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β-LACTAM SYNTHESIS BY DIASTEREOSELECTIVE CONDENSATION OF CHIRAL 3-(*p*-TOLYLSULFINYL)-2-FURALDIMINE AND ESTER ENOLATES

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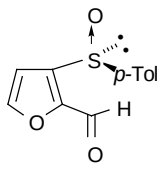
Abstract- Highly diastereoselective condensation of chiral sulfinyl-substituted furaldimine with lithium ester enolates has been achieved, affording (3*R*)-*syn*-β-lactams and/or (3*R*)-*syn*-β-amino esters, as the major products.

The Lewis acid-promoted[1] and -catalyzed[2] condensations of imines with silyl ketene acetals or ester enolates are the powerful methods for preparing β-lactams and β-amino esters.[3] To effect high levels of asymmetric induction, chiral versions of the condensation have also been devised by the use of imines with a chiral auxiliary,[1,4] chiral ester enolate derivatives,[5] and chiral Lewis acids.[6] Most studies on these enantioselective reactions, however, have dealt with 1,3-asymmetric inductions. On the other hand, little work has been done on the remote asymmetric induction for the imine—enolate condensations. As part of our own efforts to develop remote asymmetric induction using chiral sulfoxides, we previously reported the lanthanoid triflate-catalyzed Mukaiyama aldol reaction of sulfinyl aldehyde (**1**) with such silyl ketene acetals as **2**.[7] Remote stereocontrol of **1** in this reaction led us to examine the condensation of the aldimine (**3**) derived from **1** in 74% yield.



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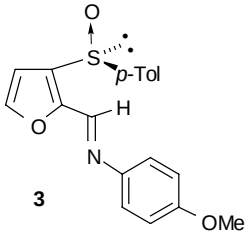

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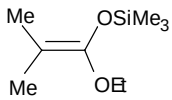


2

At first we undertook the reaction of **3** with **2** in the presence of a lanthanoid triflate, $Yb(OTf)_3$ since lanthanoid triflates are effective for the aldol condensation of the aldehyde (**1**).[7] The reaction proceeded smoothly; however, diastereoisomeric β-amino esters (**4**) and (**5**) were produced in a ratio of 1:1 (Table 1, Entry 1).[8]

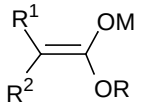
We thus next turned to the use of ester enolate (**6**) for the reaction. Table 1 indicates the metal effect of the addition reaction of **6**, which shows the lithium enolate (**6**) (M = Li) is superior to other metal enolates for both the diastereoselectivities and the yields. The reaction was carried out by the use of Et_2O or THF as solvent.[9] Attempts to use zinc and titanium enolates[10] (**6**) (M = ZnCl, $TiCl_3$) were unsuccessful, resulted in the recovery of starting material (**3**). In contrast to the reaction with **2**, β-amino esters (**4**) and (**5**) were not produced[11]; whereas, β-lactams (**7**) and (**8**) were obtained exclusively. It is probable that the products distribution (β-lactam *vs* β-amino ester) depends on the reaction conditions (amounts of enolate and/or the solvent used) and a kind of the enolates. In some case where the reaction

was carried out with less than 2 equiv of the Li enolate (Entries 4 and 5), the reaction gave not only β-lactams but also β-amino esters. Instead, the use of more than 2 equiv of the enolate resulted in the exclusive formation of β-lactams and in good yields.[12] The stereochemical assignment of C(3) center in major β-lactam (**7**) was confirmed by single crystal X-Ray analysis.[13]

Table 1. Condensation of **3** with Enolates (**2**) and (**6**)[a]

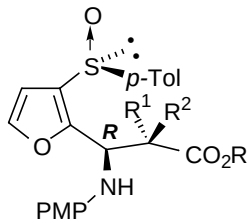
Entry	Enolate	(M)	(Equiv)	Solvent	Time/h	yield/%	Product Ratio	de/%
1	**2**[b]		2	THF	15	98	50:50 (**4**:**5**)	0
2	**6**	MgBr[c]	4	Et_2O	1	70	94:6 (**7**:**8**)	88
3	**6**	$AlCl_2$[d]	4	THF	1	93	90:10 (**7**:**8**)	80
4	**6**	Li	1.5	THF	1	67	95.5:4.5 (**7**:**8**)[e]	91
5	**6**	Li	1.5	Et_2O	1	85	98.5:1.5 (**7**:**8**)[e]	97
6	**6**	Li	4	THF	1	84	95.5:4.5 (**7**:**8**)	91
7	**6**	Li	4	Et_2O	1	99	97.5:2.5 (**7**:**8**)	95

[a] Reaction was carried out at −78 °C for 15 min and then the reaction mixture was allowed to room temperature over a period of 45 min except for Entry 1. [b] The reaction was conducted at room temperature in the presence of 0.2 equiv of $Yb(OTf)_3$ as a promotor. [c] Prepared from the lithium enolate and $MgBr_2$•Et_2O. [d] Prepared from the lithium enolate and $AlCl_3$. [e] With the use of less than 2 equiv of LDA, the amino esters (**4**) and (**5**) were also produced in 7—11% yields.

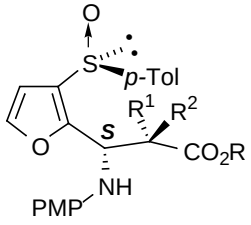


6: R = Et, R^1 = R^2 = Me, M = metal
9: R = *t*-Bu, R^1= R^2 = H, M = Li
12: R = Et, R^1 = H, R^2 = Me, M = Li
(*E*)-17: R = Me, R^1= H, R^2 = OTBDMS, M = Li
(*Z*)-17: R = Me, R^1= OTBDMS, R^2 = H, M = Li

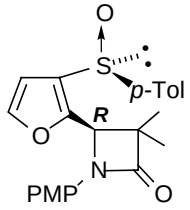
PMP = *p*-methoxyphenyl
TBDMS = *t*-butyldimethylsilyl



4: R = Et, R^1 = R^2 = Me
10: R = *t*-Bu, R^1= R^2 = H
18: R = Me, R^1 = H, R^2 = OTBDMS
19: R = Me, R^1 = OTBDMS, R^2 = H



5: R = Et, R^1= R^2 = Me
11: R = *t*-Bu, R^1= R^2 = H



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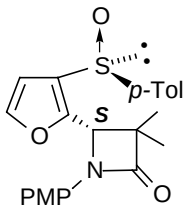

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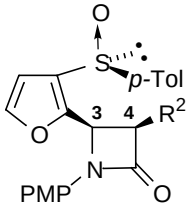
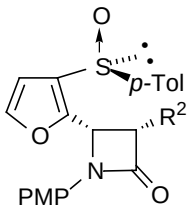
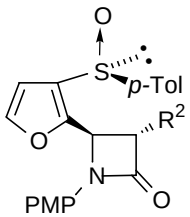


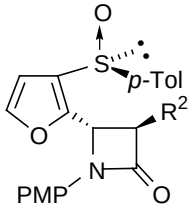
13: R^2 = Me
20: R^2 = OTBDMS



14: R^2 = Me
21: R^2 = OTBDMS



15: R^2 = Me
22: R^2 = OTBDMS



16: R^2 = Me
23: R^2 = OTBDMS

Some results of the condensation with other enolates are summarized in Table 2. When the reaction was carried out with the lithium enolate (**9**) under the similar conditions, (3*R*)-β-amino ester (**10**) was obtained exclusively, accompanied by a small amount of (3*S*)-isomer (**11**) (96% de, 98% yield).[14] On the other hand, the condensation of **3** with a trisubstituted lithium enolate (**12**) gave rise to *syn*-β-lactam (**13**) and *anti*-β-lactam (**15**) as the major isomers, respectively.[15] The major *syn*-β -lactam (**13**) was isolated in isomerically pure form, and the stereochemistry was unequivocally established by single crystal X-Ray analysis.[13] Although the *anti* relationship of the major β-lactam (**15**) was assumed by the vicinal coupling constant between C(3) and C(4) protons ($J_{syn} > J_{anti}$)[3−5] in the ^{1}H NMR spectrum, the absolute stereochemistry was confirmed by transformation of **13** into **15** by isomerization experiments. With the silyloxy enolate (**17**) {(*E*)-enolate enriched[16]}, (3*R*)-amino esters (**18**) and (**19**)[14] were produced as the major *syn*- and *anti*-products, accompanied by small amounts of (3*R*)-β-lactams (**20**) and (**22**). Amino esters (**18**) and (**19**) obtained were cyclized respectively into **20** and **22** upon treatment with lithium hexamethyldisilazide.[3,5]

Table 2. Condensation of **3** with Lithium Enolates[a]

Entry	Enolate	Product	*syn* : *anti*	de/% (*syn/anti*)	Yield/%
1	**9**	**10** and **11**	—	96	98
2	**12**	**13**—**16**[b]	67:33	89/71	89
3	**17**	**18** and **19**[c]	84:16	>98/>98	80

[a] All the reaction was conducted in *ca*. 0.3 mmol scale with 4 equiv of the lithium enolate in THF at −78 °C (15 min), and then the mixture was allowed to warm to room temperature (45 min). [b] Small amounts of the corresponding amino esters were also produced in variable yields. The ratio of the amino esters was not determined. [c] The β-lactams (**20**) and (**22**) were also produced in 8% and <1% yields, respectively; however, the formation of (**21**) and (**23**) was not detected in the ^{1}H NMR spectrum of the crude product.

Although the detailed reaction mechanism is not clear, it is likely that the facts obtained are consistent with the stereochemical outcome which involves the conventional Zimmerman—Traxler chair transition state model[17] (Figure 1). With the lithium enolates, a chelating model A would be favored over a transition state B. The six-membered chelate B should not be attained preferentially by a severe steric repulsion of the alkoxy group with the bulky *p*-tolyl substituent.

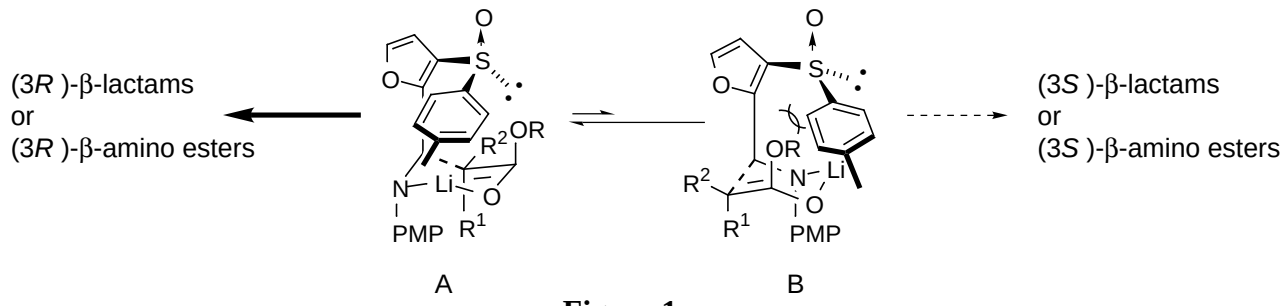


Figure 1

In summary, chirally functionalized β-lactams were synthesized from the imine and the lithium enolate with high diastereoselectivities and in excellent yields. In sharp contrast to 1,2- or 1,3-asymmetric inductions in imine—ester enolate condensations reported previously, our results obtained revealed that 1,4-stereocontrol (= remote asymmetric induction) has been achieved by the use of the sulfinyl furaldimine (**3**). Further studies are in progress on the condensation with other enolates.

ACKNOWLEDGMENT

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11. Predominant formation of β-lactams would reflect that the ring closure reaction proceeds at a greater rate on the geminal (*i.e.* dimethyl) substitution: P. D. Bartlett, *J. Chem. Educ.*, 1953, **30**, 22; T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, 1960, **82**, 5858.
Hydrolysis of **7** and subsequent esterfication gave **4**, thus confirming the assignment of structure (**4**).
12. For example, see: P. Andreoli, G. Cainelli, M. Contento, D. Giacomini, G. Martelli, and M. Panunzio, *J. Chem. Soc., Perkin Trans. 1*, 1988, 945.
13. Details for X-Ray data will be reported in full paper. X-Ray measurements were performed on a RIGAKU AFC5R and a RIGAKU RAXIS—RAPID diffractometer with Mo–Kα radiation. Crystal data; **7**: $C_{23}H_{23}NO_4S$, M = 409.5, monoclinic, space group $P2_1/c$(No 14), a = 11.072(4) Å, b = 9.032(5) Å, c = 21.936(5) Å, β = 101.95(3)°, V = 2146(1) Å^3, D_{calc} = 1.267 g cm^{-3}, Z = 4; Number of reflections observed (I>3σ(I)) = 1901, R = 0.056, R_w = 0.094; **13**: $C_{22}H_{21}NO_4S$, M = 395.5, triclinic, space group P1(No 2), a = 11.244(2) Å, b = 11.755(3) Å, c = 8.168(2) Å, α = 99.05(1)°, β = 109.73(1)°, γ = 91.52(2)°, V = 999.9(4) Å^3, D_{calc} = 1.313 g cm^{-3}, Z = 2; Number of reflections observed (I>3σ(I)) = 3584, R = 0.045, R_w = 0.067.
All new compounds have been characterized by IR, NMR, and MS spectrometry. Selected physical data: **3**: mp 60—61 °C (hexane—EtOAc); $[\alpha]_D^{24}$ −444° (*c* 1.0, $CHCl_3$); **7**: mp 150—152 °C (Et_2O), $[\alpha]_D^{23}$ −30.9° (*c* 1.3, $CHCl_3$); **10**: An oil; $[\alpha]_D^{22}$ −69.4° (*c* 0.3, $CHCl_3$); **13**: mp 113—114 °C (Et_2O), $[\alpha]_D^{19}$ +20.8° (*c* 0.8, $CHCl_3$).
14. Stereochemical assignments are by analogy with the results obtained with **2** and **6**.
15. THF was used as solvent since when the reaction was carried out in Et_2O and/or in the presence of HMPA, β-amino esters were also produced in variable yield. Judging from preliminary experiments in the presence of HMPA, the ratio of *syn*- and *anti*-esters was reversed, affording the *anti*-β-amino esters preferentially. For example, a report of the reversal in diastereoselection in HMPA—THF, see: T. Chiba, M. Nagatsuma, and T. Nakai, *Chem. Lett.*, 1984, 1927.
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