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A highly diastereoselective synthesis of homoallylic alcohol/amine appended uracils: the role of the uracil C-4 carbonyl in diastereoselectivity control

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Abstract—5-Formyluracil derivatives and their Schiff bases with chiral amino alcohols undergo highly diastereoselective 1,2- and 1,3-allylations. The absence of the C-4 carbonyl in the case of 2,4-dimethoxy-5-formylpyrimidine and its Schiff bases leads to loss of diastereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

In asymmetric synthesis, the participation of a catalyst–substrate–metal complex appears to be an absolutely essential requirement. The metal complexing ability of 1,3-amidic carbonyl groups in *N*-acyloxazolidin-2-ones having appropriately placed prochiral centers has been extensively exploited for asymmetric induction through a variety of reactions, viz. Diels–Alder,[1] hetero Diels–Alder,[2] 1,3-dipolar cycloaddition,[3] Michael addition,[4] aldol type condensations,[5] etc. Uracil derivatives are the backbone of the life cycle and modifications at C-5 provide many bioactive molecules. In 5-formyluracil and its derivatives the carbonyl group of the cyclic amide and the C-5-formyl are oriented as in *N*-acyloxazolidin-2-one derivatives and should constitute excellent synthons for procuring chiral uracil nucleosides. In the present investigation, indium induced 1,2-stereospecific allylation of 5-formyluracils **1** and 1,3-highly stereoselective allylation of uracil derived imines **8** to prepare the title compounds have been studied. It has been found that indium-mediated allylation of **1** under aqueous conditions (THF: H_2O, 1:1) and that of **8** in dry THF–toluene (2:3) proceed in a highly diastereoselective manner. The absence of the C-4 carbonyl in **3**/**10** leads to either total loss or lowering of the diastereoselectivity and points towards the projected role of 1,3-carbonyl groups in diastereoselectivity control.

Table 1. The allylation of uracils **1** with allyl halides

Entry	Uracil	Halide R^2	Reaction time (h), (temp. (°C))	Product (% yield)	Mp (°C)	M^+ m/z	Diastereomer ratio[a,b]
1	**1a**	Ph	8 (30)	**2a** (62)	122	286 (M^+)	>99:1
2	**1b**	Ph	8 (30)	**2b** (80)	138	300 ($M^+ - H_2O$)	>99:1
3	**1c**	Ph	6 (30)	**2c** (75)	118	438 ($M^+ - H_2O$)	>99:1
4	**1a**	COOMe	36 (40)	**2d** (60)	–[c]	268 ($M^+ - H_2O$)	>99:1
5	**1c**	COOMe	36 (40)	**2e** (55)	–[c]	420 (M^+)	>99:1
6	**1a**	Me	12 (30)	**2f** (72)	–[c]	223 (M^+)	7:3
7	**1a**	3-Chlorobut-1-ene	18 (30)	**2f** (69)	–[c]	223 (M^+)	6:4
8	**3**	Ph	36 (30)	**4a** (65)	–[c]	286 (M^+)	1:1
9	**3**	COOMe	48 (40)	**4b** (52)	–[c]	268 (M^+)	1:1

[a] Determined by 200 and 300 MHz ^{1}H NMR.
[b] Absolute stereochemistry was not determined.
[c] These compounds are liquids.

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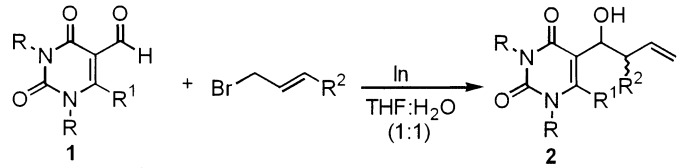
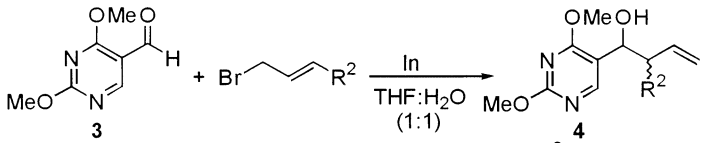


1

1a R = Me, R^1 = H
1b R = Me, R^1 = Me
1c R = CH_2Ph, R^1 = H

2

2a R = Me, R^1 = H, R^2 = Ph
2b R = Me, R^1 = Me, R^2 = Ph
2c R = CH_2Ph, R^1 = H, R^2 = Ph
2d R = Me, R^1 = H, R^2 = COOMe
2e R = CH_2Ph, R^1 = H, R^2 = COOMe
2f R = Me, R^1 = H, R^2 = Me

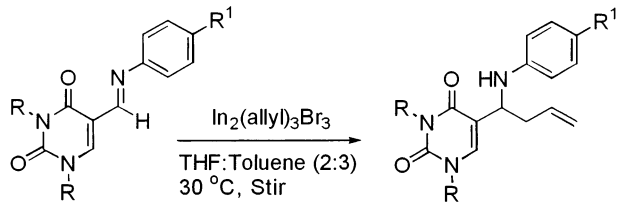


3

4

4a R^2 = Ph
4b R^2 = COOMe

A solution of **1a**, cinnamyl bromide and indium metal (suspension) (1:1.5:1) in THF–H_2O (1:1) on stirring at 30±1°C for 8–10 h, after HCl hydrolysis, CH_2Cl_2 extraction and chromatographic purification provides the γ-addition product **2a** (62%), mp 122°C, *m*/*z* 286 (M^+), which in its ^1H and ^{13}C NMR spectra shows the presence of only one diastereomer. In order to assess the scope of this reaction, the effect of substituents on both the reactants has been investigated (Table 1). Uracils **1b** and **1c** with cinnamyl bromide; and **1a** and **1c** with methyl 4-bromocrotonate give highly diastereoselective addition products, but in the cases of crotyl bromide and 3-chlorobut-1-ene poor diastereoselectivity is observed. The 2,4-dimethoxy-5-formylpyrimidine **3** with cinnamyl bromide and methyl 4-bromocrotonate under aqueous Barbier conditions gives γ-addition products but lacks diastereoselectivity (Table 1, entries 8 and 9).

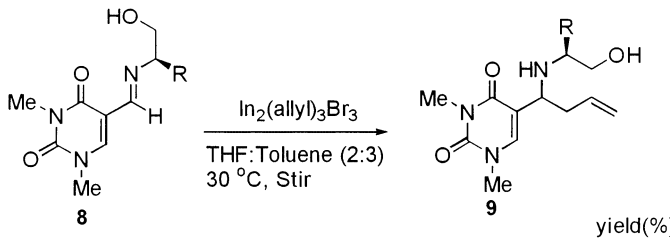


6a R^1 = OMe
6b R^1 = NO_2

7a R^1 = OMe 68%
7b R^1 = NO_2 70%

and $In_2(allyl)_3Br_3$ in THF–toluene (2:3), the allylation was completed in 6 h to provide **7a** (68%), *m*/*z* 467 (M^+) and **7b** (70%), *m*/*z* 482 (M^+), respectively.

The reaction of optically active Schiff base **8a** and $In_2(allyl)_3Br_3$ in THF–toluene (2:3) gave allylation (6 h) product **9a**, M^+ *m*/*z* 329 (M^+) in >98:2 dr.[6] Similarly, **8b** and **8c** prepared from **1a** with phenylalaninol and valinol gave respective allylation products **9b**, M^+ *m*/*z* 343 (M^+) and **9c**, M^+ *m*/*z* 295 (M^+).



8

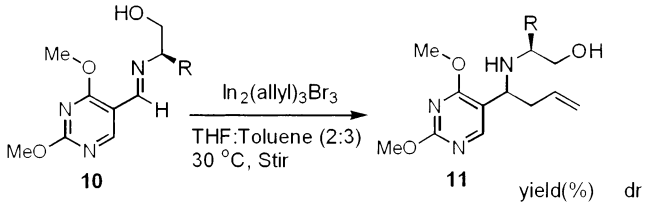
8a R = Ph
8b R = CH_2Ph
8c R = Isopropyl

9

	yield(%)	dr
9a R = Ph	62	>98:2
9b R = CH_2Ph	66	>96:2
9c R = Isopropyl	68	>98:2

Further, to elaborate the scope of these reactions, allylations on the Schiff bases of uracils and chiral amino alcohols were planned and for optimizing the reaction conditions, the model Schiff bases **6a**–**b** were prepared from **1c** with anisidine and *p*-nitroaniline. Under the above aqueous conditions, **6a**–**b** failed to undergo allylation with allyl bromide. The pregenerated $In_2(allyl)_3Br_3$ reagent in THF does not react with **6a**–**b** even after 48 h. However, on stirring a solution of **6a**–**b**

The Schiff bases **10a**–**c**, derived from **3** and the respective amino alcohols, under similar reaction conditions undergo allylations to provide **11a**–**c**. However, stereoselectivity was not observed and the completion of the reactions required longer periods (48 h) in comparison with **8a**–**c**. All these reactions require only one equivalent of the allyl indium reagent and unlike other organometallic reagents alcoholic protons do not interfere.[7]



10

10a R = Ph
10b R = CH_2Ph
10c R = Isopropyl

11

	yield(%)	dr
11a R = Ph	66	1:1
11b R = CH_2Ph	68	1:1
11c R = Isopropyl	68	2:1

The high diastereoselectivity observed in case of allylation of 5-formyluracils **1a–c** and their Schiff bases **8a–c** is lost in the respective reactions of 2,4-dimethoxy-5-formylpyrimidine (**3**) and its Schiff bases **10a–c**. The loss of diastereoselectivity and longer time required for the completion of the reactions in case of **3** and **10a–c**, suggest that complexation of the C-4 carbonyl oxygen in the uracils **1a–c** and **8a–c** with indium may be responsible for both the high diastereoselectivity and faster reactions.

Hence, 5-formyluracil derivatives and their Schiff bases with chiral amino alcohols undergo highly diastereoselective 1,2- and 1,3-allylations to form homoallylic alcohol/amine appended uracils (**2a–e** and **9a–c**).

Acknowledgements

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6. For the preparation of the Schiff bases and their reactions, the solution of **1**/**3** and the amino alcohol (1.2 equiv.) in dry dichloromethane containing molecular sieves (3 Å) was kept for 36 h at 30°C with occasional shaking. The measured amount of CH_2Cl_2 solution was taken, and the solvent was removed under vacuum. The residual Schiff base was dissolved in toluene and the solution was injected into the THF solution of the allyl indium reagent.
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