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STEREOSELECTIVE SYNTHESIS OF α-METHYLENE-γ-BUTYRO-LACTAMS FROM ETHYL 2-(BROMOMETHYL)ACRYLATE AND CHIRAL SULFINYL ALDIMINES MEDIATED BY INDIUM

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Abstract – The reaction of ethyl 2-(bromomethyl)acrylate (**1**) with chiral *N*-*tert*-butylsulfinyl aldimines **2** and indium powder in THF at 100 ºC for 48 h affords, after hydrolysis, a mixture of *N*-*tert*-butylsulfinyl aminoesters **3** and α-methylene-γ-butyrolactams **4**. From the reaction mixture, compounds **3** were quantitatively converted to the expected butyrolactams **4** after removal of the *tert*-butylsulfinyl group under acidic conditions and final basic workup. The whole process takes place in high overall yields and with fairly good stereoselectivities.

Homoallylic amines,[1] which are compounds of interest themselves because they can be intermediates in the synthesis of other nitrogenated materials, are easily accessible in enantioenriched form by asymmetric allylation of imines using chiral auxiliaries[2] or under asymmetric catalysis,[3] as well. Allyl indium species[4] are ideal allylating reagents in these processes. They can be generated in the presence of the imine from allyl halides and indium metal under mild reaction conditions and exhibit high tolerance to a wide range of functional groups in many solvents.[5] Among chiral auxiliaries, sulfinimines[6] have been widely studied, specially the *N*-*tert*-butylsulfinyl derivatives, due to the possibility of preparing both enantiomers in large scale processes,[7] and also because the chiral auxiliary can be easily removed under acidic conditions.[8] In addition, a practical process for recycling the *tert*-butylsulfinyl group upon deprotection of the *N*-*tert*-butylsulfinylamines has been recently reported.[9] On the other hand, the α-methylene-γ-butyrolactone and γ-butyrolactam rings are present in many bioactive natural products

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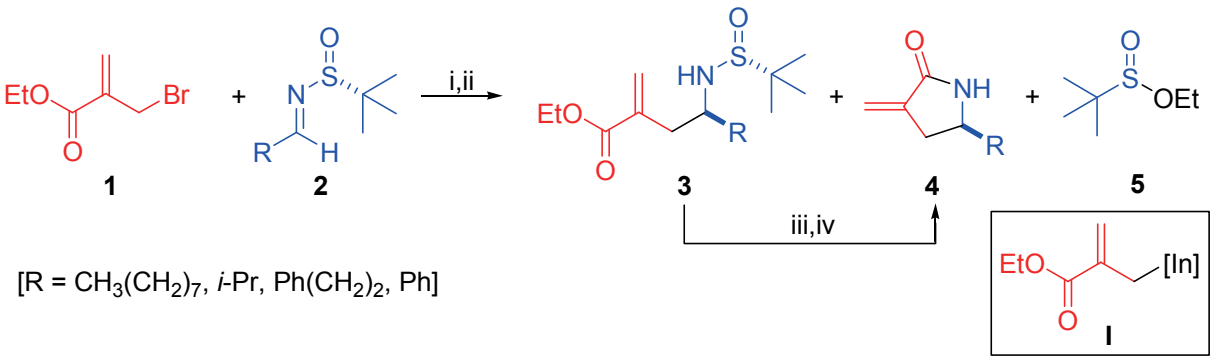
This paper is dedicated to Professor Dr. Akira Suzuki on occasion of his 80th birthday.

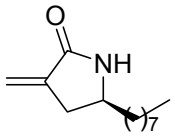
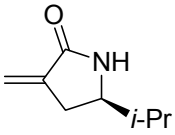
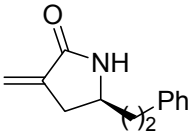
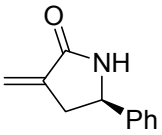
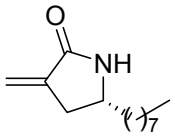
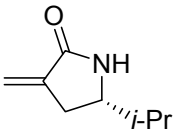
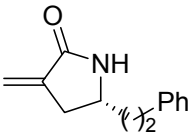
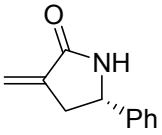
with interesting cytotoxic, allergenic, antiinflammatory, phytotoxic, and antimicrobial properties.[10] These compounds interact with nucleophiles in the active site of enzymes, due to the electrophilic character of the α,β-unsaturated carbonyl unit, acting as inhibitors. Lactone derivatives are more abundant in Nature, however they exhibit higher cytotoxic activity than lactams, the last ones being more promising candidates for drugs in the pharmaceutical industry. Synthetic methodologies to access efficiently to α-methylene-γ-butyrolactams[11] include nucleophilic addition of 2-alkoxycarbonyl allyl metal intermediates to imines.[12] More recently, an expeditious synthesis of these compounds through a three component assembling of an aldehyde, ammonia and a 2-alkoxycarbonylallylboronate in a single synthetic operation has been reported.[13] Because of our interest in indium-promoted reactions,[14] we report here the use of this metal for the stereoselective preparation of α-methylene-γ-butyrolactams[15] from ethyl 2-(bromomethyl)acrylate and chiral *N*-*tert*-butylsulfinyl aldimines.

Equimolecular amounts of ethyl 2-(bromomethyl)acrylate (**1**), indium powder and the corresponding chiral *N*-*tert*-butylsulfinyl aldimines **2** in THF were heated at 100 ºC in a pressure flask for 48 h and then hydrolyzed with water. After extraction and evaporation, a mixture of the corresponding *N*-*tert*-butylsulfinyl aminoester **3** and α-methylene-γ-butyrolactam **4** was obtained (Scheme 1 and Table 1). This reaction did not take place when the process was performed at 66 ºC (THF reflux), and very low conversion was observed at 80 ºC after one week. Fortunately, nucleophilic addition of the proposed initially formed allylindium sesquihalide intermediate of type **I** (Scheme 1) to the imine **2** took place at 100 ºC, in spite of the thermal liability of the *N*-*tert*-butylsulfinyl group, leading first to *N*-*tert*-butylsulfinyl aminoester **3**. Under these reaction conditions, compound **3** could partially cyclize to give α-methylene-γ-butyrolactam **4** and ethyl *tert*-butanesulfinate (**5**, Scheme 1), which was not detected. Finally, the aminoester **3** was converted into butyrolactam **4** from the reaction mixture upon removal of the *tert*-butylsulfinyl group under acidic conditions and final basic workup (Scheme 1).



Scheme 1. Reagents and conditions: (i) In, THF, 100 ºC, 48 h; (ii) H_2O; (iii) HCl-dioxane, MeOH, 0 ºC, 2 h; (iv) $NaHCO_3$-H_2O, 20 ºC, 1 h.

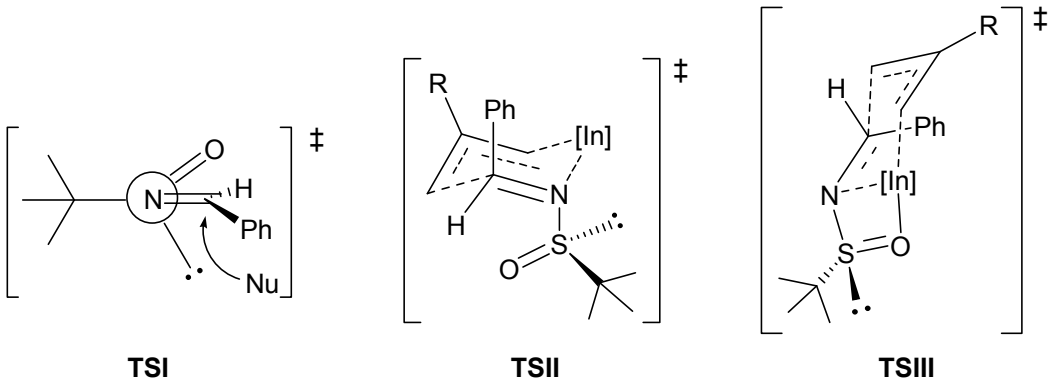
Table 1. Preparation of α-methylene-γ-butyrolactams **4**

	Aldimine **2**			Butyrolactam **4**[b]				
Entry	No.	R	**3**:**4** Ratio[a]	No.	Structure	Yield (%)[c]	er[d]	t_{ret} (min)[e]
1	(*R*)-**2a**	$CH_3(CH_2)_7$	1:1	**4a**		74	75:25	16.89
2	(*R*)-**2b**	*i*-Pr	1:5	**4b**		84	81:19	20.26
3	(*R*)-**2c**	$Ph(CH_2)_2$	1:3	**4c**		75	70:30	43.84
4	(*R*)-**2d**	Ph	3:1	**4d**		69	91:9	36.92
5	(*S*)-**2a**	$CH_3(CH_2)_7$	1:1	**4e**		72	68:32	11.25
6	(*S*)-**2b**	*i*-Pr	1:5	**4f**		79	71:29	14.20
7	(*S*)-**2c**	$Ph(CH_2)_2$	1:3	**4g**		73	80:20	12.01
8	(*S*)-**2d**	Ph	3:1	**4h**		68	92:8	33.20

[a] Ratio determined by ^{1}H-NMR analysis of the crude reaction mixture. [b] All products were >95% pure (GLC and/or 300 MHz ^{1}H RMN). [c] Isolated yield after column chromatography (silica gel, hexane/EtOAc) based on the starting aldimine **2**. [d] Enantiomeric ratio determined by HPLC using a Chiralcel OD-H column (condidtions: hexane/isopropanol, 9:1; 0.5 mL/min). [e] Retention time of the major enantiomer.

In general, overall yields of the isolated products **4**,[16] after column chromatography, are good (Table 1). Regarding the diastereoselectivity of the nucleophilic addition to the chiral imines, the er values were determined by chiral HPLC analysis, ranging from 92:8 in the case of the aldimine (*S*)-**2d** derived from benzaldehyde (Table 1, entry 8) to 68:32 in the case of aldimine (*S*)-**2a** derived from nonanal (Table 1, entry 5). In order to determine the configuration of the newly created stereogenic centre in the major diasteroisomer, we found that specific rotation of **4d** {$[\alpha]_D^{22}$ -10 (*c* 0.54, $CHCl_3$)}, which derived from aldimine (*R*)-**2d** matched with that provided in the literature for (*R*)-3-methylene-5-phenylpyrrolidin-2-one {$[\alpha]_D^{26}$ -17 (*c* 1.35, $CHCl_3$)}.[12b] This result is consistent with an approach of the nucleophile from the

Re-face of C=N through an open transition state **TSI** (Chart 1)[6g] or a monochelate chair-like model **TSII** (Chart 1)[17] instead of a six-membered ring model **TSIII** (Chart 1), with a four-membered metallacycle, in which the metal is chelated both by the oxygen and the nitrogen atoms of the imine moiety. The last one has been proposed for the indium-promoted allylation of these chiral aldimines with allyl bromide[14b] and it would lead to the opposite configuration. The imine adopts in all these cases a kind of *s-cis* conformation which is the less energetic conformation in the *N-tert*-butylsulfinyl aldimines. After this result, we assume that the nucleophilic attack occurs predominantly to the *Re*-face of the imine unit for R_S-isomers (Table 1, entries 1-4) and to the *Si*-face in the case of S_S-derivatives (Table 1, entries 5-8) according to the proposed transition states **TSI** and **TSII** (Chart 1).



TSI **TSII** **TSIII**

Chart 1

In conclusion, we have reported herein a stereoselective synthesis of α-methylene-γ-butyrolactam from ethyl 2-(bromomethyl)acrylate (**1**) and chiral *N-tert*-butylsulfinyl aldimines **3**. The key step of the process is an indium promoted nucleophilic addition to the chiral imine. Studies are currently in progress trying to find milder reaction conditions and to improve the stereoselectivity.

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16. *Typical procedure for the synthesis of **4d***.- A mixture of aldimine (*R*)-**2a** (0.104 g, 0.5 mmol), ethyl 2-(bromomethyl)acrylate (**1**, 0.106 g, 0.55 mmol) and indium powder (0.075 g, 0.65 mmol) in THF (3 mL) was stirred for 48 h at 100 °C in a pressure flask. Then, the resulting mixture was hydrolyzed with water (10 mL), extrated with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was dissolved in MeOH (1 mL) and a HCl 4M dioxane solution (0.5 mL) was added at 0 ºC. After 2 h stirring at the same temperature, a $NaHCO_3$ saturated aqueous solution (3 mL) was added, and after 1 h stirring at room temperature, the reaction mixture was extrated with EtOAc (3 × 15 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to give 0.062 g (71%) of (*R*)-3-methylene-5-phenylpyrrolidin-2-one (**4d**): White solid; mp 172-174 ºC (pentane/CH_2Cl_2) [mp 191-192 ºC (hexane/EtOAc)];[12b] $[\alpha]_D^{22}$ -10 (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64-2.78 (1H, m, C*H*H), 3.26-3.36 (1H, m, CH*H*), 4.75 (1H, dd, *J* = 4.7, 8.2 Hz, PhC*H*), 5.38 (1H, br s, C=C*H*H), 6.06 (1H, t, *J* = 2.7 Hz, C=CH*H*), 6.55 (1H, br s, NH), 7.26-7.40 (5H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8 (CH_2), 54.8 (CH), 116.6 (CH_2), 125.7, 128.1, 129.0 (CH), 138.6, 142.6 (C), 170.6 (CO); LRMS (EI) *m/z* 173 [(M^+), 100%], 172 (56), 144 (31), 104 (57), 96 (18), 78 (19), 77 (40), 68 (21), 51 (33); HRMS (EI) calcd for $C_{11}H_{11}NO$ 173.0841, found 173.0848.
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