Cis-Selective Intermolecular Amidoalkylations of an α-*tert*-Butyldimethylsilyloxy *N*-Acyliminium Ion

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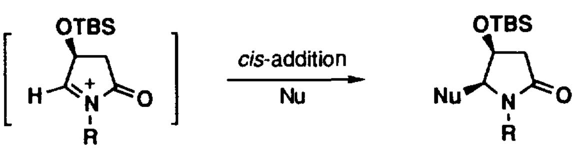
Recently the control of *syn* addition to an adjacent OH group has been explored using the *tert*-butyldimethylsiyl protecting group in Lewis acid catalyzed reactions with remarkable selectivity.[1] Similarly, in the case of intermolecular amidoalkylations the *syn* approach of nucleophiles to the OTBS group was observed, albeit the selectivity margins were moderate.[2] Since the analogues of intermediate **2** are valuably used in γ-amino acids synthesis,[3] we have decided to investigate the stereoselective amidoalkylations on the acyliminium ion **1** (Scheme 1).

Amide **3** was prepared from (+)-malic acid by modification of the known sequence[3a] (overall 51%). The optical purity of the precursor imide of **3** was determined by ^{1}H-NMR analysis of the S-(-)-α-methoxy-α-(trifluoromethyl)phenyl acetate (MTPA) ester[4] and found to be >90% *ee*.

Table 1 summarizes the results observed for the acid-induced alkylations of **3**[6] at C-5. Allyltri-n-butylstannane was found to be superior to allyltrimethylsilane with $MgBr_2$ in *cis*-selectivity[7] (Table, Entry 1-2). In addition, the nonpolar solvent toluene was proved to induce best selectivity, albeit the reaction proceeded rather slowly to afford **4** in 99% yield and a 21 : 1 *cis* : *trans* ratio (Entry 2).

In the allenylation (Entry 3-4), similar results were observed. While compound **5**[8] was obtained in a 1 : 7.5 *cis* : *trans* ratio with propargyltrimethylsilane[9] (Entry 3), switching propargyltrimethylsilane to propargyltriphenylstannane[10] reversed the ratio in favor of *cis* in toluene, a 6.9 : 1 *cis* : *trans* ratio (Entry 4). In the propargylation with propanedienyltriphenylstannane,[11] virtually a single isomer of **6**[8] was detected (Entry 6) in toluene, and a better yield was observed in CH_2Cl_2 (Entry 5) with slightly lower selectivity (*cis* : *trans* 19 : 1). This remarkable *cis*-selectivity in Lewis acid catalyzed alkylations may be equally explained by the stabilization of the incipient σ* orbital at C-5 *via* the interaction with σ bonds of C-4 as in the case of alkylations in enones.[1,12]

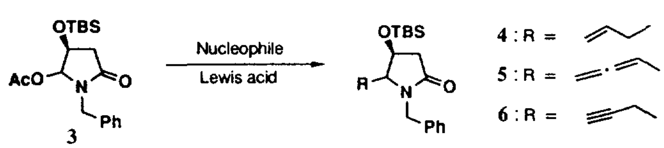
In summary, high *cis*-selective amidoalkylations on the acyliminium ion are achieved by exploiting the adjacent OTBS group and stannane reagents in the presence of Lewis acid. Stereoselective alkylations on properly fuctionalized enantiomerically pure lactams and their synthetic applications are in progress.



1 2

Scheme 1.

Table 1.



Entry	Nucleophile	Lewis acid[a]/solvent	Conditions[a]/[conc]	Product	*cis* : *trans*[b]	Yield (%)[c]
1	$SiMe_3$	$MgBr_2/CH_2Cl_2$	12 hr/[0.05 M]	**4**	3.8 : 1	80
2	$SnBu_3$	$MgBr_2$/toluene	18 hr/[0.10 M]	**4**	21 : 1	99
3	$SiMe_3$	$TMSOTf/CH_2Cl_2$	12 hr/[0.05 M]	**5**	1 : 7.5	23
4	$SnPh_3$	$MgBr_2$/toluene	18 hr/[0.12 M]	**5**	6.9 : 1	82
5	$Snph_3$	$MgBr_2/CH_2Cl_2$	12 hr/[0.14 M]	**6**	19 : 1	85
6	$SnPh_3$	$MgBr_2$/toluene	18 hr/[0.11 M]	**6**	>100 : 1	54

[a] All reactions were performed under anhydrous condition, adding 2.5 eq. of Lewis acid to a solution of the substrate and 3 eq. of the nucleophile at 0°C, and slowly warming up to r.t. TMSOTf : 0.2 eq. [b] As determined by ^{1}H-NMR. [c] Isolated yields.

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5. Chamberin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653. In the reduction with $NaBH_4$ a mixture of two isomers was obtained, the *cis*-product was major.
6. Each isomer of **3** was treated respectively, no significant

differences in selectivity between the two were detected.

7. The stereochemistry of products was determined by the observation of ^{1}H-NMR vicinal coupling constants. $J_{4,5}$ (*ca.* 6 Hz in *cis*-products and *ca.* 0 Hz in *trans*-products); See ref. 2(a), (b) and 3(a), (b).
8. For the analytical data of the *cis*-products careful separations were performed on MPLC. *cis*-compound **5**: $[\alpha]_D^{28}$ $-17.5°$ ($c=1.02$, $CHCl_3$), ^{1}H-NMR (300 MHz $CDCl_3$) δ 7.3-7.1 (m, 5H), 5.9-5.7 (m, 1H), 5.05 (dd, $J=3.2$, 1.4 Hz, 1H), 5.00 (d, $J=1.0$ Hz, 1H), 4.95 (d, $J=15.2$ Hz, 1H), 3.98 (d, $J=15.2$ Hz, 1H), 3.44 (dt, $J=4.7$, 6.6 Hz, 1H), 2.51 (dd, $J=7.0$, 16.5 Hz, 1H), 2.44 (dd, $J=16.4$, 6.1 Hz, 1H), 0.82 (s, 9H), 0.0, 0.03 (2s, 6H), ^{13}C-NMR (75 MHz $CDCl_3$) δ 172.9, 137.0, 134.5, 128.9, 128.1, 127.8, 127.7, 127.6, 118.3, 67.5, 61.7, 44.4, 40.7, 32.0, 26.0, 18.2, -4.2, -4.8, IR ($CHCl_3$) 2955, 2931, 2858, 1702, 1422, 1362, 1309, 1256, 1126, 1101, 955, 869, 837, 778, 701, 629. MS (EI) m/z 346 ($M^{+}+H$). *Cis*-compound **6**: $[\alpha]_D^{26}$ $-10.9°$ ($c=0.86$, $CHCl_3$), ^{1}H-NMR (300 MHz) $CDCl_3$) δ 7.4-7.1 (m, 5H), 4.91 (d, $J=15.3$ Hz, 1H), 4.38 (q, $J=6.3$ Hz, 1H), 4.14 (d, $J=15.3$ Hz, 1H), 3.54 (dt, $J=5.0$, 6.4 Hz, 1H), 2.52 (d, $J=6.5$ Hz, 2H), 2.51-2.3 (m, 2H), 1.92 (t, $J=2.6$ Hz, 1H), 0.83 (t, $J=2.8$ Hz, 9H), 0.00, 0.03 (2s, 6H). ^{13}C-NMR (75 MHz $CDCl_3$) δ 173.1, 136.8, 128.9, 128.1, 127.8, 81.1, 71.1, 67.1, 60.8, 44.5, 40.3, 25.9, 17.8, -4.3, -4.9. IR ($CHCl_3$) 3310, 2953, 2928, 2856, 1697, 1415, 1364, 1310, 1256, 1177, 1107, 1075, 970. MS (EI) m/z 344 ($M^{+}+H$).
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