Stereocontrol in the Addition of Allyl Metal Reagents to an Optically Active Imine Derived from Malic Acid, Leading to a Formal Synthesis of (+)-Negamycin

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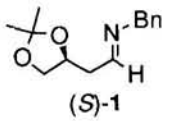
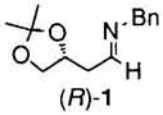
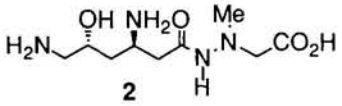
Complete *anti*-stereoselection has been achieved on the addition of allyl metal reagents to an optically active imine derived from malic acid. The homoallyl amine thus obtained was converted into the known intermediate for the synthesis of (+)-Negamycin in enantiomerically pure form.

Whereas there are relatively a good number of methods for 1,3-asymmetric induction on the addition of nucleophiles to the aldehydes possessing chiral carbons at their β-positions,[1] only limited examples are available for their imino versions.[2] Difficulties associated with the stereocontrol on a nucleophilic addition to β-functionalized aldimines stem from relatively low reactivity of the imino functionality, imine-enamine interconversion, and isomerization of the imine geometry. We have been interested in the stereocontrol on an addition of nucleophiles to chiral imines and aldehydes, and already disclosed applications to short-step syntheses of (+)-deoxybiotin and (2*S*,3*S*,4*R*)-phytosphingosine in enantiomerically pure forms.[3] In that study the stereocontrol was accomplished using chelation or non-chelation intermediates. The present paper describes a highly stereocontrolled approach to 1,3-*anti*-amino alcohols using addition of allyl metals to a chiral β-alkoxyimine **1** derived from malic acid, leading to a short-step synthesis of a known intermediate for (+)-negamycin **2**.[4]


(*S*)-**1**


(*R*)-**1**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The starting imine **1** was prepared from the parent aldehyde which was synthesized from D- or L-malic acid in 40-47% overall yield according to the reported procedure.[5] The examination into the addition of allyl metal reagents to the imine (*S*)-**1** was carried out under a variety of conditions, and the results are summarized in Table 1.

As shown in Table 1 the ratio of the adduct **3** was dependent mainly on the metal species used. Effect of the halogen ligand in the Grignard reagent is noteworthy. The use of chloromagnesium derivative recorded the predominant formation of the *anti*-adduct **3** in a ratio of 67 : 33, whereas an almost equal amount of the diastereomers was obtained using the bromomagnesium counterpart (Entries 1 & 3). The presence of additives also dramatically altered the diastereomer ratio. Cerium chloride which has a relatively strong chelation ability effected the formation of *anti*-adduct.[6] (Entry 2). The best diastereoselectivity

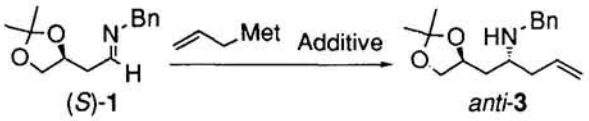

(*S*)-**1** → *anti*-**3**

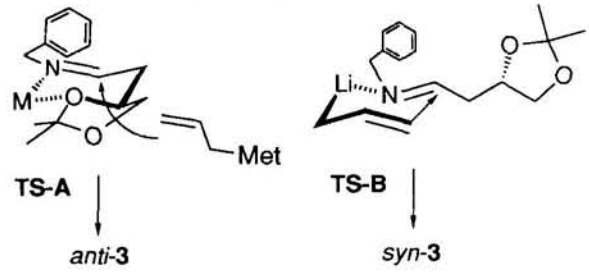
Table 1. Addition of Allyl Metal Reagents to Imine (*S*)-**1**[a]

Entry	Metal	Additive	Solv.	Temp./°C	Yield/%[b]	*anti* : *syn*[c]
1	MgCl	none	Et_2O	-78 ~ -30	62	67 : 33
2	MgCl	$CeCl_3$	THF	-78 ~ rt	54	89 : 11
3	MgBr	none	Et_2O	-78 ~ -55	19	52 : 48
4	$SnBu_3$[d]	$AlCl_3$	CH_2Cl_2	-78 ~ 0	33	>99 : <1
5	$SnBu_3$[e]	$AlCl_3$	CH_2Cl_2	-78 ~ 0	54	>99 : <1
6	$SnBu_3$[e]	$TiCl_4$	CH_2Cl_2	-78 ~ rt	trace	- : -
7	Li	none	Et_2O	-78 ~ rt	46	29 : 71

[a]The reaction was carried out with (*S*)-**1** : allyl metal : (additive) = 1.0 : 2.0 : (2.0). [b]Isolated yield. [c]Determined by HPLC analysis using a Merck Hibar column, and the relative configuration determined by ^{1}H-NMR coupling constant of the corresponding oxazolidinone derivatives.[8] [d](*S*)-**1** : allyl metal : additive = 1.0 : 0.9 : 0.9. [e](*S*)-**1** : allyl metal : additive = 1.0 : 0.8 : 0.7.

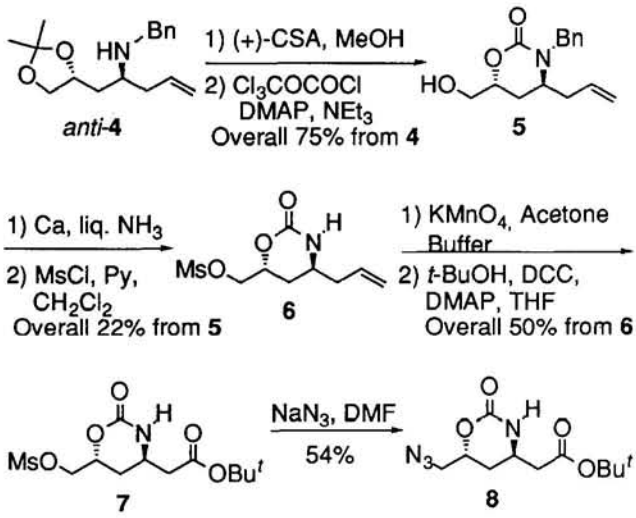
was obtained when the addition was carried out using allyltributylstannane in the presence of $AlCl_3$ and the *anti*-adduct *anti*-**3** was obtained as a sole product (Entries 4 & 5).[7] However, the use of $TiCl_4$ or $SnCl_4$ did not give the desired adduct in good yield but produced considerable amounts of decomposed products. It is also of note that the reversal of the diastereoselectivity was observed using allyl lithium, in which the *syn*-adduct was predominantly formed (Entry 7). The separation of the *anti*- from the *syn*-isomer was readily carried out on silica-gel thin layer chromatography.

The high *anti*-diastereoselectivity of the present addition is most reasonably explained in terms of a metal-chelated cyclic transition state, in which allyltributylstannane attacks from the stereo-electronically favored axial position (**TS-A**). On the other hand, in the case of allyl lithium, an allylation via a cyclic transition state may give the *syn*-adduct (**TS-B**).


TS-A → *anti*-**3**　　**TS-B** → *syn*-**3**

Thus, with the *anti*-selective addition conditions in hand, we next applied the present allylation to the synthesis of (+)-negamycin.[4] (+)-Negamycin **2** is an unusual antibiotic containing

an α-hydrazino acid and β-amino acid, which was isolated by Umezawa et al. in 1970 from *Streptomyces purpeofuscus*. It has a strong activity against gram-negative bacteria. The same allylation methodology was used for (*R*)-**1** prepared from D-malic acid. Hydrolysis of the acetonide of homoallyl amine *anti*-**4** in refluxing methanol in the presence of a catalytic amount of (+)-CSA was followed by oxazolidinone formation using trichloromethyl chloroformate and 4-dimethylaminopyridine to give **5** in 75% overall yield. The benzyl-protecting group at the nitrogen atom was removed with Ca in liquid ammonia, and subsequently the primary hydroxy group was mesylated to give **6** in 22% overall yield. The olefinic bond was oxidized with potassium permanganate in acetone-phosphate buffer (pH 7) to give the carboxylic acid, which was esterified with *t*-buty alcohol and DCC-DMAP to afford the ester **7** in 50% overall yield. Azidation was carried out with NaN_3 in DMF at 75 °C to give the azide **8** in 54% yield.[9] The azide **8** is a known key intermediate for the synthesis of (+)-negamycin **2**.[4f]



Scheme 1.

In conclusion, 1,3-asymmetric induction using allylation of β-alkoxyimine was successfully conducted utilizing a chelation intermediate to give *anti*-homoallyl amine with high diastereomeric excess. The homoallyl amine thus obtained was readily converted into a key intermediate for the synthesis of an antibiotic, (+)-negamycin. This kind of strategy for 1,3-asymmetic induction will find useful applications for the preparation of 1,3-amino alcohols of biological importance.

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1 See for example, "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford, Vol. 1, (1991), and the references cited therein. M. T. Reetz, in "Organometallics in Synthesis," ed by M. Schlosser, John Wiley & Sons, New York, pp. 198-282 (1994).

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7 A typical procedure for the allylation is as follows: To a susupension of $AlCl_3$ (6.4 mg, 0.048 mmol) in CH_2Cl_2 (0.7 mL) was added a solution of the imine (*S*)-**1** (15.8 mg, 0.068 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C. To the resulting mixture was added allyltributylstannane (17.9 mg, 0.054 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C, and the whole mixture was gradually warmed to 0 °C during 12 h. Usual work-up followed by purification on preparative silica-gel TLC gave the adduct *anti*-**3** (8.1 mg, 54%) as a pale yellow oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.40 (s, 3 H), 1.48-1.84 (m, 2 H), 2.28 (dd, 2 H, *J* = 6.75 & 13.05 Hz), 2.70-2.85 (m, 1 H), 3.50 (dd, 1 H, *J* = 7.92 & 15.51 Hz), 3.75 (d, 1 H, *J* = 12.86 Hz), 3.83 (d, 1 H, *J* = 12.86 Hz), 3.99-4.31 (m, 2 H), 5.10 (unresolved d, 1 H, *J* = 15.17 Hz), 5.13 (unresolved d, 1 H, *J* = 12.86 Hz), 5.70-5.85 (m, 1 H), 7.28-7.32 (m, 5 H); $[\alpha]_D^{23}$ -2.72 (c 0.37, $CHCl_3$).

8 Oxazolidinone formation was carried out as follows: To a mixture of the diol (88.4 mg, 0.32 mmol) prepared by the deacetonization of the adduct *anti*-**4**, Et_3N (0.18 mL, 1.28 mmol), and DMAP (1.9 mg, 0.016 mmol) in CH_2Cl_2 (3.0 mL) was added trichloromethyl chloroformate (0.02 mL, 0.55 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2.5 h and then at room temp. for 7.0 h. The mixture was cooled to 0 °C, added with another portion of trichloromethyl chloroformate (0.017 mL, 0.45 mmol), and allowed to stand at room temp. for 19 h. Usual work-up followed by purification on silica-gel TLC gave the oxazolidinone **5** (62 mg, 75% from *anti*-**4**) as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.85-1.89 (m, 2 H), 2.19-2.31 (m, 1 H), 2.53-2.58 (m, 1 H), 3.31-3.45 (m, 2 H including a hydroxy proton), 3.66 (dd, 1 H, *J* = 4.95 & 12.21 Hz), 3.80 (dd, 1 H, *J* = 3.30 & 12.21 Hz), 4.21 (d, 1 H, *J* = 16.16 Hz), 4.47-4.56 (m, 1 H), 5.10 (d, 1 H, *J* = 16.16 Hz), 5.12 (unresolved d, 2 H, *J* = 9.90 Hz), 5.56-5.71 (m, 1 H), 7.24-7.35 (m, 5 H). On irradiation at 4.54 or 3.65 ppm, protons appeared in 1.85-1.89 (m) or 4.47-4.56 (m) became double doublets at 1.85 (dd, 1 H, *J* = 2.44 & 14.04 Hz) and 1.88 (dd, 1H, *J* = 5.03 & 14.04 Hz), or at 4.54 (unresolved dd, 1 H, *J* = 4.28 & 10.39 Hz), respectively. $[\alpha]_D^{23}$ -53.8 (c 0.98, $CHCl_3$).

9 ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 9 H), 1.71-1.92 (m, 2 H), 2.35 (dd, 1 H, *J* = 3.97 & 5.26 H), 2.42 (dd, 1 H, *J* = 9.76 & 15.26 Hz), 3.50 (dd, 1 H, *J* = 5.49 & 12.82 Hz), 3.57 (dd, 1 H, *J* = 5.49 & 12.82 Hz), 3.70-3.80 (m, 1 H), 4.39-4.44 (m, 1 H) 5.88 (brs, 1 H); $[\alpha]_D^{23}$ -73.9 (c 0.046, $CHCl_3$).