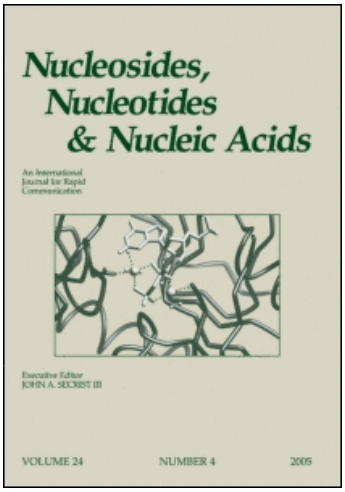

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PALLADIUM-CATALYZED AMINATION OF 6-CHLOROPURINE. SYNTHESIS OF N^6-SUBSTITUTED ADENOSINE ANALOGUES

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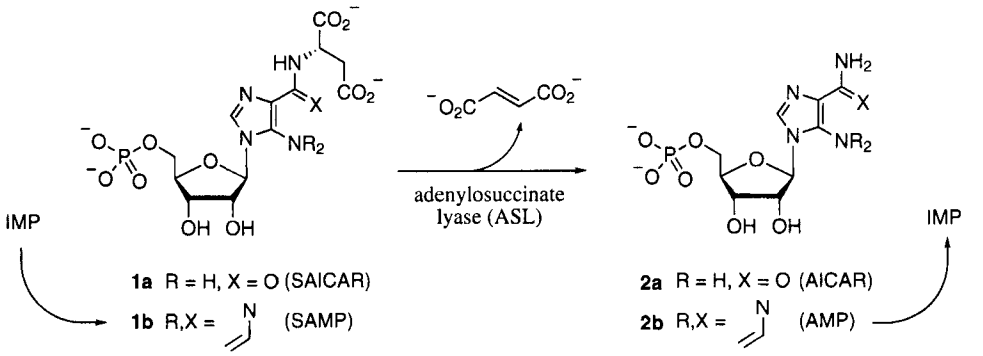
ABSTRACT. Room-temperature treatment of persilylated 6-chloro-9-β-D-ribofuranosylpurine with a variety of aliphatic and aromatic amines, in the presence of $Pd_2(dba)_3$, BINAP and base, leads to N^6-substituted adenosine analogues in fair to good yields. Coupling of chloropurine with a chiral aziridinyl diester is applied in the synthesis of a potential adenylosuccinate lyase inhibitor.

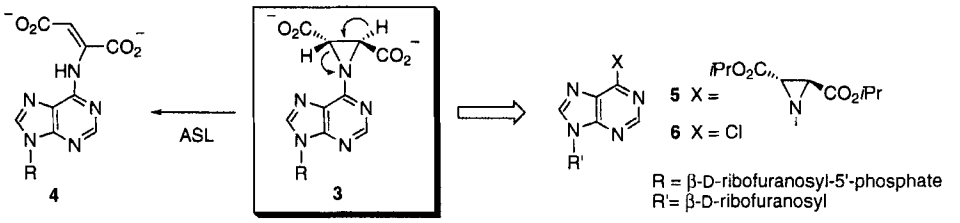
The enzyme adenylosuccinate lyase (ASL, EC 4.3.2.2) catalyses two distinct steps in the *de novo* biosynthesis of adenosine from D-ribose-5'-phosphate, involving elimination of fumarate from succinocarboxamide **1a** or adenylosuccinate **1b**, respectively.[1,2] In addition, the conversion of **1b** into adenosine-5'-monophosphate (AMP, **2b**) is part of the adenine purine nucleotide cycle (IMP→**1b**→**2b**→IMP), a cycle that plays a pivotal metabolic role in skeletal muscle, kidney and brain.[3,4]



Scheme 1

Our long-standing interest[5] in the adenylosuccinate system, originally based on the cytostatic activity exerted by 6-mercaptopurine[6] *via* inhibition of ASL, was further stimulated by reports that enzymatic activity is significantly enhanced in biopsies of malignant tumors,[7] particularly breast tumors.[8] Since rapidly dividing cancer cells require abundant availability of nucleotides, it was hypothesised that an effective inhibitor of ASL may be an interesting new lead for the development of therapeutic cytostatics.

Among others,[5,9-12] target compound **3** was chosen as a potential candidate for the inhibition of ASL; recognition of **3** by ASL may induce the usual β-elimination of an amino group and lead to formation of enamine **4**. Since the *in situ* formed compound **4** is a potential transition state analogue in that it resembles a covalently linked dimer of **2b** with fumarate, we have termed precursor **3** a 'pre-transition state analogue'.

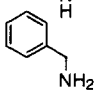
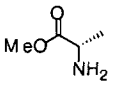
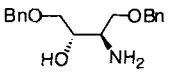


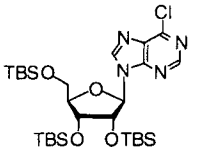
Scheme 2

A possible synthetic route towards inhibitor **3** proceeds *via* diester **5**, which may be prepared by amination of 6-chloropurine riboside (**6**) with diisopropyl (2*S*,3*S*)-(+)-aziridine-2,3-dicarboxylate (**10**). Unfortunately, all attempts to couple **6** with aziridine esters of type **10**, by refluxing under basic conditions in a variety of solvents, failed, presumably due to the inherent low nucleophilicity of the aziridine nitrogen.[13] These disappointing results drew our attention to recently described procedures for the synthesis of aryl amines from aryl halides or triflates by use of late transition metal (Pd, Ni) catalysis, conditions that were found suitable for coupling with a wide variety of amino compounds.[14] The significantly milder conditions, as compared to classical methods, prompted us to investigate if transition metal catalyzed amination would also be applicable to 6-chloropurine, in a novel procedure for the preparation of N^6-substituted adenosines.

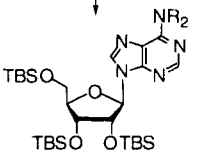
Table 1 summarizes the results obtained for treatment of tri-*O*-TBS protected 6-chloropurine riboside **7**[15] with a variety of alkyl and aryl amines in the presence of $Pd_2(dba)_3$ (1 mol%) and BINAP (2.5 mol%). With a few exceptions, it was found that room temperature reaction in the presence of KO*t*Bu[16] or Cs_2CO_3[17] smoothly afforded the desired adducts **8**, in yields varying from fair to excellent. Particular clean conversion was observed for amination of chloropurine **7** with aliphatic amines (entries 1-4), in yields comparable to those reported for amination using conventional conditions. Unfortunately,

Table 1. Palladium-catalyzed condensation of **7** with alkyl and aryl amines.[18,19]

entry	amine	KO*t*-Bu time (h)	KO*t*-Bu yield (%)	Cs_2CO_3 time (h)	Cs_2CO_3 yield (%)	product
1		16	70	16	95	**8a**
2		16	36	16	80	**8b**
3		16	32	16	78	**8c**
4		72	86	48	91	**8d**
5		144	17	60	10	**8e**
6		16	26	48	0	**8f**
7		48	28	48	6	**8g**
8		16	39	72	0	**8h**



7

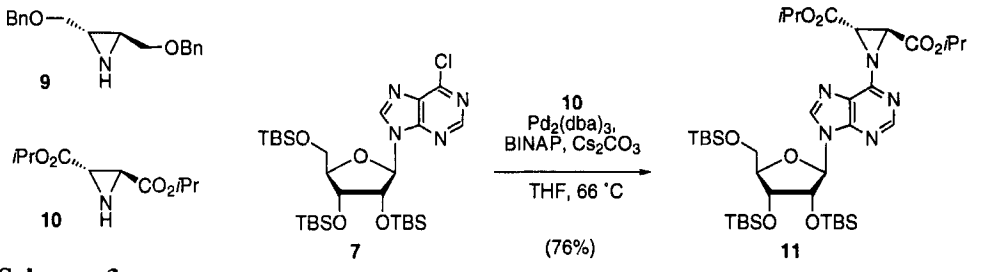


8a-h

condensation of **7** with aryl amines (entries 5 and 6) gave inferior results. The disappointing yield of entry 7 may possibly be explained by the low nucleophilicity of the α-nitrogen due to the electronegative ester function.

With the conditions for amination of **7** properly established, attention was focused on the synthesis of the potential ASL inhibitor **3**. Due to the fact that coupling with L-alanine methyl ester proceeded poorly (entry 7), amination with aziridine **9**,[20] having electron-rich benzyloxymethyl substituents instead of esters, was first attempted (Scheme 3). However, reaction of **7** and **9** under standard conditions, in the presence of KO*t*Bu or Cs_2CO_3 as base, did not lead to coupling, whereas slow decomposition of **7** was observed upon prolonged heating. On the other hand, clean conversion of **7** to a more polar product was observed upon amination with aziridine diisopropyl ester **10**,[21] by performing the reaction at elevated temperature (66 °C) in the presence of Cs_2CO_3. Condensation proceeded sluggishly, but additional amounts of palladium-catalyst (3 mol%) and BINAP (7.5 mol%) significantly accelerated the reaction: TLC-analysis after 48 h showed the presence of one predominant product, along with only minor amounts of starting material **7**. Work-up and purification afforded a homogeneous product in 76% yield (90% based on recovered **7**),

unambiguously identified as the desired aziridine **11** by spectroscopic analysis (NMR, IR, HRMS).[22]



Scheme 3

In conclusion, we have successfully extended the palladium-catalyzed amination of aryl bromides to the coupling of 6-chloropurine with amines.[23] Although the yields obtained for simple amines do not substantially differ from those reported for coupling by conventional means, the reaction may be found useful for introduction of sterically hindered or sensitive amines. For instance, application of palladium catalysis to coupling with aziridine **10** afforded in good yield the desired product **11**, further transformation of which to a potential ASL-inhibitor is currently in progress in our laboratory.

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18. Isolated yields. Typical procedure: To a solution of chloropurine **7** (1 mmole), coevaporated twice with toluene (2 mL), in freshly distilled THF (5 mL) was added consecutively the indicated amine (2 mmole), base (1.5 mmole), BINAP (0.025 mmole) and $Pd_2(dba)_3$ (0.01 mmole). After stirring the indicated time at room temperature under a nitrogen atmosphere, the reaction was quenched by the addition of a saturated solution of NH_4Cl and extracted with EtOAc. The organic phase was washed with H_2O and brine, dried with $MgSO_4$ and filtered before concentration and purification by silica gel column chromatography (eluent: EtOAc/PE 60-80).
19. All compounds showed satisfactory analytical and spectroscopic data. TBS = *tert*-butyldimethylsilyl, Bn = benzyl, $Pd(dba)_2$ = bis(dibenzylideneacetone)palladium, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl.
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22. Spectroscopic data for compound **11**. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.60 (s, 1H, H-2), 8.23 (s, 1H, H-8), 6.06 (d, 1H, *J* = 5.3 Hz, H-1'), 4.97 (h, 2H, *J* = 6.3 Hz, 2x C*H*$(CH_3)_2$), 4.62 (t, 1H, *J* = 4.8 Hz, H-2'), 4.29 (t, 1H, *J* = 3.8 Hz, H-3'), 4.11 (m, 1H, H-4'), 3.99 (dd, 1H, *J* = 11.4, 3.9 Hz, H-5a'), 3.77 (dd, 1H, *J* = 11.3, 2.7 Hz, H-5b'), 3.76 (s, 2H, C*H*N), 1.22 (d, 3H, *J* = 6.2 Hz, CH(CH_3)$_2$), 1.16 (d, 3H, *J* = 6.3 Hz, CH(CH_3)$_2$), 0.94, 0.92, 0.77 (3x s, 27H, SiC(CH_3)$_3$), 0.12, 0.12, -0.06, -0.26 (4x s, 18H, Si(CH_3)$_2$; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.1, 157.2, 152.2, 151.2, 141.6, 125.6, 88.1, 85.5, 75.9, 71.9, 69.9, 62.6,

41.4, 26.4, 26.0, 25.8, 25.6, 21.5, 21.5, 20.1, 18.5, 18.0, 17.8, -4.5, -4.7, -4.8, -5.1, -5.4, -5.4; FT-IR (neat): ν_{max} 2930, 2857, 1736, 1593, 1458, 1256, 1200, 1106, 837 cm^{-1}. HRMS (FAB): calcd for $C_{38}H_{70}N_5O_8Si_3$ (M + H^+): 808.4532, found 808.4532.

23. Transition-metal catalysis has also been applied in the condensation of 6-halopurines with Grignard,[15] organotin[24,25] and organozinc[26] reagents.
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