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Diastereoselective Addition of Allylic Reagents to Chiral α-Ketoimides Derived from Oppolzer's Sultam

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Abstract:
Additions of allylmagnesium chloride and allyl bromide in the presence of zinc dust to *N*-methyl- and *N*-phenylglyoxyloyl-(2*R*)-bornane-10,2-sultam and the Lewis acid-mediated additions of allyltrimethylsilane to these chiral α-ketoimides were studied. High diastereoselection in these reactions was observed, and in the case of the allyltrimethylsilane/$TiCl_4$ additions, a change of direction of asymmetric induction was found.
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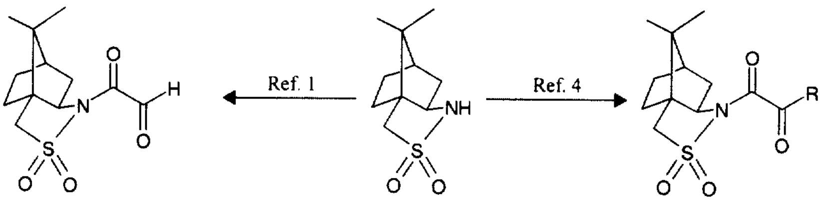
There is a growing interest in synthetic applications of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**2**) [1,2], readily available from Oppolzer's (2*R*)-bornane-10,2-sultam (**1**) [3]. Recently, we have reported [4] a convenient procedure for preparation of two chiral α-ketoimides, derived from sultam **1**: *N*-methyl- (**3**) [5] and *N*-phenylglyoxyloyl-(2*R*)-bornane-10,2-sultam (**4**) (Scheme 1).



2 **1** **3** R=Me
4 R=Ph

Scheme 1

On the other hand, we have found that asymmetric addition of allylic reagents to suitably protected α-amino aldehydes [6] and to *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**2**) [7] opens an interesting synthetic route to some natural products. These two facts prompted us to study

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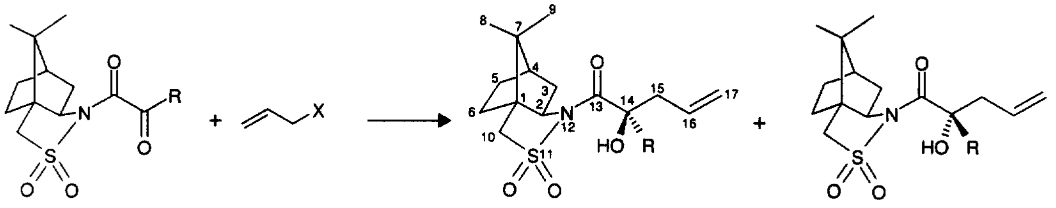
the diastereoselectivity in the allylation reaction of chiral α-ketoimides **3** and **4**, leading to formation of tertiary stereogenic centers. In the present communication, we report detailed studies on stereocontrol in these allylic additions (Scheme 2).



3 R=Me
4 R=Ph

5 X=MgCl
6 X=Br
7 X=SiMe$_3$

(14*R*)-**8** R=Me
(14*S*)-**9** R=Ph

(14*S*)-**8** R=Me
(14*R*)-**9** R=Ph

Scheme 2

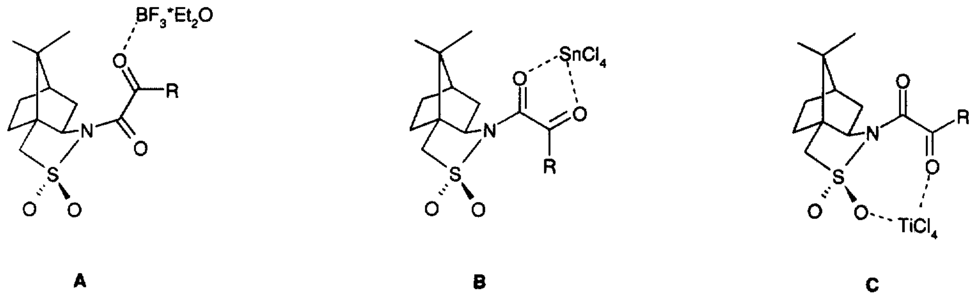
N-Methyl- (**3**) and *N*-phenylglyoxyloyl-(2*R*)-bornane-10,2-sultam (**4**) were reacted with allylic Grignard reagent **5** [8, 9], with allyl bromide **6** in the presence of zinc dust [8, 10] and with silane **7** in the presence of various Lewis acids [6a, 11]. The results of our experiments are shown in Table 1.

Table 1. Allylic additions to α-ketoimides **3** and **4**

Entry	Substrate	Reagent	Solvent	Temp. [°C]	Time [h]	Yield [%]	Diastereoisomer Ratio[b]	Abs. Conf. of C-14[c]
1	**3**	AllMgCl	THF	-78	1	50	93:7	*R*
2	**4**	AllMgCl	THF	-78	0.5	74	87:23	*S*
3	**3**	AllMgCl, $ZnBr_2$	THF	-78	1	50	73:27	*R*
4	**4**	AllMgCl, $ZnBr_2$	THF	-78	0.5	87	95:5	*S*
5	**3**	AllBr, Zn	THF	-78	48	60	52:48	*R*
6	**4**	AllBr, Zn	THF	-78	24	80	86:14	*S*
7	**3**	AllBr, Zn, $NH_4Cl_{aq.}$	THF	RT	48	90	74:26	*R*
8	**4**	AllBr, Zn, $NH_4Cl_{aq.}$	THF	RT	20	20	88:12	*S*
9	**3**	$AllSiMe_3$, $BF_3.Et_2O$[a]	CH_2Cl_2	RT	17	74	63:37	*R*
10	**4**	$AllSiMe_3$, $BF_3.Et_2O$[a]	CH_2Cl_2	RT	70	70	91:9	*S*
11	**3**	$AllSiMe_3$, $SnCl_4$	CH_2Cl_2	-20	1	84	62:38	*R*
12	**4**	$AllSiMe_3$, $SnCl_4$	CH_2Cl_2	-20	48	82	70:30	*S*
13	**3**	$AllSiMe_3$, $TiCl_4$	CH_2Cl_2	-20	1	75	62:38	*S*
14	**4**	$AllSiMe_3$, $TiCl_4$	CH_2Cl_2	-20	48	82	63:37	*R*

[a] The reaction was performed in the presence of 2.2 equiv of $BF_3.Et_2O$ under high pressure (12 kbar).
[b] The diastereoisomer ratio was established by ^1H NMR analysis of the reaction mixtures.
[c] The relative configurations of (14*S*)-**8** and (14*S*)-**9** were determined by X-ray analysis.

The data show that both α-ketoimides **3** and **4** afforded adducts (14*R*)-**8**[1] and (14*S*)-**9**,[2] respectively, as main products when Grignard reagent **5** was applied (entries 1-4). A similar diastereoselectivity was observed for **3** and **4** when they were reacted with allyl bromide **6** in the presence of zinc dust (entries 5-8). Adducts (14*R*)-**8** and (14*S*)-**9** were also the major products of the reaction of silane **7** with α-ketoimides **3** and **4**, catalyzed by $BF_3.Et_2O$ (entries 9 and 10) as a result of the predominance of nonchelated conformer **A** (Scheme 3).



Scheme 3

Analogous results obtained for the reaction catalyzed by $SnCl_4$ (entries 11 and 12) could be explained by the predominance of α-chelated conformer **B**. Surprisingly, adducts (14*S*)-**8** and (14*R*)-**9** were the major products of the reaction mediated by $TiCl_4$ (entries 13 and 14). This fact is easily explained by the γ-chelated conformer **C** (Scheme 3). Similar seven-membered chelates were observed by Garner and Ramakanth [12], Kunz *et al.* [13], and very recently by ourselves [14] for compounds possessing the (*N*)-Cbz protecting group.

The results presented demonstrate that it is possible to control the diastereoselectivity of allylation of α-ketoimides **3** and **4**, leading to formation of tertiary stereogenic centers, by means of changing of reaction conditions (reagents and catalysts). Investigations of these findings and their application to the total syntheses of natural products are in progress.

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[1] Data for (14*R*)-**8**: mp 91-92°C; $[\alpha]_D^{20}$ = -29.37 (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.81-5.69 (m, 1H, $C\underline{H}{=}CH_2$), 5.22-5.15 (m, 2H, $C{=}C\underline{H}_2$), 4.05 (dd, J=7.8, 4.61 Hz, 1H, $C\underline{H}N$), 3.55 ($^1/_2$ABq, J=13.5 Hz, 1H, $C\underline{H}SO_2$), 3.45 ($^1/_2$ABq, J=13.5 Hz, 1H, $C\underline{H}SO_2$), 3.19 (s, 1H, $O\underline{H}$), 2.83-2.73 (m, 1H, $C\underline{H}{-}CH{=}CH_2$), 2.44-2.32 (m, 1H, $C\underline{H}{-}CH{=}CH_2$), 2.1-1.8 (m, 5H, 2×$C\underline{H}_2$ and 1×$C\underline{H}$), 1.49 (s, 3H, $C\underline{H}_3$), 1.45-1.26 (m, 2H, $C\underline{H}_2$), 1.19 (s, 3H, $C\underline{H}_3$), 0.98 (s, 3H, $C\underline{H}_3$).

[2] Data for (14*S*)-**9**: mp 157-158°C, $[\alpha]_D^{20}$ = -157.23 (c 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.53-7.25 (m, 5H, $Ar\underline{H}$), 5.78-5.67 (m, 1H, $C\underline{H}{=}CH_2$), 5.17-5.09 (m, 2H, $C{=}C\underline{H}_2$), 4.31 (s, 1H, $O\underline{H}$), 4.0 (dd, J=7.7, 4.9 Hz, 1H, $C\underline{H}N$), 3.41 ($^1/_2$ABq, J=13.6 Hz, 1H, $C\underline{H}SO_2$), 3.29 ($^1/_2$ ABq, J=13.6 Hz, 1H, $C\underline{H}SO_2$), 3.13-3.05 (m, 1H, $C\underline{H}{-}CH{=}CH_2$), 2.67-2.58 (m, 1H, $C\underline{H}{-}CH{=}CH_2$), 2.09-1.82 (m, 5H, 2×$C\underline{H}_2$ and 1×$C\underline{H}$), 1.41-1.24 (m, 2H, $C\underline{H}_2$), 1.17 (s, 3H, $C\underline{H}_3$), 0.94 (s, 3H, $C\underline{H}_3$).

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