>95:5 (98:2)

[a] Yields are those of diastereomeric mixtures isolated after silica gel chromatography. [b] Diastereoselectivity determined by ^{1}H-NMR of the crude reaction mixture. [c] Reaction was performed in THF/DMSO (1:1, 0.4 M) at 130 °C for 2 h. [d] Reaction was performed on a 0.2 mmol scale based on **2a**. [e] Reaction was performed with 4 mol% $[Rh(cod)Cl]_2$ and 12 mol% **L2**.

The subsequent ring-closing metathesis was achieved with Stewart's catalyst to afford the desired cyclopentene **12** in high yield (Scheme 2). Grubbs II catalyst afforded the desired compound in lower yield (62%). At this stage, NOESY

experiments confirmed the relative configuration of the *syn*- and *anti*-stereoisomers. The final introduction of the guanidine function in 2-position followed literature-known steps consisting of S_NAr with PMB amine under harsh conditions followed by cleavage of the PMB group in refluxing TFA.[5k] Under these conditions the silyl ether protecting group was simultaneously cleaved making an additional deprotection step unnecessary. The advantage of the late-stage introduction of the guanidine function is the minimization of coordination effects during catalysis and a simplification of workup procedures during earlier stages. Nevertheless, we also explored a more direct introduction of the guanidine group using aqueous ammonia as the nucleophile in the presence of a copper(I) salt.[22] While the silyl ether **12** did not react at all, the deprotected free alcohol substrate **13** reacted in the presence of 20 mol% of copper iodide with aqueous ammonia to furnish abacavir (**14**) in 63% isolated yields.

To conclude, an efficient asymmetric, regiodivergent and selective atom-economic addition of purines to terminal allenes has been developed, employing a commercially available rhodium catalyst system. A large variety of functional groups was tolerated and provided N^9-substituted branched allylic purines in high yields and excellent enantioselectivity. For adaptable regiodivergent synthesis of linear allylic purines, a Pd/dppf catalyst system was identified. Additionally, a new and straightforward synthesis towards carbocyclic nucleosides exemplified by total synthesis of the HIV drug abacavir was devised displaying the synthetic potential of this new methodology.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: abacavir · allenes · asymmetric catalysis · carbanucleoside · rhodium

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Communications

Asymmetric Synthesis

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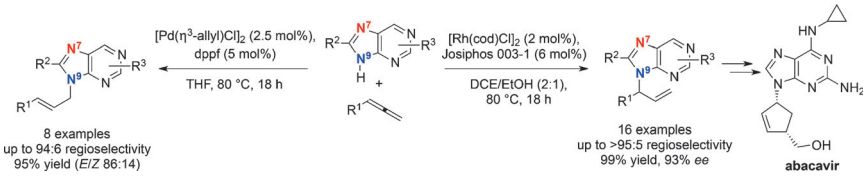
Enantioselective and Regiodivergent Addition of Purines to Terminal Allenes: Synthesis of Abacavir



An atom-economic and regiodivergent Rh- and Pd-catalyzed coupling of purine derivatives and terminal allenes has been developed. High regioselectivity and excellent enantiomeric excess and yields were achieved with various functionalized substrates. Additionally, the developed methodology was applied to a straightforward synthesis of carbocyclic nucleoside abacavir.