Tributyltin radical-induced addition–carbocyclization on chiral perhydro-1,3-benzoxazines: a facile entry to enantiopure tin-containing auxiliaries

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***N*-Acryloylperhydro-1,3-benzoxazines 1a,b undergo stereoselective addition–carbocyclization when reacted with Bu_3SnH, leading to stannylated lactamic rings that can be transformed into enantiopure pyrrolidines.**

The design and synthesis of optically active alkylstannanes is currently considered a challenge in both organic and organometallic chemistry.[1] Activated non-racemic stannanes have been used in a variety of reactions which include allylation of aldehydes catalysed by Lewis acids,[2] tin–lithium exchange,[3] palladium cross-coupling[4] and cyclopropanation;[5] however, the number of examples reported to date is small.

Except for the ready accessibility of chiral α-heterosubstituted stannanes,[6] there is a lack of general methods for preparation of non-racemic organotin compounds and therefore chirality transfer from another reagent is generally preferred.[2,7]

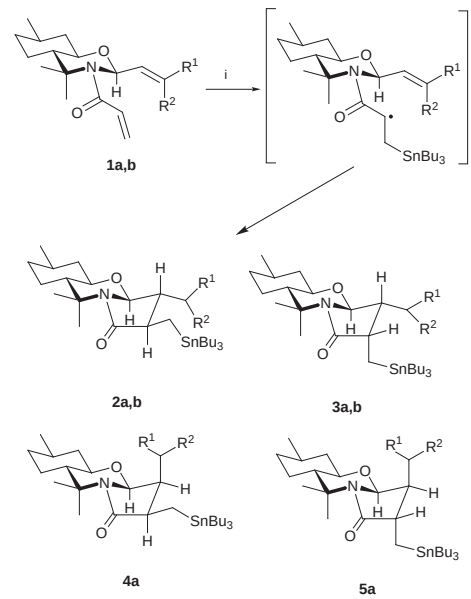
The carbon–tin bond is easily activated in the neighbourhood of a functional group.[8] In this context α-alkoxystannanes and allyltin compounds are suitable substrates for metal exchange[9] and nucleophilic addition reactions[2] respectively. On the other hand the nature of the alkyl substituents at the Sn atom is sometimes crucial since large substituents causes diminished reactivity.

As part of a project on stereoselective radical cyclizations in perhydrobenzo-1,3-benzoxazines[10] we focused our attention on the preparation of alkylstannanes attached to a perhydrobenzoxazine chiral auxiliary. This new type of structure plays a highly versatile role in synthesis since it behaves as a source of organometallic species as well as a classical organic auxiliary.[11]

Encouraged by the stereoselectivity of intramolecular radical cyclizations, the synthesis of organotin compounds was tested *via* addition–cyclization of acrylamides[10] **1a**,**b** with Bu_3SnH, a less toxic and volatile reagent than trimethyltin derivatives[12] (Scheme 1).

Treatment of **1a** with commercial Bu_3SnH in the presence of AIBN as initiator was performed under different conditions as summarized on Table 1. Attempts to use the Stork method (Bu_3SnCl + $NaCNBH_3$)[13] or palladium catalysis [$Pd(PPh_3)_3$][14] failed. The best chemical yield corresponded to a short heating of a mixture of Bu_3SnH, AIBN and the acrylamide in refluxing benzene (entry 3), or alternatively, without solvent at 80–90 °C (entry 4). This one is an extremely rapid, violent reaction and it is not recommended for preparative purposes. Slow addition of reagent (entry 1) or ultraviolet irradiation at room temperature (entry 2) causes a decrease in the chemical yield although a slight improvement in the diastereomeric ratio is observed at that temperature.

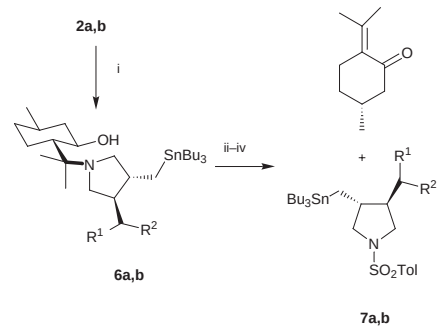
The four diastereomeric stannylated lactams **2a**–**5a**† were separated by flash chromatography and their stereochemistry was determined by NOESY experiments. Interestingly, although two stereocenters were created, addition–cyclization on acrylamide **1b** under thermal conditions (entries 5, 6) led to a mixture of only two diastereomers (**2b** and **3b**) which are epimers at the α-lactamic carbon. It is worth noting in both cases that major cyclization products **2a**,**b** showed a C-2/C-3 *trans* relationship at the newly created stereocenters. This result is contrary to that predicted by the Beckwith radical model[15] and no satisfactory reasons have been ascertained to date.[16]



Scheme 1 *Reagents and conditions*: i, Bu_3SnH (1.2 equiv.), AIBN (5–10 equiv.), 80–90 °C (see Table 1).

Table 1 Radical addition-cyclization of acrylamides **1a**,**b**

						Products (%)				
Entry	R^1	R^2	Solvent	*T*/°C	*t*/min	**2**	**3**	**4**	**5**	Yield (%)
1	Ph	H	PhH	80	720	**2a** (59)	**3a** (21)	**4a** (16)	**5a** (4)	76
2	Ph	H	PhH	25	900	**2a** (65)	**3a** (22)	**4a** (9)	**5a** (4)	48
3	Ph	H	PhH	80	30	**2a** (59)	**3a** (21)	**4a** (16)	**5a** (4)	99
4	Ph	H	–	90	5	**2a** (56)	**3a** (22)	**4a** (16)	**5a** (6)	99
5	Me	Me	PhH	80	30	**2b** (68)	**3b** (32)			98
6	Me	Me	–	90	5	**2b** (68)	**3b** (32)			99

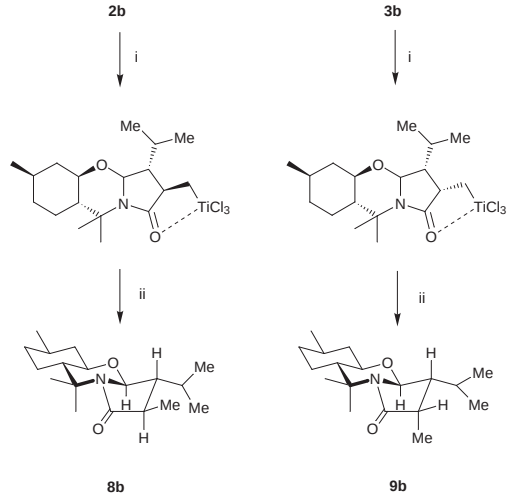


Scheme 2 *Reagents and conditions*: i, $LiAlH_4$ (5 equiv.), $AlCl_3$ (2 equiv.), THF, 0 °C, 5 min; ii, PCC (4 equiv.), CH_2Cl_2, 1 h; iii, KOH (2.5 M)–THF–MeOH (1:2:1), 2 h; iv, TsCl (2 equiv.), $Pr^1{}_2NEt$ (4 equiv.), CH_2Cl_2, 24 h.

Preliminary MO calculations (UHF/PM3) performed in our system suggested that the major lactams **2a**,**b** arise from biased conformations in which allylic 1,3-strain controls the olefinic appendage and a planar *Z* isomer is preferred for the intermediate amide radical. As a consequence, late transition states or thermodynamic equilibration can be discarded as explanations for the *trans* selectivity of such processes.

Once isolated, the major diastereomeric lactams **2a**,**b** were transformed quantitatively into the stannylated menthol derivatives **6a**,**b** by reduction with $LiAlH_4$ at 0 °C in THF. Sequential PCC oxidation of **6a**,**b** followed by treatment with methanolic KOH[17] of the intermediate amino ketone led to enantiopure stannylated pyrrolidines **7a**,**b** isolated as tosylates, although in modest overall yield (34 and 44% respectively) (Scheme 2).

On the other hand, it was interesting to explore the reactivity at the metal center and the possibility of easy destannylation. To this end, after isolation by flash chromatography, pure diastereomers **2b** and **3b** obtained in the reaction of **1b** with Bu_3SnH were subjected to Sn–Ti exchange[18] to generate the corresponding titanium homoenolates by reaction with $TiCl_4$ in CH_2Cl_2 at 0 °C (Scheme 3). This kind of metal homoenolates has been described for alkyl propionates but, to the best of our knowledge, no examples concerning lactams are known.



Scheme 3 *Reagents and conditions*: i, $TiCl_4$ (1.3 equiv.), CH_2Cl_2, 0 °C, 10 h; ii, SiO_2, CH_2Cl_2 or HCl, H_2O.

The titanium intermediates were transformed into enantiopure lactams **8b** and **9b** respectively by hydrolytic cleavage of the metal–carbon bond with silica gel or aq. HCl. It is noteworthy that the *trans* relationship of the substituent at the lactam coincides with the stereochemistry of the starting stannylated compounds, indicating that the metal interchange does not affect the configuration at the α-carbon in the lactamic ring. The reactivity of these titanium homoenolates with other electrophiles is currently being examined and the results will be published in due course.

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Notes and references

† *Selected data* for **2a**: $[\alpha]_D{}^{23}$ −9.38 (*c* 1.20 $CHCl_3$); δ_H(300 MHz, $CDCl_3$) 0.80 (m, 6H), 0.90 (t, 12 H), 0.95 (d, 3H), 1.12 (s, 3H), 1.20–1.35 (m, 8H), 1.35–1.50 (m, 8H), 1.70 (s, 3H), 1.72 (m, 2H), 1.94 (m, 2H), 2.10–2.20 (m, 1H), 2.71 (dd, 1H, *J* 7.9, 13.6), 2.98 (dd, 1H, *J* 5.9, *J* 13.6), 3.31 (dt, 1H, *J* 4.2, 10.6), 4.53 (d, 1H, *J* 6.2), 7.1–7.3 (m, 5H); δ_C(75.5 MHz, $CDCl_3$) 10.0, 11.2, 13.7, 18.3, 22.0, 23.9, 25.4, 27.4, 29.1, 31.1, 34.5, 37.4, 41.0, 45.0, 49.5, 49.8, 56.0, 76.0, 87.7, 126.2, 128.3, 129.2, 138.8, 175.2. For **2b**: $[\alpha]_D{}^{23}$ −5.38 (*c* 1.0 CH_2Cl_2); δ_H(300 MHz, $CDCl_3$) 0.80–1.00 (m, 26H), 1.13 (s, 3H), 1.20–1.35 (m, 9H), 1.35–1.55 (m, 10H), 1.67 (s, 3H), 1.72 (m, 2H), 1.95 (m, 1H), 2.15 (m, 1H), 3.34 (dt, 1H, *J* 4.1, 10.6), 4.54 (d, 1H, *J* 6.9); δ_C(75.5 MHz, $CDCl_3$) 10.0, 13.6, 13.7, 18.5, 19.9, 20.7, 21.9, 23.9, 25.3, 27.4, 29.2, 30.0, 31.2, 34.4, 41.2, 43.4, 49.7, 56.6, 76.6, 86.9, 175.3. For **7a**: $[\alpha]_D{}^{23}$ +36.9 (*c* 1.06 CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.52 (dd, 1H, *J* 10.0, 13.1), 0.75–1.00 (m, 7H), 0.89 (t, 9H, *J* 7.2), 1.20–1.35 (m, 6H), 1.35–1.50 (m, 6H), 1.7–1.9 (m, 2H), 2.30 (dd, 1H, *J* 9.1, 13.7), 2.42 (s, 3H), 2.71 (dd, 1H, *J* 8.7, 9.5), 2.80 (dd, 1H, *J* 4.2, 13.7), 2.95 (dd, 1H, *J* 8.0, 10.0), 3.30 (dd, 1H, *J* 6.8, 10.0), 3.50 (dd, 1H, *J* 6.7, 9.5), 7.05 (d, 2H, *J* 8.2), 7.20–7.40 (m, 5H), 7.65 (d, 2H, *J* 8.2); δ_C(75.5 MHz, $CDCl_3$) 9.2, 11.0, 13.7, 21.5, 27.3, 29.1, 37.9, 42.6, 49.6, 52.8, 55.7, 126.2, 127.4, 128.4, 128.6, 129.5, 133.7, 139.5, 143.2. For **7b**: $[\alpha]_D{}^{23}$ +33.3 (*c* 1.56 CH_2Cl_2); δ_H(300 MHz, $CDCl_3$) 0.51 (dd, 1H, *J* 10.5, 13.2), 0.74 (d, 3H, *J* 6.9), 0.80 (d, 3H, *J* 8.0), 0.85–1.00 (m, 6H), 0.89 (t, 9H, *J* 7.1), 1.20–1.35 (m, 8H), 1.35–1.50 (m, 6H), 1.69 (octuplet, 1H, *J* 6.8), 1.8–2.0 (m, 1H), 2.43 (s, 3H), 2.60 (t, 1H. *J* 9.2), 3.01 (dd, 1H, *J* 8.9, 9.7), 3.28 (dd, 1H, *J* 8.3, 9.7), 3.44 (dd, 1H, *J* 7.2, 9.2), 7.32 (d, 2H, *J* 8.0); 7.70 (d, 2H, *J* 8.0); δ_C(75.5 MHz, $CDCl_3$) 9.2, 11.6, 13.6, 17.3, 21.4, 21.7, 27.3, 27.5, 29.1, 39.7, 49.2, 53.9, 56.1, 127.5, 129.5, 133.4, 143.2.

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