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Diastereoselective cascade synthesis of azabicyclo[3.1.0]hexanes from acyclic precursors

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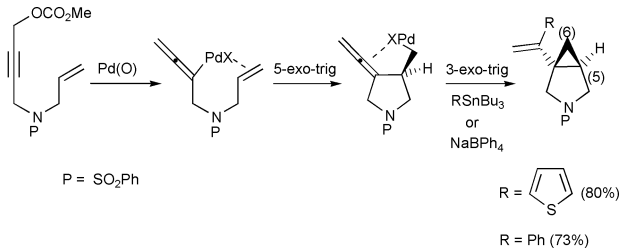
Received (in Cambridge, UK) 28th November 2001, Accepted 5th March 2002
First published as an Advance Article on the web 12th March 2002

The diastereoselective synthesis of azabicyclo[3.1.0]hexanes bearing different substituents on all positions of the cyclopropane ring has been achieved in moderate to good yields.

Propargylic carbonates are valuable substrates in Pd(0)-catalysed processes. Their reactivity towards the catalyst differs mechanistically from that of simple alkynes in that they form allenylpalladium(II) complexes.[1]

We[2] along with others[3] have shown that these versatile intermediates can serve a double function as both starter and terminating species in a biscylisation–anion capture cascade process[4] generating azabicyclo[3.1.0]hexanes (Scheme 1).



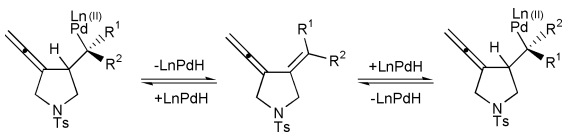
Scheme 1

The reported examples of this process have not addressed substitution at the C(6) position. Due to the fact that a number of substituted azabicyclo[3.1.0]hexanes occur as core structures in biologically active compounds, *e.g.* Trovan,[5] it was important to establish the diastereoselectivity of the process at C(6).

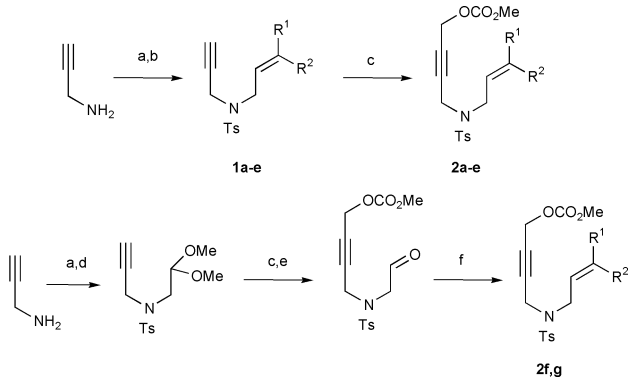
Substrates **2a**–**g** with R^1 or $R^2 \neq H$ were therefore prepared. Provided that no isomerisation occurs during the cyclisation process, *e.g. via* β-hydride elimination–readdition processes (Scheme 2), the stereochemistry of **2a**–**g** should control the diastereoselectivity of C(6) in the azabicyclo[3.1.0]hexanes.

Carbonates **2a**–**g** were synthesised from propargylamine (Scheme 3) and the stereochemistry of the double bond of each compound was confirmed by ^{1}H NMR.

For this study, organotin(IV) reagents were chosen as the anion capture agents due to their ease of preparation and tolerance to air and moisture. The experimental conditions for the palladium-catalysed cascade were as follows: carbonate **2a**–**g** (1.0 mol eq.), $Pd(OAc)_2$ (0.1 mol eq.), PPh_3 (0.2 mol eq.) and Bu_3SnY (Y = organic group) were dissolved in THF (4 ml $mmol^{-1}$) and heated at reflux under nitrogen for 2–4 h. The results of this study (Table 1) show that *E*-substituted olefins (entries 1–6) and *Z*-substituted olefins (entries 7–13) afford azabicyclo[3.1.0]hexanes **3** and **4** diastereoselectively in moderate to good yield. The relative stereochemistry of **3** and **4** was assigned on the basis of NOE data and the characteristic *cis* (~8 Hz) and *trans* (~4 Hz) coupling constants between the C(5) and C(6) protons.



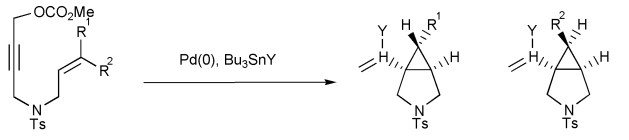
Scheme 2



Scheme 3 *Reagents and conditions*: a) TsCl, pyridine, DMAP 2 mol%, 0 °C to rt, 15 h, 96%; b) *allyl alcohol* (see Table 1), DEAD, PPh_3, THF, 0 °C to rt, 15 h, (**1a**, 89%; **1b**, 96%; **1c**. 78%; **1d**, 57%; **1e**, 62%); c) ^{n}-BuLi, −78 °C, THF, 30 min then $(CH_2O)_n$, −78 °C to rt, 15 h, then $ClCO_2Me$, −78 °C to rt, 6 h, (**2a**, 68%; **2b**, 75%; **2c**, 72%; **2d**, 58%; **2e**, 68%); d) bromoacetaldehyde dimethyl acetal, CH_3CN, reflux, 36 h, 74%; e) 80% AcOH(aq), 100 °C, 2 h, 84%; f) $Ph_3P{=}CO_2Me$, MeOH, 0 °C, 30 min, 85% (1:2 mixture of **2f**:**2g**).

No products resulting from elimination–readdition processes are observed, showing that 3-*exo*-trig cyclisation is faster than β-hydride elimination, even in the presence of two further β-hydrogen atoms (entries 1–3 and 7). Possible coordination by an NTs substituent has been suggested as a mechanism for suppressing β-hydride elimination.[6] However, the oxygen

Table 1 Diastereoselective synthesis of azabicyclo[3.1.0]hexanes



2 **3** **4**

Entry	R^1	R^2	Y	Yield (%)[a] **3**	**4**
1(**2a**)	Et	H	2-Furyl	81	
2(**2a**)	Et	H	2-Thienyl	85	
3(**2a**)	Et	H	(Phenyl)ethynyl	40	
4(**2b**)	Ph	H	2-Furyl	68	
5 (**2b**)	Ph	H	(Phenyl)ethynyl	38	
6 (**2f**)[b]	CO_2Me	H	2-Furyl	74[c]	
7 (**2c**)	H	Et	2-Thienyl		53
8 (**2d**)	H	Ph	2-Thienyl		51
9 (**2e**)	H	CH_2OBn	2-Furyl		60
10 (**2e**)	H	CH_2OBn	2-Thienyl		73
11 (**2e**)	H	CH_2OBn	(Phenyl)ethynyl		53
12 (**2g**)	H	CO_2Me	2-Furyl		56[d]
13 (**2g**)	H	CO_2Me	2-Thienyl		68[d]

[a] Isolated yield. [b] 8:1 mixture of *E*/*Z* isomers. [c] 8:1 mixture of diastereoisomers. [d] Trace (<5%) of other diastereoisomer observed (NMR).

DOI: 10.1039/b110890e

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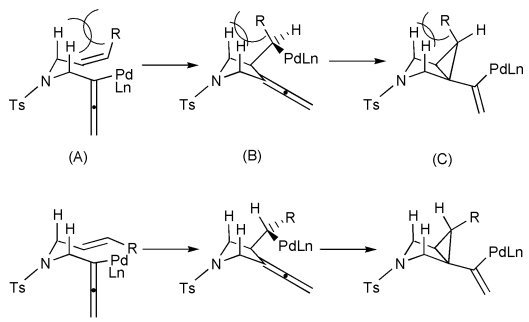
atoms of a sulfonamide are expected to be poor donors and there are other examples in which no proximal NTs substituent is present.[7] The trace amounts of alternate diastereoisomer observed in a few instances (entries 12 and 13) are thought to be caused by conjugate addition–elimination of methoxide which is generated *in-situ* from the carbonate group, rather than elimination–readdition processes. The observed diastereoselectivity demonstrates the configurational stability of the intermediate alkylpalladium(II) species (B) (Scheme 4).

The origin of the diastereoselectivity can be accounted for by examining the transition state of the reaction prior to anion capture (Scheme 4).



Scheme 4

A pseudo 1-3 diaxial interaction which exists between the protons and the *Z*-olefin substituent in the allenylpalladium(II) species (A) increases in (B) and in the vinylpalladium(II) species (C) and in the transition state leading to (C). This steric interaction decreases the rate of 5-*exo*-trig cyclisation, resulting in competitive premature cross coupling (direct capture)[8] in some cases.

In conclusion, this powerful methodology allows access to azabicyclo[3.1.0]hexanes bearing a wide variety of substituents diastereoselectively.

We thank Leeds University, the EU and EPSRC for support.

Notes and references

1 J. Tsuji and T. Mandai, *Angew. Chem., Int. Ed. Engl*., 1995, **34**, 2598.
2 R. Grigg, R. Rasul, J. Redpath and D. Wilson, *Tetrahedron Lett*., 1996, **37**, 4609.
3 W. Oppolzer, A. Pimm, B. Stammen and W. E. Hume, *Helv. Chim. Acta*., 1997, **80**, 623; A. G. Steinig and A. de Meijere, *Eur. J. Org. Chem*., 1999, 1333.
4 For a definition of anion capture and other examples of biscyclistion–anion capture see: R. Grigg and V. Sridharan, *J. Organomet. Chem*., 1999, **576**, 65.
5 K. W. Garey and G. W. Amsden, *Pharmacotherapy*, 1999, **19**, 21.
6 C.-W. Lee, K. S. Oh, K. S. Kim and K. H. Ahn, *Org. Lett*., 2000, **2**, 1213.
7 R. Grigg and V. Sridharan, *J. Organomet. Chem*., 1999, **576**, 65.
8 For a study of the occurrence of direct capture in Pd catalysed cyclisations see: E. Negishi, Y. Noda, F. Lamaty and E. J. Vawter, *Tetrahedron Lett*., 1990, **31**, 4393.