Pergamon

Tetrahedron Letters 42 (2001) 5489–5492

TETRAHEDRON
LETTERS

Indium-mediated diastereoselective allylation reactions: preparation of *tert*-α-hydroxy acids

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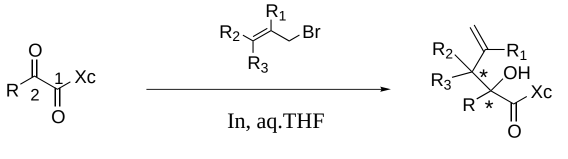
Received 16 March 2001; revised 11 June 2001; accepted 15 June 2001

Abstract—Indium-mediated allylation reactions of α-ketoimides derived from Oppolzer's sultam were accomplished in aqueous THF in good yields and excellent diastereomeric excesses. It could be a useful method for the preparation of enantiopure *t*-α-hydroxy acids. When the substituent of α-ketoimides was changed from phenyl to thiophenyl or furyl group, diastereoselectivity decreased in comparison to *N*-phenyl derivatives, but changing solvent to aqueous ethanol provided improved levels of diastereoselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

Much effort has been devoted to the preparation of α-hydroxy acids in enatiomerically pure form of either configuration, because of their important, diverse biological functions and the utility as chiral building blocks.[1] Several methods for the preparation of optically active α-hydroxy acids have been reported.[2] Especially, Jurczak reported diastereoselective addition to chiral α-ketoimides derived from Oppolzer's sultam with several allylic reagents.[3]

Herein, we report a highly diastereoselective indium-mediated allylation to chiral α-ketoimides derived from Oppolzer's sultam (Scheme 1).



1 Xc = (+) Oppolzer's sultam
2 Xc = (-) Oppolzer's sultam
R = phenyl, thiophenyl, furyl

3
4

Scheme 1.

Indium-mediated allylation to *N*-phenylglyoxyloyl-(2*R* or 2*S*)-bornane-10,2-sultam (**1** and **2**) with various allyl bromides in aqueous THF ($H_2O/THF = 3/1$, *v*/*v*) at room temperature for 1 ∼ 3 h afforded the corresponding homoallylic alcohols **3** and **4**, respectively with >99:1 dr at C2 in high yields. The results are summarized in Table 1. The absolute configuration of homoallylic alcohol **3a** (entry 1) was determined by X-ray crystallography (Fig. 1). In the case of crotyl bromide (entry 3 and 4), only a single isomer **3b** and **4b** of expected four diastereomers were obtained, respectively, and absolute configuration of **3b** was also determined by X-ray crystallography (Fig. 2).

In entries 5 and 6, 4-bromo-2-methyl-2-butene also provided a single isomer in lower yield compared to other allyl bromides presumably due to the steric crowding.

The high diastereoselectivity of allylation could be explained by the chelated conformer **A** where allylation prefers the less hindered face (Fig. 3).[6] The origin of the excellent selectivity of *syn*/*anti* in crotyl case (entries 3 and 4) is not entirely clear at this moment. However, if the 6-membered ring chelation with indium as shown in Fig. 3 is formed, structure **B** with methyl group of crotyl indium in the axial position might be more favored than structure **C** due to the interaction of methyl group in the equatorial position and phenyl group of α-ketoimide. All the addition products were

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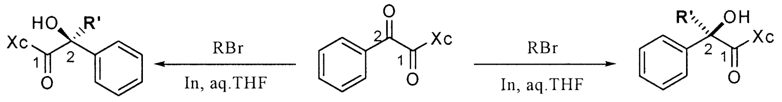
PII: S0040-4039(01)01064-4

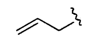
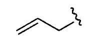
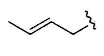
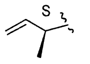
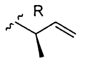
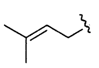
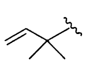
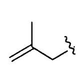
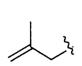
Table 1. Allylation reactions of *N*-phenylglyoxyloyl-(2*R*/2*S*)-bornane-10,2-sultam (**1**, **2**)



4
Xc = (-) sultam

1: Xc = (+) sultam
2: Xc = (-) sultam

3
Xc = (+) sultam

Entry	Substrate	R	Product (R')	Yield (%)^a		$[\alpha]_D^{25}$ (c=1, $CHCl_3$)	dr^b (R:S at C2)	Config^d
1	**1**			**3a**	97	+149.6°	>99:1	*R*
2	**2**			**4a**	98	-145.4°	>1:99	*S*
3	**1**			**3b**	86	+111.5°	>99:1	*R*
4	**2**			**4b**	96	-111.1° (c=0.65)	>1:99	*S*
5	**1**			**3c**	55(69^c)	+156.1°	>99:1	*R*
6	**2**			**4c**	54(70^c)	-156.9°	>1:99	*S*
7	**1**			**3d**	82	+146.2° (c=0.90)	>99:1	*R*
8	**2**			**4d**	84	-146.2° (c=0.90)	>1:99	*S*

^{a}Isolated yields, ^{b}Diastereomeric ratio was determined by HPLC. ^{c}Yield based on the consumed starting substrate ^{d}Absolute configuration at C2 of the major compound

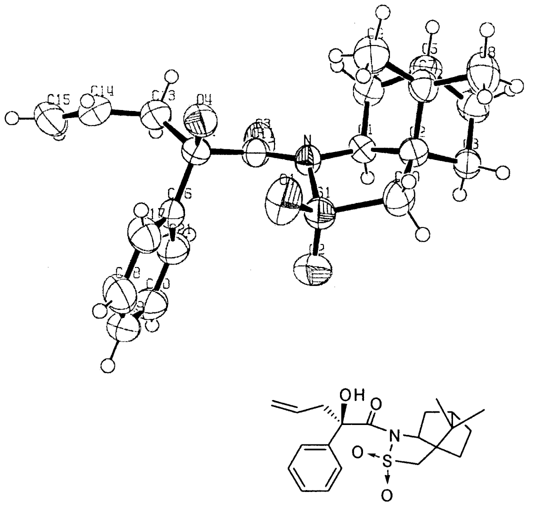


Figure 1. ORTEP drawing of **3a**.[4]

obtained with excellent diastereoselectivity that showed superiority over other allylic metal reagents reported[3].

The indium-mediated allylations to *N*-thiophenylglyoxyloyl-(2*R*)-bornane-10,2-sultam **5** and *N*-furylglyoxyloyl-(2*R*)-bornane-10,2-sultam **7** were investigated (Tables 2 and 3). In most cases, diastereoselectivity decreased in comparison with the *N*-phenyl derivatives under the same reaction conditions. In order to enhance the diastereoselectivity, several solvents were employed. Among them, 90% aqueous EtOH gave improved diastereoselectivity compared to the 25% aqueous THF condition as shown in Table 2. However, in the case of entry 4, 3-bromo-2-methylpropene, high diastereoselectivity was achieved in 25% aqueous THF, while no reaction occurred in 90% aqueous EtOH. The lower diastereoselectivity of thiophenyl and furyl α-ketoimides compared to the phenyl deri-

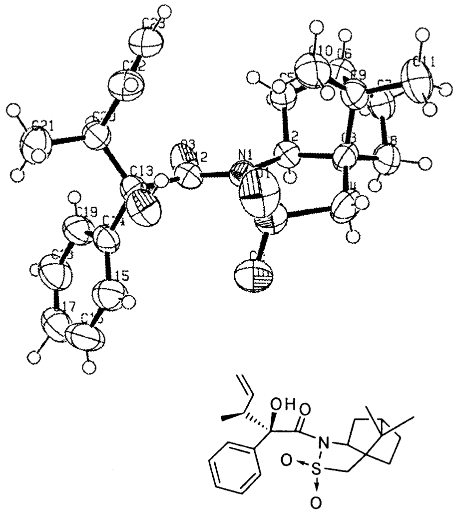


Figure 2. ORTEP drawing of **3b**.[5]

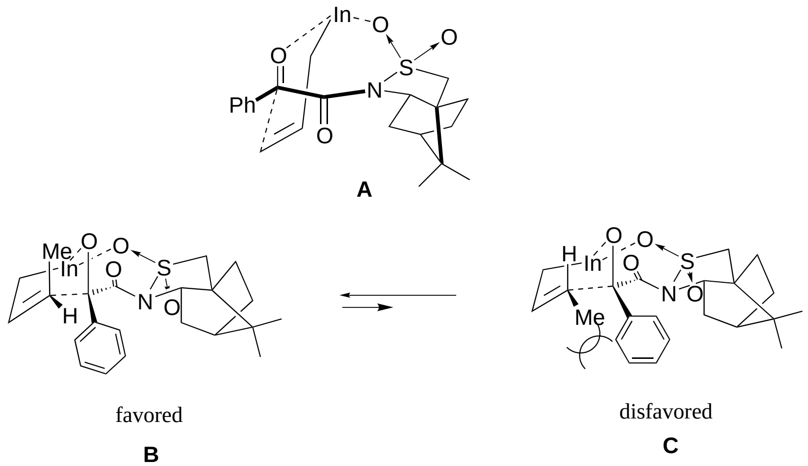
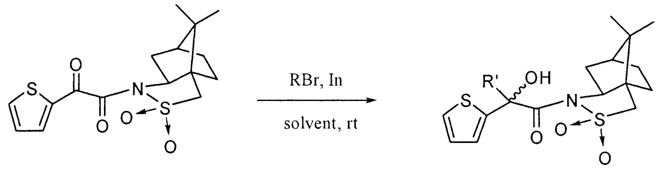


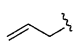
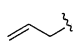
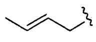
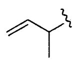
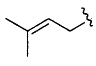
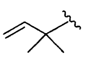
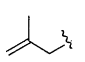
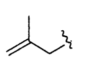
Figure 3. Plausible transition state model.

Table 2. Allylation reactions of *N*-thiophenylglyoxyloyl-(2*R*)-bornane-10,2-sultam



5

6

Entry	R	Product (R')	Solvent	Yield (%)[a]	dr[b]
1			25% aq. THF	81	72:28
			90% aq. EtOH	89	95:5
2			25% aq. THF	89	92:8
			90% aq. EtOH	95	95:5
3			25% aq. THF	77	75:25
			90% aq. EtOH	62	84:16
4			25% aq. THF	56	99:1
			90% aq. EtOH	nr[c]	-

[a]Isolated yields, [b]Diastereomeric ratio was determined by HPLC. [c]No reaction

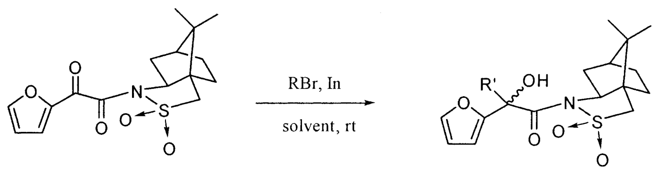
vatives might be due to the chelation of the sulfur or oxygen atom of heterocylcles with indium, which, as a result, could disturb a chelation of carbonyl and indium.

In conclusion, indium-mediated allylation reactions of α-ketoimides derived from Oppolzer's sultam were accomplished in aqueous media in good yields and with high diastereoselectivity.[7] When the substituent of α-ketoimides was changed from phenyl to thiophenyl or furyl group, a decrease in diastereoselectivity was observed, but improvement could be achieved by changing solvent to aqueous ethanol.

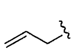
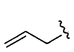
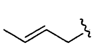
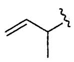
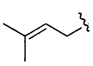
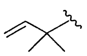
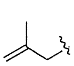
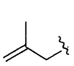
Acknowledgements

This project was financially supported by the Korea Ministry of Science and Technology (Critical Technology-21) and the Center for Molecular Design and Synthesis (CMDS), KAIST.

Table 3. Allylation reactions of *N*-furylglyoxyloyl-(2*R*)-bornane-10,2-sultam



7 **8**

Entry	R	Product (R')	Solvent	Yield (%)^a	dr^b
1			25% aq. THF	89	69:31
			90% aq. EtOH	88	75:25
2			25% aq. THF	79	64:36
			90% aq. EtOH	84	71:29
3			25% aq. THF	trace	-
			90% aq. EtOH	trace	-
4			25% aq. THF	54	62:38
			90% aq. EtOH	61	69:31

^{a}Isolated yields, ^{b}Diastereomeric ratio was determined by HPLC.

References

1. (a) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids In Enantioselective Synthesis*; Academic Press: Weinheim, 1977; (b) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D. J. W., Ed.; Academic Press: New York, 1984; Vol. 4; (c) Lee, J. B.; Downie, I. M. *Tetrahedron* **1967**, *23*, 357; (d) Mori, K; Takigawa, T.; Matsuo, T. *Tetrahedron* **1979**, *25*, 933.
2. (a) Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120; (b) Wang, Z.; La, B.; Fortunak, J. M. *Tetrahedron Lett.* **1998**, *39*, 5501; (c) Chang, J.-W.; Jang, D.-P.; Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *Org. Lett.* **1999**, *1*, 2061; (d) Wang, Z.; Meng, X.-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5677; (e) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221.
3. Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 1009.
4. Data are as follows: $C_{21}H_{27}NO_4S$, monoclinic, space group; $P2_1$ (No. 4), final R indices; [I>2 sigma(I)] $R1=0.0440$, $wR2=0.1089$
5. Data are as follows: $C_{21}H_{27}NO_4S$, monoclinic, space group; $P2_1$, final R indices; [I>2 sigma(I)] $R1=0.0464$, $wR2=0.1205$
6. Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149.
7. Typical reaction procedure is as follows: *N*-phenylglyoxyloyl-(2*R*)-bornane-10,2-sultam (**1**, entry 1, Table 1) (1.0 mmol) was dissolved in aqueous THF (5 mL, H_2O/THF = 3/1, *v*/*v*) followed by the addition of allyl bromide (5.0 mmol) and indium metal (3.0 mmol) at rt. After 2 h, the reaction mixture was filtered through Celite and washed with ethyl acetate. The filtrate was treated with a usual aqueous work-up procedure and purified by column chromatography on silica gel to give final products **3a** (377 mg, 97%). **3a**: ^{1}H NMR (300 MHz, $CDCl_3$ δ): 7.44 (d, 2H, Ar*H*), 7.30 ~ 7.19 (m, 3H, Ar*H*), 5.64 (m, 1H, CH_2=C*H*CH_2), 5.08 (2d, 2H, C*H*$_2$=CHCH$_2$), 4.24 (s, 1H, -O*H*), 3.93 (t, 1H, NC*H*CH$_2$), 3.28 (q, 2H, SO$_2$C*H*$_2$), 3.0 (dd, 1H, CH$_2$=CHC*H*$_2$), 2.55 (dd, 1H, CH$_2$=CHC*H*$_2$), 2.0 (m, 1H, camphor C*H*), 1.89 ~ 1.78 (m, 4H, camphor C*H*$_2$), 1.33 ~ 1.26 (m, 2H, camphor C*H*$_2$), 1.09 (s, 3H, (C*H*$_3$)$_2$C-), 0.87 (s, 3H, (C*H*$_3$)$_2$C-). ^{13}C NMR (300 MHz, $CDCl_3$ δ): 174.79, 139.59, 132.90, 128.51, 128.34, 125.88, 120.50, 80.97, 67.45, 53.68, 49.16, 48.20, 48.17, 45.06, 39.24, 33.34, 26.82, 21.34, 20.29. Elemental analysis: $C_{21}H_{27}NO_4S$: C, 64.6; H, 6.97; N, 3.57; S, 8.22%, [α] = +147.2° ($c=0.56$ in $CHCl_3$), mp 140.5 ~ 141.5°C