Regioselective and enantiospecific rhodium-catalyzed allylic amination with thymine: synthesis of a new conformationally rigid nucleoside†

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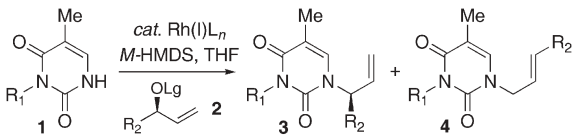
The regioselective and enantiospecific rhodium-catalyzed allylic amination of secondary allylic carbonates with N^3-benzoyl thymine in conjunction with a stereoselective free radical cyclization provides a convenient method for the construction of a new conformationally rigid nucleoside.

Transition metal-catalyzed allylic amination using nucleoside bases provides an important method for the construction of biologically important nucleosides.[1–3] Although this reaction has been extensively studied in the context of cyclic allylic systems, the ability to accomplish the analogous transformation with acyclic unsymmetrical allylic alcohol derivatives has proven problematic.[4] Nonetheless, the development of new methods that facilitate the construction of novel nucleoside analogs remains an important area of interest, due in part to their significance as antiviral and antitumor agents.[5] Recently, attention has shifted to the preparation of carbanucleoside analogs, which have increased hydrolytic stability compared to conventional derivatives due to the absence of the glycosidic linkage.[6] We envisioned an alternative approach to fulfilling this requirement, wherein the sugar and pyrimidine base are fused. Herein, we now describe the development of a new metal-catalyzed allylic amination, which in combination with a radical cyclization, facilitates the construction of a new conformationally rigid nucleoside.



As part of a program directed towards the development of stereospecific rhodium-catalyzed allylic substitution reactions of acyclic chiral non-racemic allylic carbonates, we envisioned that the utilization of thymine as a pronucleophile would facilitate the construction of a new class of nucleosides.[7] We now describe the development of a regioselective and enantiospecific rhodium-catalyzed allylic amination of enantiomerically enriched allylic carbonates **2**, using the lithium salt of N^3-benzoyl thymine **1**, to afford the branched N^1-substituted thymine derivatives **3** in excellent yield (eqn. (1)). Preliminary studies demonstrated that the lithium counter-ion (M = Li > Na > K) was optimum for the regioselective formation of *rac*-**3a** (R_1 = Bz; R_2 = $Ph(CH_2)_2$), consistent with our previous studies (Table 1, entry 1).[7–9] Although a reasonable yield of *rac*-**3a** (R_1 = Bz) was obtained, there was also a significant quantity of the debenzoylated adduct *rac*-**3a** (R_1 = H) formed, which presumably results from transacylation with lithium methoxide liberated from the methyl carbonate leaving group (Table 1, entry 1). We anticipated that altering the relative size and/or nucleophilicity of the alcohol may minimize the amount of transacylation. Surprisingly, the *tert*-butyl and *para*-nitrophenyl carbonates proved less reactive under the reaction conditions, affording *rac*-**3a/4a** in low yield, albeit with analogous amounts of the debenzoylated derivative (Table 1, entries 2 and 3). Gratifyingly, when the reaction was performed at 0 °C, significantly less transacylation product was obtained, which resulted in an improved yield of *rac*-**3a** (R_1 = Bz, Table 1, entry 4). Finally, we decided to optimize the formation of the debenzoylated derivatives by affecting the removal of the N^3-benzoyl group. Treatment of the crude amination products *rac*-**3a/4a** (R_1 = Bz) in methanol with conc. NH_4OH at room temperature, furnished the N^1-substituted thymine *rac*-**3a/4a** (R_1 = H) in 98% overall yield with ⩾99 : 1 regioselectivity favoring *rac*-**3a** (Table 1, entry 5).[10] Hence, this approach provides versatility in terms of the ability to either retain (Table 1, entry 4) or cleave the benzoyl protecting group (Table 1, entry 5).

Table 1 Optimization of the regioselective rhodium-catalyzed allylic amination (eqn. (1); **1**, R_1 = Bz; *rac*-**2**, R_2 = $Ph(CH_2)_2$)[a]

Entry	Temp./°C	Lg	Ratio of *rac*-**3a** : **4a**[b]	Yield of *rac*-**3a/4a** (%)[c]	
				R_1 = Bz	R_1 = H
1	30	MeOCO–	⩾ 99 : 1	76	19
2	30	^{t}BuOCO–	⩾ 99 : 1	33	10
3	30	*p*-$NO_2C_6H_4OCO$–	⩾ 99 : 1	49	11
4[d]	0	MeOCO–	⩾ 99 : 1	84	2
5[e]	30	MeOCO–	⩾ 99 : 1	—	98

[a] All reactions were carried out on a 0.25 mmol reaction scale using 10 mol% $RhCl(PPh_3)_3$ modified with 40 mol% $P(OMe)_3$ and 2 equiv. of the lithium anion of N^3-benzoyl thymine for *ca.* 12 h. [b] Ratios of regioisomers and product ratios were determined by HPLC analysis of crude reaction mixtures. [c] Yield based on the HPLC ratio of the combined isolated products. [d] The reaction was stirred at 0 °C for 24 h. [e] The crude reaction mixture was dissolved in methanol and treated with conc. NH_4OH at room temperature for *ca.* 4 h.

Table 2 summarizes the application of the optimized reaction conditions (Table 1, entry 5) to a variety of racemic secondary allylic carbonates (*vide infra*). The observed regioselectivity for the allylic amination with N^3-benzoyl thymine is excellent for an array

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† Electronic Supplementary Information (ESI) available: Experimental procedures, X-ray crystallographic analysis of **9**, and spectral data (IR, ^{1}H and ^{13}C NMR), including high resolution MS, for *rac*-**3a–l**, (*S*)-**3j** and **5–10**. See DOI: 10.1039/b513083b

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Table 2 Scope of the regioselective rhodium-catalyzed allylic amination (eqn. (1); **1**, R_1 = Bz; *rac*-**2**, Lg = MeOCO)[a]

Entry	Allylic carbonate *rac*-**2**		Ratio of *rac*-**3** : **4**[b,c]	Yield (%)[d]
	R_2 =		R_1 = H	
1	$Ph(CH_2)_2$	a	⩾ 99 : 1	98
2	Me	b	⩾ 99 : 1	98
3	^{n}Pr	c	⩾ 99 : 1	92
4	CH_2=$CH(CH_2)_3$	d	⩾ 99 : 1	81
5	^{i}Pr	e	⩾ 99 : 1	77
6	c-Hexyl	f	58 : 1	64
7	$(CH_3)_2CHCH_2$	g	32 : 1	86
8	$PhCH_2$	h	29 : 1	91
9	$TBSOCH_2$	i	⩾ 99 : 1	68
10	$BnOCH_2$	j	⩾ 99 : 1	87
11	Ph	k	⩾ 99 : 1	94
12	Naphthyl	l	⩾ 99 : 1	96

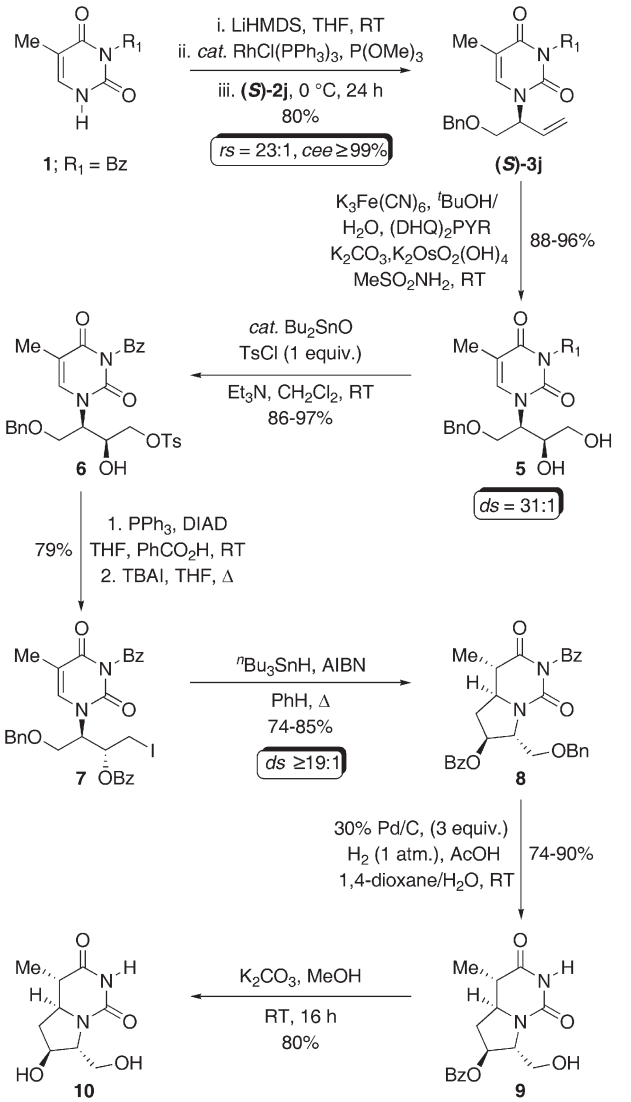
[a] All reactions were carried out on a 0.25 mmol reaction scale. [b] Ratios of regioisomers were determined by HPLC analysis of crude reaction mixtures. [c] The primary products **4** were prepared independently *via* Pd(0) catalysis. [d] Isolated yields.

of acyclic allylic alcohol derivatives. For example, linear and branched alkyl (Table 2, entries 1–7), benzyl (Table 2, entry 8), protected hydroxymethyl (Table 2, entries 9 and 10) and aryl substituents (Table 2, entries 11 and 12) provide exquisite regiocontrol in this transformation. Gratifyingly, the challenging α-branched alkyl derivatives are remarkably well tolerated, which contrasts with the results obtained with the *N*-alkyl sulfonamides examined previously (Table 2, entries 5 and 6).[11]

Additional studies examined stereospecificity, which is a key component to the rhodium-catalyzed allylic substitution (Scheme 1). Treatment of the chiral non-racemic allylic carbonate (*S*)-**2j** (R_2 = CH_2OBn, 99% *ee*) under the optimized reaction conditions (Table 1, entry 5) furnished the enantiomerically enriched N^1-substituted thymines (*S*)-**3j/4j** (R_1 = H) in 81% yield, favoring (*S*)-**3j** (2° : 1° ⩾99 : 1, ⩾99% *cee*§).[11,12] Overall, this transformation represents an important new method for the cross-coupling of pyrimidine bases.

Herein, we now describe the combination of a rhodium-catalyzed allylic amination with a radical cyclization to prepare a new conformationally rigid nucleoside **10** (Scheme 1). Preliminary studies focused on the dihydroxylation of (*S*)-**3j** (R_1 = H), wherein the Sharpless asymmetric dihydroxylation afforded good selectivity (*ds* = 10 : 1), favoring the desired *anti*-diastereoisomer (not shown).[13] Although the selectivity was acceptable, we envisioned that the N^3-benzoyl derivative would significantly enhance the selectivity, in an analogous manner to that described by Corey and co-workers.[14] Thus, the allylic amination protocol that retains the N^3-benzoyl group was employed to prepare the substrate necessary to test this hypothesis (Table 1, entry 4).

Treatment of the enantiomerically enriched allylic carbonate (*S*)-**2j** with trimethyl phosphite-modified Wilkinson's catalyst and the lithium salt of N^3-benzoyl-protected thymine **1** at 0 °C for 24 hours afforded the *N*,*N*-disubstituted thymine (*S*)-**3j** (R_1 = Bz) in 80% yield with excellent regioselectivity and enantiospecificity (2° : 1° = 23 : 1, ⩾ 99% *cee*). Interestingly, although the Sharpless asymmetric dihydroxylation of the allylamine (*S*)-**3j** (R_1 = Bz) furnished the *syn*-diastereoisomer **5** (R_1 = Bz) with significantly improved selectivity (*ds* = 31 : 1) the *pseudo*-enantiomeric ligand was mismatched with this particular substrate, thereby affording significantly lower selectivity for the *anti*-diastereoisomer



Scheme 1 Synthesis of the conformationally rigid nucleoside **10**.

(*ds* = 4 : 1). Nonetheless, we envisioned that the *syn*-diastereoisomer **5** could be simultaneously inverted and protected as the benzoate ester, which would provide a greater degree of versatility to the synthetic strategy, potentially facilitating the introduction of other nucleophiles, *i.e.* azide *etc*.

The diol **5** was selectivity converted to the primary tosylate **6** in excellent yield with *para*-toluenesulfonyl chloride and catalytic dibutyltin oxide.[15] Mitsunobu inversion of the residual secondary alcohol **6**, followed by the displacement of tosylate with *n*-tetrabutylammonium iodide (TBAI), provided the radical cyclization precursor **7** in 79% overall yield.[16] Treatment of the iodide **7** with tributyltin hydride and a catalytic amount of AIBN in refluxing benzene, furnished the corresponding azabicycle **8** in 74–85% yield with excellent diastereoselectivity (*ds* ⩾19 : 1 by 400 MHz ^{1}H NMR).

The origin of the diastereocontrol in the initial addition is consistent with our previous model, in which non-bonding interactions between the C-2 carbonyl of the thymine and the α-amino stereogenic center control the facial delivery.[17,18] The resulting radical intermediate is then preferentially reduced *via* a

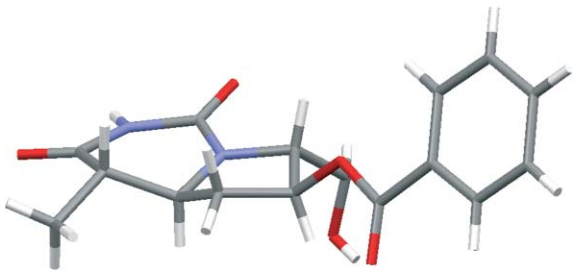


Fig. 1 X-ray structure of **9**.

pseudo-axial hydrogen atom delivery to afford the *trans*-orientation.[18,19] The relative configuration of the free radical cyclization was unambiguously confirmed by an X-ray crystallographic analysis of **9**,¶ which was obtained through hydrogenolysis of **8** (Fig. 1). The synthesis of the novel conformationally rigid nucleoside **10** was completed through methanolysis of the benzoyl group in **9**.[20]

In conclusion, we have developed the first regioselective and enantiospecific allylic amination of unsymmetrical chiral non-racemic allylic alcohol derivatives using N^3-benzoyl thymine. This study demonstrates that the thymine protecting group, while essential for selective amination, may either be retained or removed, thus increasing the synthetic versatility of this transformation. Finally, this reaction was utilized in conjunction with a free radical cyclization to prepare the novel conformationally rigid nucleoside **10** in eight linear steps and 36% overall yield from the allylic carbonate (*S*)-**2j**.

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Notes and references

§ Conservation of enantiomeric excess *cee* = (product *ee*/starting material *ee*) × 100.

¶ Crystal structure data for **9**, $C_{16}H_{18}N_2O_5$, colorless, monoclinic, $P2_1$, a = 6.2583(7), b = 7.3007(8), c = 16.5882(16) Å, β = 98.717(3) °, V = 749.16(14) Å^3, Z = 2, T = 118(2) K, ρ_{calc} = 1.411 Mg m^{-3}, μ = 0.106 mm^{-1}, *GOF* = 0.985, $R(F)$ = 0.0367 and $wR(F)2$ = 0.0851 for 2212 observed reflections, $I > 4\sigma$, 2.5° ⩽ θ ⩽ 27.5°. CCDC 284326. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b513083b

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9 The attempted allylic amination reaction with the lithium anion of thymine gave a complex mixture of products, thereby illustrating the importance of the protecting group.

10 *Representative procedure for the rhodium-catalyzed allylic amination:* Trimethyl phosphite (12 μL, 0.102 mmol) was added directly to a red solution of Wilkinson's catalyst (23.1 mg, 0.025 mmol) in anhydrous THF (1 mL) at room temperature under an atmosphere of argon. The catalyst was allowed to form over *ca.* 15 min, resulting in a light yellow homogeneous solution. Lithium hexamethyldisilylazide (475 μL, 0.475 mmol, 1.0 M solution in THF) was added to N^3-benzoylthymine **1** (115.1 mg, 0.500 mmol) in anhydrous THF (3 mL) at 30 °C and the anion allowed to form over *ca.* 30 min. The catalyst was then added *via* Teflon cannula to the anion solution, followed by addition of allylic carbonate *rac*-**2a** (54.2 mg, 0.246 mmol) *via* a tared 100 μL syringe. The mixture was then stirred at 30 °C for *ca.* 12 h (TLC control). The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution and methanol at room temperature, and partitioned between ethyl acetate and water. The combined phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford a crude oil. The residue was re-dissolved in methanol (15 mL) followed by the addition of conc. NH_4OH (2.5 mL) at room temperature. After stirring at the same temperature for *ca.* 4 h (TLC control), the reaction mixture was concentrated *in vacuo* to afford a crude oil. Purification by flash column chromatography (eluting with 20–50% ethyl acetate/hexanes) furnished the N^1-alkylated thymine *rac*-**2a** (R_1 = H; 65.1 mg, 98%) as a colorless oil.

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18 (*a*) P. A. Evans and T. Manangan, *Tetrahedron Lett.*, 2001, **42**, 6637; (*b*) P. A. Evans and T. Manangan, *Tetrahedron Lett.*, 2005, **46**, 8811.

19 For a related free radical reduction in a related thymine derivative, see: D. J. Fenick and D. E. Falvey, *J. Org. Chem.*, 1994, **59**, 4791.

20 The desired product was also obtained with a minor amount of the product from the epimerization of the methyl group (⩽5%).

