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Highly Diastereoselective Addition of Grignard Reagents to *N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam – Comparative Studies

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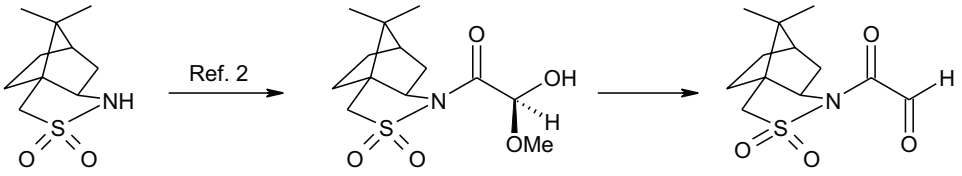
***N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam (**3**), readily prepared from (2*R*)-bornane-10,2-sultam (**1**), was used in the Grignard reaction with methylmagnesium bromide (**4a**), phenylmagnesium chloride (**4b**), benzylmagnesium chloride (**4c**), allylmagnesium chloride (**4d**), and vinylmagnesium bromide (**4e**). Reactions of **3** with Grignard reagents **4a–d** led to the desired adducts **5** with predominance of the (14*S*)-diastereoisomer. The reaction of **3** with vinylmagnesium bromide (**4e**) failed to give the adduct of type **5**. Stereochemical models for the reactions studied are proposed.

Key words: Grignard reaction, asymmetric synthesis, diastereoselection, chiral auxiliary

There is a growing interest in synthetic applications of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**3**) [1], readily available from the Oppolzer's (2*R*)-bornane-10,2-sultam (**1**) [2] *via* a crystalline, very stable hemiacetal **2** (Scheme 1).

Scheme 1



1 **2** **3**

Recently, we have shown that a highly diastereoselective addition of allyltrimethylsilane to compound **3** opens an efficient route to optically pure (*S*)-1,2-pentanediol, a useful chiral building block [3]. On the other hand, we have also found that allylmagnesium chloride (**4d**) can be used as an effective reagent for diastereoselective addition to chiral carbonyl compounds – derivatives of pyruvic and phenylglyoxylic acids [4]. These facts prompted us to perform comparative studies on the diastereoselectivity of the Grignard reaction of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**3**) with several addends, such as methylmagnesium bromide (**4a**), phenylmagnesium

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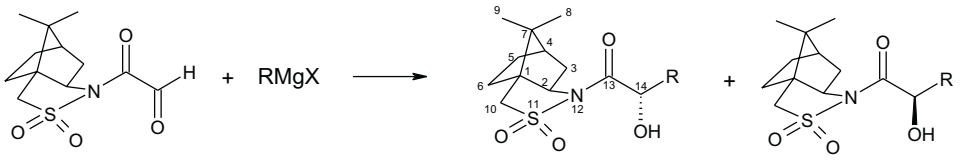
chloride (**4b**), benzylmagnesium chloride (**4c**), allylmagnesium chloride (**4d**), and vinylmagnesium bromide (**4e**). This paper summarizes the detailed studies on stereocontrol in these additions (Scheme 2).

RESULTS AND DISCUSSION

Scheme 2



3

4a R=Me, X=Br
4b R=Ph, X=Cl
4c R=Bn, X=Cl
4d R=All, X=Cl
4e R=Vin, X=Br

(14S)-**5a**
(14S)-**5b**
(14S)-**5c**
(14S)-**5d**

(14R)-**5a**
(14R)-**5b**
(14R)-**5c**
(14R)-**5d**

First, *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**3**) was reacted with five Grignard reagents **4a–e** under thermal conditions. Additions were carried out under argon atmosphere in tetrahydrofuran as a solvent (except for **4c**, which was reacted with **3** also in other solvents), and at various temperatures. The results of this set of experiments are shown in Table 1.

Table 1. Addition of Grignard reagents **4a–d** to aldehyde **3** under thermal conditions.

Entry	RMgX	Solvent	Temperature [°C]	Time [h]	Yield [%]	Diastereoisomeric ratio (14*S*)-**5** : (14*R*)-**5**
1	**4a**	THF	–78	3	28	95:5
2	**4a**	THF	–20	3	42	95:5
3	**4a**	THF	0	3	46	93:7
4	**4a**	THF	25	3	25	90:10
5	**4b**	THF	–78	4	80	84:16
6	**4c**	Toluene	–78	2	25	95:5
7	**4c**	CH_2Cl_2	–78	2	10	95:5
8	**4c**	Et_2O	–78	2	17	95:5
9	**4c**	THF	–78	2	15	95:5
10	**4c**	THF	–20	2	34	95:5
11	**4c**	THF	0	2	14	95:5
12	**4c**	THF	25	2	8	95:5
13	**4d**	THF	–78	23	35	85:15

Several aspects of the data presented in Table 1 are noteworthy. For all additions studied, the diastereoisomeric excess was very high (68% < d.e. < 90%), but the chemical yields were rather low (8–46%) with one exception, namely for the reaction of **3** with **4b**. In this latter case the yield was relatively high – 80% (Table 1, entry 5). Moreover, in all additions of **4c** to **3** studied, the asymmetric induction was extremely

high, better than 95:5 (Table 1, entries 6–12). Owing to low chemical yields of thermal additions (Table 1), we decided to study the stereochemical course of the additions carried out in the presence of various Lewis acids. The results are shown in Table 2.

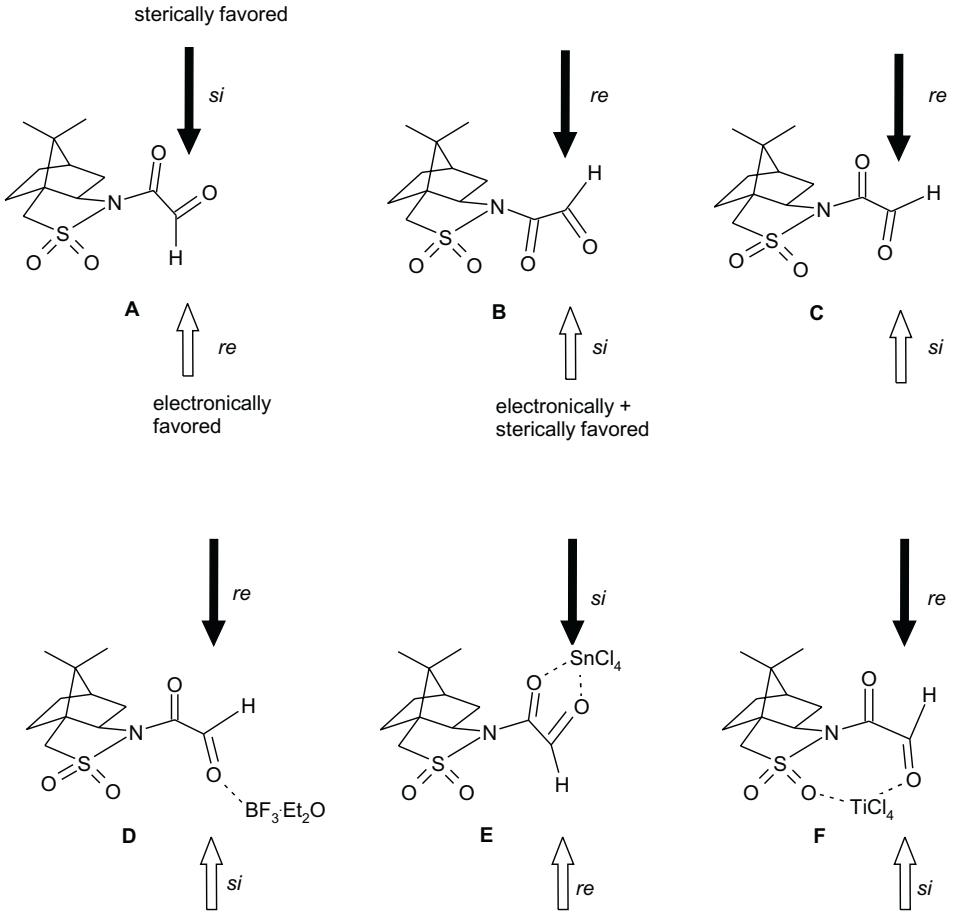
Table 2. Addition of Grignard reagents **4a–d** to aldehyde **3** in the presence of Lewis acids.

Entry	RMgX	Lewis Acid	Time [h]	Yield [%]	Diastereoisomeric ratio (14*S*)-**5** : (14*R*)-**5**
1	**4a**	$BF_3{\cdot}Et_2O$	5	17	95:5
2	**4a**	$SnCl_4$	5	43	95:5
3	**4b**	$BF_3{\cdot}Et_2O$	4	86	93:7
4	**4b**	$SnCl_4$	4	60	90:10
5	**4b**	$TiCl_4$	4	72	84:16
6	**4c**	$BF_3{\cdot}Et_2O$	2	17	95:5
7	**4c**	$AlCl_3$	2	10	95:5
8	**4c**	$ZnBr_2$	2	20	95:5
9	**4c**	$SnCl_4$	2	24	95:5
10	**4c**	$TiCl_4$	2	20	95:5
11	**4d**	$Ti(Pr^iO)_4$	3	63	85:15

The use of non-chelating Lewis acids ($BF_3{\cdot}Et_2O$, $AlCl_3$) did not improve both the chemical yield and diastereoisomeric excess (Table 2, entries 1, 3, 6, 7). The additions carried out in the presence of strongly chelating Lewis acids ($SnCl_4$, $TiCl_4$) afforded the mixtures of diastereoisomers **5** with similar, as for thermal reactions, stereoselectivity but with slightly lower yield (Table 2, entries 2, 4, 5, 9, 10). Unfortunately, addition of vinylmagnesium bromide (**4e**) to **3** completely failed to give the expected products of type **5** under both thermal and catalytic conditions. In all cases, the diastereoisomeric ratio (14*S*)-**5** : (14*R*)-**5** was established *via* ^{1}H NMR analysis of the crude product mixtures. The relative configurations of major diastereoisomers (14*S*)-**5a**, (14*S*)-**5b**, (14*S*)-**5c**, and (14*S*)-**5d** were determined *via* correlation with the results obtained from X-ray analyses, which were either already published (**5a** and **5b**) [5] or will be published in the near future (**5c** [6] and **5d** [7]).

Several concepts can be considered for the rationalization of diastereoselectivites in the reactions of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**3**) with Grignard reagents described in this work. An explanation concerning thermal addition reactions involves analogy with the proposed rationale for the hetero-Diels-Alder reaction, that was based on two concepts (Scheme 3): (a) the sterically-controlled approach of the thermodynamically more stable SO_2/CO antiperiplanar, CO/CHO s-*cis* planar conformer **A**, as proposed by Oppolzer *et al*. [8] and by Curran *et al.* [9] for *N*-acryolyl- and *N*-crotonoyl-(2*R*)-bornane-10,2-sultam; and (b) the high reactivity of less stable SO_2/CO synperiplanar, CO/CHO s-*cis* planar conformer **B**, reinforced by the cooperative stereoelectronic effect, as recently formulated by Chapuis *et al.* [10]. The conformational equilibrium may be even more complicated in view of, as recently proposed by Pindur *et al.* [11], the reactive SO_2/CO antiperiplanar, CO/CHO s-*trans* planar conformation **C**.

Scheme 3



For reactions catalysed by nonchelating Lewis acid $BF_3 \cdot Et_2O$, conformer **D**, which is analogous to the Pindur's conformer C, explains very well the results obtained. On the other hand, the results obtained for the additions catalysed by chelating Lewis acids ($SnCl_4$ and $TiCl_4$) could be explained by the predominance of α-chelated conformer **E**. The conformer **F**, recently postulated for $TiCl_4$-catalysed reactions [12], seems to play an important role in Grignard additions, investigated by us.

The results presented demonstrate a useful and highly efficient route to enantiomerically pure 1,2-diols, useful for the synthesis of natural products.

EXPERIMENTAL

General: Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using the sodium D line at 589 nm. The ^1H NMR spectra were recorded on Varian Gemini AC200 (200 MHz) and on Varian Unity Plus500 spectrometers in $CDCl_3$ using TMS as an internal standard. ^{13}C NMR spectra were also recorded on Varian Gemini AC200 (50 MHz) and Varian Unity Plus500 (125 MHz) spectrometers and were proton-decoupled. High

resolution mass spectra (EI) were recorded on Intectra AMD 604 Spectrometer. Elemental analyses (C, H, N, and S) were performed by the in-house analytical service. Analytical TLC was carried out using commercially available plates coated with 0.25 mm silica gel (Merck Kieselgel 60 F_{254}). The preparative flash chromatography was performed using silica gel (Merck Kieselgel 60, 230–400 mesh). All reagents and solvents were purified and dried as necessary according to standard procedures.

General procedure of addition of Grignard compounds to *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (3): To the solution of the *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**3**) in tetrahydrofuran in –78°C under argon was added 1 eq. Lewis acid (if required for the reaction). After 15 min, the Grignard reagent (2 eq.) was added dropwise at –78°C. The reaction was stirred for several hours and then worked up with NH_4Cl, extracted with ether and washed by $NaHCO_3$ and brine. The organic extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography using mixtures of 5–30% ethyl acetate in hexane as eluent. The following compounds were obtained:

***N*-((14*S*)-14-hydroxy)propyloyl-(2*R*)-bornane-10,2-sultam (5a):** m.p. 171–172°C (ethyl acetate); $[\alpha]_D^{20} = -101.2°$ (c 3.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ: 4.79–4.86 (m, 1H); 3.96–3.90 (m, 1H); 3.56–3.41 (m, 2H); 3.05 (d, 1H J = 7.8 Hz); 2.17–1.86 (m, 5H); 1.52–1.30 (m, 2H); 1.456 (d, 3H J = 6.8 Hz) 1.13 (s, 3H); 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$); δ: 175.7, 67.5, 64.9, 52.8, 48.9, 47.9, 44.5, 38.0, 32.7, 26.4, 22.3, 20.6, 19.9.

***N*-((14*R*)-14-hydroxy)propyloyl-(2*R*)-bornane-10,2-sultam (5a):** oil; $[\alpha]_D^{20} = -84.8°$ (c 3.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ: 4.76–4.70 (m, 1H); 3.92–3.88 (m, 1H); 3.55–3.45 (m, 2H); 3.2 (d, 1H J = 7 Hz); 2.21–1.85 (m, 5H); 1.49–1.26 (m, 2H); 1.42 (d, 3H J = 6.8 Hz) 1.16 (s, 3H); 0.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$); δ: 175.6, 67.6, 64.5, 52.7, 48.9, 47.9, 44.5, 38.1, 32.6, 26.5, 22.3, 20.9, 19.9.

***N*-((14*S*)-14-hydroxy,14-phenyl)acetyloyl-(2*R*)-bornane-10,2-sultam (5b):** m.p. 150–151°C (hexane/ethyl acetate); $[\alpha]_D^{20} = -40.5°$ (c 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ: 7.46–7.43 (m, 2H); 7.36–7.28 (m, 3H); 5.72 (bs, 1H); 3.92 (bs, 1H); 3.71 (bs, 1H); 3.42 (s, 2H); 2.02–1.96 (m, 1H); 1.92–1.73 (m, 4H); 1.44–1.28 (m, 2H); 0.88 (s, 3H); 0.69 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$); δ: 171.7, 136.9, 128.7, 128.6, 127.2 73.4, 64.7, 52.8, 48.9, 47.7, 44.4, 37.5, 32.6, 26.4, 19.9, 19.8.

***N*-((14*R*)-14-hydroxy,14-phenyl)acetyloyl-(2*R*)-bornane-10,2-sultam (5b):** oil; $[\alpha]_D^{20} = -97.2°$ (c 0.9, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ: 7.44–7.31 (m, 5H); 5.67 (d, 1H, J = 8 Hz); 3.91–3.88 (m, 1H); 3.62 (d, 1H, J = 8 Hz); 3.42 (s, 2H) 2.29–2.23 (m, 1H); 2.10–2.04 (m, 1H); 1.97–1.83 (m, 3H); 1.48–1.25 (m, 2H); 1.17 (s, 3H); 0.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$); δ: 171.3, 137.1, 128.7, 128.4, 127.8 73.0, 65.4, 52.7, 49.2, 47.9, 44.4, 38.0, 32.7, 26.4, 20.7, 19.8.

***N*-((14*S*)-14-hydroxy,14-benzyl)acetyloyl-(2*R*)-bornane-10,2-sultam (5c):** m.p. 156–158°C; $[\alpha]_D^{20} = -61.1°$ (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$); δ: 7.30–7.22 (m, 5H); 4.97 (s, 1H); 3.91 (brs, 1H); 3.26 (dd, J_1 = 3.5 Hz, J_2 = 13.5 Hz, 1H); 3.00 (brs, 1H); 2.81 (dd, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 1H); 2.07 (dd J_1 = 2.5 Hz, J_2 = 13.5 Hz, 1H); 2.00–1.84 (m, 6H); 1.12 (s, 3H); 0.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ: 174.3, 136.7, 129.9, 128.6, 127.1, 72.3, 65.3, 63.1, 53.2, 48.1, 44.8, 42.1, 38.3, 33.0, 26.7, 20.8, 20.1; MS ESI HR: Calculated: $C_{19}H_{25}NO_4SNa$ 386.1397; Found: $C_{19}H_{25}NO_4SNa$ 386.1363; Anal. Calcd. for $C_{19}H_{25}NO_4S$: C 62.8; H 6.9; N 3.9; S 8.8; Found: C 63.0; H 7.1; N 3.8; S 8.6.

***N*-((14*S*)-14-hydroxy,14-allyl)acetyloyl-(2*R*)-bornane-10,2-sultam (5d):** m.p. 138–139°C; $[\alpha]_D^{20} = -105°$ (c 2.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ: 5.9–5.7 (m, 1H); 5.2–5.05 (m, 2H); 4.83 (dd, J = 11.8, 6.2 Hz, 1H); 3.51 ($^1/_2$ ABq, J = 13.8 Hz, 1H); 3.47 ($^1/_2$ ABq, J = 13.8 Hz, 1H); 3.08 (d, J = 7.7 Hz, 1H); 2.8–1.2 (m, 9H); 1.14 (s, 3H); 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$); δ: 174.2, 132.0, 118.9, 70.3, 64.9, 52.9, 48.9, 47.8, 44.5, 39.8, 38.2, 32.7, 26.4, 20.6, 19.8; EIMS m/z (%): 313 (M^+, 1.3), 295 (1.8), 272 (33), 199 (9), 135 (100), 93 (47), 71 (13), 55 (6); Anal. Calcd. for $C_{15}H_{23}NO_4S$: C 57.5, H 7.4, N 4.0, S 10.2; Found: C 57.3, H 7.5, N 4.4, S 10.2.

***N*-((14*R*)-14-hydroxy,14-allyl)acetyloyl-(2*R*)-bornane-10,2-sultam (5d):** m.p. 69–70°C; $[\alpha]_D^{20} = -97.7°$ (c 1.08, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$); δ: 6.0–5.7 (m, 1H); 5.3–5.1 (m, 2H); 4.57 (dd, J = 7.6, 4.7 Hz, 1H); 3.90 (dd, J = 7.7, 5.1 Hz, 1H); 3.9 (ABq, J = 14.0 Hz, 2H); 2.8–1.2 (m, 9H); 1.15 (s, 3H); 0.97 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$); δ: 171.8, 133.1, 118.5, 70.3, 65.3, 52.9, 49.3, 47.9, 44.5, 38.1, 37.0, 32.8, 26.5, 20.7, 19.9; EIMS m/z (%): 313 (M^+, 3), 295 (6), 272 (31), 199 (8), 135 (100), 93 (48), 71 (15), 55 (8); HR-EIMS calcd. for $C_{15}H_{23}NO_4S$ (M^+): 313.1352; Found: 313.1352.

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