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Enantioselective One-Pot Synthesis of β-Lactams from Achiral 2-Pyridylthioesters and Aromatic Imines

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Abstract: *The enolates derived from 2-pyridylthioesters by reaction with $BCl_3 \cdot SMe_2$ and enantiomerically pure aminoalcohols react with aromatic imines in an enantioselective fashion (ee up to 78%) to afford β-lactams in a convenient one-pot procedure.*

In the last few years we described a convenient one-pot synthesis of β-lactams by the condensation of titanium[1] and tin[2] enolates of 2-pyridylthioesters with imines. The enolates were easily generated by addition of triethylamine to a mixture of MX_4 (M = Ti, Sn; X = Cl, Br) and of the thioester in CH_2Cl_2 at low temperature.[3] While control of the absolute stereochemistry of the products was efficiently achieved with enantiomerically pure substrates [4] and auxiliaries,[5] the use of chiral metal ligands has given unsatisfactory results so far.

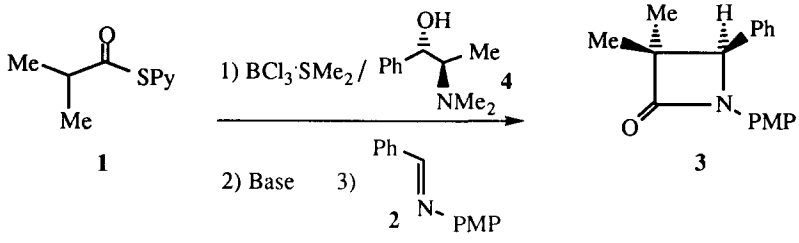
Continuing the study in this field, we have recently found that also BCl_3 and BBr_3 can promote the azetidinone synthesis.[6] More interestingly, we also discovered and we here report that the combined use of BCl_3 and chiral aminoalcohols in our reaction results in an operationally very simple, enantioselective *one-pot* synthesis of β-lactams. To the best of our knowledge, this is the first example of such a process to be described in the literature.[7]

The condensation of 2-pyridylthioisobutyrate **1** with *N*-4-methoxyphenyl (PMP) benzaldimine **2** to give azetidinone **3** was chosen as a model reaction. The chiral boron species was prepared by stirring $BCl_3 \cdot SMe_2$ (2 mol equiv, 1M in CH_2Cl_2) with (1S,2R)-*N*-methylephedrine **4** (1 mol equiv) in CH_2Cl_2 at RT.[8] To a mixture of this adduct and of the thioester **1** (1 mol equiv) cooled at -78°C in CH_2Cl_2, a tertiary amine (1 mol equiv) was added. After an enolization time of 30 min, imine **2** was also added, and the reaction was allowed to warm up to RT and continued overnight at that temperature. β-Lactam **3** was obtained after work up with aq. $NaHCO_3$ and flash chromatography. Isolated yields and enantiomeric excesses (ee)[9] are reported in Table 1. The absolute configuration of the major enantiomer of **3** was easily assigned as described elsewhere[10] on the basis of the sign of the optical rotation of the *N*-unprotected β-lactam obtained in 92% yield by $Ce(NH_4)_2(NO_3)_4$ promoted degradation[11] of the PMP group.

As can be seen from the reported data, the use of (1S,2R)-**4** both as the chiral ligand and as the tertiary

amine (entries 5-7) resulted in a good yield (up to 74%) and stereoselectivity (up to 78%). Ancillary experiments carried out in the conditions of entry 1 (Table 1) with (1S,2R)-ephedrine (86% yield, <5% ee) and with *O,N*-dimethylephedrine (37% yield, 28% ee) instead of **4** showed the importance of both the tertiary amino and of the unprotected hydroxyl groups.

Table 1. Enantioselective Synthesis of β-Lactam **3**.



Entry	Base	Yield %[c]	ee %
1	Et_3N[a]	70	38
2	Quinuclidine[a]	61	45
3	DABCO[a]	37	65
4	DBU[a]	37	40
5	(1S,2R)-**4**[a]	41	78
6	(1S,2R)-**4**[b]	72	72
7	(1S,2R)-**4**[c]	74	78

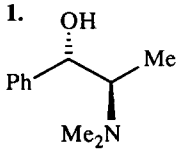
[a] NME + BCl_3 reaction time 1h. The solvent was evaporated before addition of **1**. [b] NME + BCl_3 reaction time 16h.
[c] NME + BCl_3 reaction time 1h. The solvent was not evaporated before the additon of **1**.

Aminoalcohols **5-9** (Chart 1) were also tested in the synthesis of **3** (conditions of entry 5 of Table 1) in order to find other efficient chiral promoters and to identify the factors affecting the stereochemical result. The data reported in brackets in Chart 1 clearly show that none of these N,N-dimethylaminoalcohols performed better than (1S,2R)-**4**. The presence of two stereocenters on the aminoalcohols appears to be important for achieving a good stereocontrol, as can be seen comparing the results obtained with (1S,2R)-**4** to those obtained with (S)-**8** and (R)-**9**. Furthermore, the two stereocenters should be arranged as in **4**, since the use of its C-2 epimer (1S,2S)-*N,N*-dimethyl *pseudo*ephedrine **7** clearly gives lower ee. However, the (1S,2R) configuration of the aminoalcohol does not secure *per se* high level of stereoselectivity as it is shown by the behavior of compound **6**. Finally, it is worth mentioning that an increase in the steric bulkiness at nitrogen (as in **5**) has virtually no effect on stereoselectivity. An increase in the bulkiness of the C-2 substituent (as in **6**) can be detrimental.

Chiral promoter (1S,2R)-**4** was then used (in the conditions of entry 7, Table 1) for the reaction of thioesters **10** and **11** with imine **2**, and of thioester **1** with imines **12-14** to afford β-lactams **15-19** (Chart 2

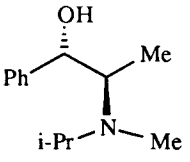
and Table 2).[12] The synthesis of compounds **15** and **16** afforded a moderate excess of the *trans* (**t**) products over the *cis* (**c**) ones.[13] The absolute configuration of the major enantiomer of **15t** was established as (3R,4S) following the procedure described above.[10] The ligand disposition at C-4 shared by the major enantiomers of β-lactams **3** and **15t** [14] was reasonably extended to the major enantiomers of compounds **16t**, **17**, **18**, and **19**.

Chart 1.



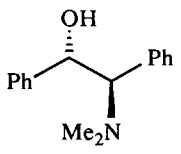
(1S,2R)-**4**

[Y = 41%; ee = 78%]



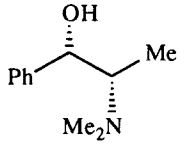
(1S,2R)-**5**

[Y = 45%; ee = 72%]



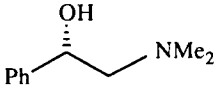
(1S,2R)-**6**

[Y = 48%; ee = 20%]



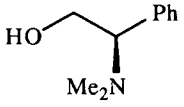
(1S,2S)-**7**

[Y = 45%; ee = 20%]



(S)-**8**

[Y = 48%; ee = 5%]

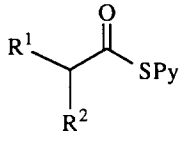


(R)-**9**

[Y = 16%; ee < 5%]

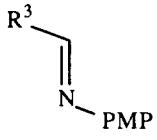
As can be seen from the data reported in Table 2, compounds **15-19** were obtained in moderate to good yields and with stereoselectivities comparable to those obtained in the synthesis of **3** (entry 7, Table 1).

Chart 2.



10 R^1 = Et; R^2 = H

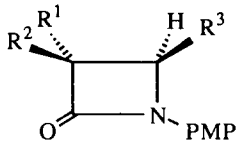
11 R^1 = $PhCH_2O$; R^2 = Et



12 R^3 = 4-MeOPh

13 R^3 = 2-Furyl

14 R^3 = 2-Thienyl



15t R^1 = Et; R^2 = H; R^3 = Ph

15c R^1 = H; R^2 = Et; R^3 = Ph

16t R^1 = $PhCH_2O$; R^2 = H; R^3 = Ph

16c R^1 = H; R^2 = $PhCH_2O$; R^3 = Ph

17 R^1 = R^2 = Me; R^3 = 4-MeOPh

18 R^1 = R^2 = Me; R^3 = 2-Furyl

19 R^1 = R^2 = Me; R^3 = 2-Thienyl

only one enantiomer is shown for simplicity

In conclusion the first one-pot enantioselective synthesis of β-lactams was performed by reaction of achiral imines with enolates that feature an enantiopure metal ligand. Work is underway in our laboratory to elucidate the role played by the aminoalcohol both as the ligand and as the base, the inter- or intramolecular

nature of the deprotonation step, the structure of the enolate, and the origin of the stereocontrol,[15] with the aim of increasing the stereoselectivity and of widening the scope of the reaction.

Table 2. Enantioselective Synthesis of β-Lactams **15 - 19**.

Thioester	Imine	Product	Yield%	t/c ratio	ee%
10	**2**	**15tc**	60	70/30	55[c]
11	**2**	**16tc**	50	75/25	74[c,d]
1	**12**	**17**	42	-	62
1	**13**	**18**	52	-	51
1	**14**	**19**	39	-	68

[a] Isolated yields. [b] As determined by 300 MHz ^{1}H NMR analysis of the crude reaction product.[c] Of the *trans* isomer. [d] Ee of *cis* isomer was 14%.

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6. No appreciable improvements in yield and diastereoselection were observed using boron instead of titanium ot tin enolates (unpublished results from this laboratory).
7. A two-step enantioselective synthesis of β-lactams promoted by boron enolates featuring chiral metal ligands has been recently reported: (a) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32* , 5287. For a multistep synthesis of β-lactams based on a doubly stereoselective approach that exploits a chiral Lewis acid and a chiral imine see: (b) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151.
8. For a similar preparation of related chiral boron reagents see: Kobayashi, S.; Murakami, M.; Harada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1341.
9. Ee's were determined by 300 MHz ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ under conditions pre-established on racemic samples.
10. Pirkle, W. H.; Tsipouras, A.; Hyun, M. H.; Hart, D. J.; Lee, C.-S. *J. Chromatogr.* **1986**, *358*, 377.
11. Georg, G. I.; Kant, J.; Gill, H. S. *J. Am. Chem. Soc.* **1987**, *109*, 1129.
12. The *N*-PMP imines derived from cinnamaldehyde, 2-methyl cinnamaldehyde, and cyclohexyl carbaldehyde were also reacted with **1**, but no β-lactam formation was observed in these cases.These imines were readily hydrolyzed under the reaction conditions, and 4-methoxyaniline isobutyramide was the main isolated reaction product.
13. *Trans* and *cis* assignments were based on the value of the HC-3/HC-4 coupling constant (J_{trans} = 2.0 Hz; J_{cis} = 5.5 Hz).
14. An analogous ligand disposition at C-4 results in different stereodescriptors for compounds **3** and **16** (4S) and for compounds **15**, **17**, **18**, and **19** (4R).
15. A boat-like cyclic transition structure that features attack of the E-imine (see ref. 7a) on the enolate face not hindered by the bulkier substituents at the stereocenters of (1S,2R)-**4** can be used as a tentative model of stereoselection to explain the observed stereochemical outcome.

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