Novel Pd(II)-catalysed *N,O*-bicyclisation as an efficient route to the 6-oxa-2-azabicyclo[3.2.1]octane skeleton†

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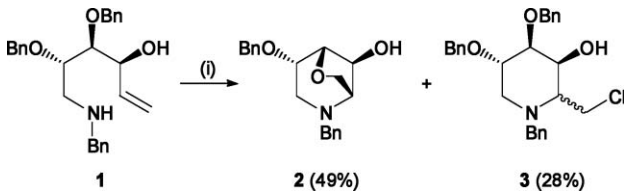
1-(Benzyloxycarbonylamino)-hex-5-en-3-ol (5) undergoes a novel Pd(II)/$CuCl_2$-catalysed bicyclisation to furnish the corresponding 6-oxa-2-azabicyclo[3.2.1]octane (6) in good yield.

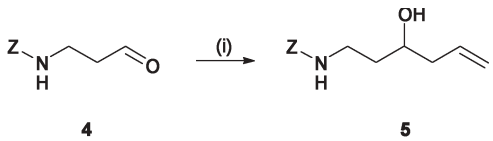
Palladium(II)-catalysed transformations of aminoalkenitols are generally regarded as highly efficient and synthetically useful tools for the preparation of sophisticated building blocks as well as valuable natural products.[1] In addition, an increasingly growing research interest in this particular field of synthetic organometallic chemistry often reveals new and unexpected reaction patterns. During our project on Pd(II)/$CuCl_2$-catalysed cyclisations of aminoalkenitol **1** (prepared in 23% overall yield over five steps starting from methyl-α-D-galactopyranoside), we have observed a rather surprising formation of bicycle **2** as a major product alongside with the diastereomeric mixture of desired (C-5)-chloromethyl piperidines **3**.[2] Clearly, the unexpected bicyclic product **2** must have been formed *via* an initial *in situ* (C-3)-*O*-debenzylation (as a result of double coordination of Pd^{2+} salt with both the BnO-group and C=C bond of **1** leading to a π-complex in geometrically favourable chair conformation, *cf*. Fig. 1) with subsequent Pd(II)/$CuCl_2$-promoted ring closure (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) 0.1 equiv. $PdCl_2$, 3 equiv. $CuCl_2$, 3 equiv. AcONa, glacial AcOH, r.t.

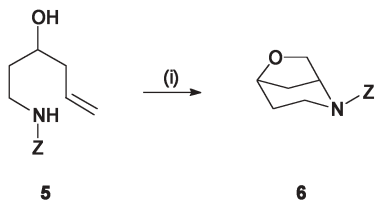
To the best of our knowledge, this reaction[3] represents a new method for the construction of the 6-oxa-2-azabicyclo[3.2.1]octane skeleton.[4] Such an *N,O*-bicyclic structural pattern can be found as a substructure in various biologically active compounds and natural products such in the alkaloids scopoline[5] and asparagamine A.[6]

Thus, we decided to explore the scope of this new Pd(II)-catalysed transformation on a racemic substrate **5**[7] serving as a suitable model compound possessing all the necessary structural elements: free hydroxyl group in β-position with respect to the terminal alkene and protected amino function on the other end of a six-carbon chain. Aminoalkenitol **5** was prepared[8] in one step *via* an addition of 0.25 equiv. of tetraallyltin to commercially available *N*-(benzyloxycarbonyl)-3-aminopropanal **4**[9] in an atom-economical fashion as this nucleophilic reagent is able to transfer all four allyl groups[10] to the carbonyl function of **4** (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) tetraallyltin, MeOH, 30 °C, 88%.

Next, the *N*-protected racemic substrate **5** was subjected to the key Pd(II)/$CuCl_2$-catalysed *N,O*-bicyclisation under various reaction conditions to furnish the corresponding 6-oxa-2-azabicyclo[3.2.1]octane **6** (Scheme 3, Table 1).[11]



Scheme 3 *Reagents and conditions*: (i) See Table 1.

First, the standard catalytic conditions: 0.1 equiv. $PdCl_2$, 3 equiv. $CuCl_2$ and 3 equiv. AcONa in glacial AcOH, were examined (entry 1). A desired bicycle **6** was obtained, however, in a low yield (45%) due to the formation of unidentified side products. Gratifyingly, an exclusion of sodium acetate (used as a base to trap the released HCl) from the gently heated reaction mixture furnished **6** in good yield (71%, entry 2). Then we decided to investigate the relative stoichiometry of reagents used in the reaction and we found that full conversion of **5** to **6** is reached not only with 2 equivalents of $CuCl_2$ (65%, entry 3), but even with an equimolar amount of copper(II) chloride with respect to the substrate **5** (74%, entry 4). Next, we explored two different (aprotic) solvents to compare the reactivity with that observed in AcOH and found dichloromethane to be an equally suitable solvent (71%, entry 5) in contrast with THF (47%, entry 6). We further looked at the nature of the palladium catalyst and found both $Pd(OAc)_2$ (64%, entry 7) and $PdCl_2(MeCN)_2$ (69%, entry 8) to perform comparably well. Finally, the role of $CuCl_2$ in the reaction was scrutinised: the replacement of copper(II) chloride by either $Cu(OAc)_2$ (entry 9) or benzoquinone (entry 10) had, however, a detrimental effect on the

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Table 1 Reaction conditions of Pd(II)-catalysed bicyclisation according to Scheme 3

Entry	Solvent	Catalyst, additive(s)	Temperature, time	Isolated yield (%) of **6**[a]
1	AcOH	0.1 equiv. $PdCl_2$, 3 equiv. $CuCl_2$, 3 equiv. AcONa	20 °C, 24 h	45
2	AcOH	0.1 equiv. $PdCl_2$, 3 equiv. $CuCl_2$	35 °C, 24 h	71
3	AcOH	0.1 equiv. $PdCl_2$, 2 equiv. $CuCl_2$	40 °C, 48 h	65
4	AcOH	0.1 equiv. $PdCl_2$, 1 equiv. $CuCl_2$	40 °C, 48 h	74
5	CH_2Cl_2	0.1 equiv. $PdCl_2$, 2 equiv. $CuCl_2$	35 °C, 22 h	71
6	THF	0.1 equiv. $PdCl_2$, 2 equiv. $CuCl_2$	35 °C, 22 h	47
7	AcOH	0.1 equiv. $Pd(OAc)_2$, 2 equiv. $CuCl_2$	40 °C, 12 h	64
8	AcOH	0.1 equiv. $PdCl_2(MeCN)_2$, 2 equiv. $CuCl_2$	40 °C, 12 h	69
9	AcOH	0.2 equiv. $Pd(OAc)_2$, 3 equiv. $Cu(OAc)_2$	30 °C, 48 h	Complex mixture
10	THF	0.2 equiv. $PdCl_2$, 1.1 equiv. benzoquinone, 2 equiv. LiCl	45 °C, 48 h	Complex mixture
11	AcOH	1 equiv. $PdCl_2$	40 °C, 26 h	0

[a] After flash column chromatography.

desired transformation of **5** to **6** and only complex reaction mixtures were obtained. In addition, when a control experiment using a stoichiometric amount of $PdCl_2$ was performed (entry 11), full consumption of **5** was observed but with no formation of desired bicycle **6**. Instead, the presence of other unidentified products was noticed. All these results clearly indicate that copper(II) chloride is an indispensable reagent and plays a crucial role in this particular transformation (Table 1, Fig. 1).

Although mechanistic studies of Pd(II)/$CuCl_2$-catalysed *N*,*O*-bicyclisation of aminoalkenitol **5** to **6** have not been carried out, we propose a following mechanistic rationale for this transformation on the basis of results in Table 1: simultaneous coordination of electrophilic $PdCl_2$ with both the terminal double bond and homoallyl hydroxyl group of **5** gives rise to a geometrically favourable chair conformation of π-complex **I**. Subsequent 6-*exo* attack of the nucleophilic nitrogen function establishes a corresponding σ-Pd-complex **II** having coplanar spatial arrangement of (C-3)OH and (C-5)CH_2 bonds. Owing to intrinsic nitrophilic properties of copper(II)-salts, the presence of $CuCl_2$ (crucial for the successful bicyclisation) may force the formation of a heterobimetallic σ-complex **III** that can possibly furnish bicycle **6** in two ways: either *via* reductive elimination of **III** with concomitant release of HCl and Pd^0 that is subsequently reoxidised to Pd^{2+} by $CuCl_2$, or alternatively, by prior transmetalation of **III** with $CuCl_2$ to form the σ-Cu-complex that undergoes an analogous reductive elimination as **III** to regenerate the Pd(II)-catalyst and to release HCl (Fig. 1).

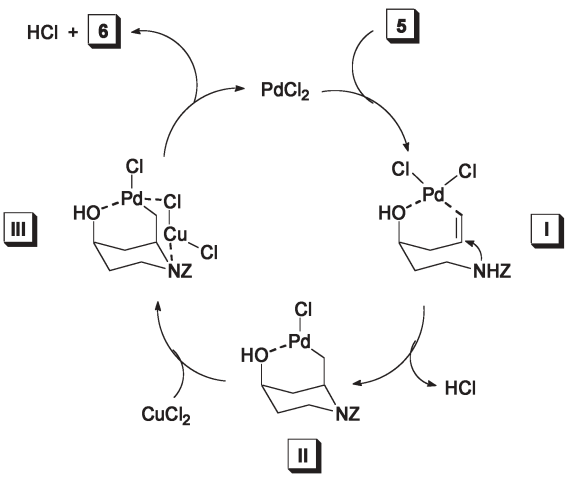

Fig. 1 Mechanistic proposal of Pd(II)/$CuCl_2$-catalysed bicyclisation.

In conclusion, we have described a novel method for the preparation of the 6-oxa-2-azabicyclo[3.2.1]octane skeleton featuring Pd(II)/$CuCl_2$-catalysed *N*,*O*-bicyclisation as a key step. We are currently applying this new transformation to other suitable substrates as well as exploring its asymmetric version.

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Notes and references

1 *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. Negishi, Wiley-Interscience, New York, 2002.
2 Presented as a part of a lecture given at *"N,O-Heterocycles and more - 1. BBS Symposium on Organic Chemistry"*, Bratislava, 2005.
3 An analogous *O*,*O*-bicyclisation of unsaturated diols under similar reaction conditions is known: Ľ. Remeň, PhD Thesis, Bratislava, 1998; M. Babjak, PhD Thesis, Bratislava, 2004; M. Babjak, Ľ. Remeň, O. Karlubíková and T. Gracza, *Synlett*, 2005, 1609–1611.
4 Selection of known reports on the preparation of 6-oxa-2-azabicyclo-[3.2.1]octane skeleton: M. Ferles, M. Lebl, P. Štern and P. Trška, *Collect. Czech. Chem. Commun.*, 1975, **40**, 2183–2190; G. W. J. Fleet and D. R. Witty, *Tetrahedron: Asymmetry*, 1990, **1**, 119–136; B. I. Glänzer, Z. Györgydeák, B. Bernet and A. Vasella, *Helv. Chim. Acta*, 1991, **74**, 343–369; H.-J. Altenbach and K. Himmeldirk, *Tetrahedron: Asymmetry*, 1995, **6**, 1077–1080; C. K. Lee, H. Jiang and A. M. Scofield, *J. Carbohydr. Chem.*, 1997, **16**, 49–62; A. T. Soldatenkov, K. B. Polyanskii, A. W. Temesgen, S. A. Soldatova, N. D. Sergeeva, N. M. Kolyadina and N. N. Lobanov, *Mendeleev Commun.*, 2001, 27–29; J. G. Knight and K. Tchabanenko, *Tetrahedron*, 2003, **59**, 281–286; H. Takahata, Y. Banba, H. Ouchi and H. Nemoto, *Org. Lett.*, 2003, **5**, 2527–2530.
5 A. G. Malmberg and O. Theander, *Phytochemistry*, 1980, **19**, 1739–1742.
6 T. Sekine, N. Fukusawa, Y. Kashiwagi, N. Ruangrungsi and I. Murakoshi, *Chem. Pharm. Bull.*, 1994, **42**, 1360–1362.
7 The asymmetric synthesis of enantiomerically enriched (*R*)-**5** (with 91% ee) is known: Ch.-M. Yu, J.-M. Kim, M.-S. Shin and D. Cho, *Tetrahedron Lett.*, 2003, **44**, 5487–5490.
8 Aminoaldehyde **4** (1 g, 4.8 mmol) was dissolved in dry MeOH (5 ml), tetraallyltin (342 mg, 1.21 mmol, 0.25 equiv.) was added at once and the resulting pale yellow solution was stirred under Ar at 23 °C over 22 h. Water (12 ml) was added, the resulting white suspension was filtered over Celite and solids were washed with CH_2Cl_2 (3 × 30 ml). The organic phase was separated, the water layer extracted with CH_2Cl_2 (30 ml), and the combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo* to yield a crude syrup (1.1 g) that was purified by FLC (33 g of silica gel, 2.5 × 16 cm, hexanes–AcOEt–Et_3N = 3 : 2 : 0.03) to afford pure **5** (980 mg, 88%) as a colourless oil.
9 Aldrich, Product No. 592951.
10 T. M. Cokley, R. L. Marshall, A. McCluskey and D. J. Young, *Tetrahedron Lett.*, 1996, **37**, 1905–1908; A. McCluskey, D. M. Mayer and D. J. Young, *Tetrahedron Lett.*, 1997, **38**, 5217–5218.

11 *Typical procedure*: Aminoalkenitol **5** (100 mg, 0.4 mmol), $PdCl_2$ (7 mg, 0.04 mmol, 0.1 equiv.) and $CuCl_2$ (54 mg, 0.4 mmol, 1 equiv.) were suspended in a glacial AcOH (4 ml) and the resulting light brown mixture was stirred under Ar at 40 °C over 48 h. The brown–black suspension was filtered over Celite, solids were washed with AcOH (5 ml) and the filtrate was co-evaporated with toluene (10 ml) *in vacuo*. The resulting green oil was taken up to CH_2Cl_2 (20 ml), washed with 10% aq. $NaHCO_3$ solution (20 ml) and the water layer was extracted with CH_2Cl_2 (20 ml). Combined organic extracts were washed with brine (20 ml), dried over $MgSO_4$ and evaporated *in vacuo* to yield a yellow–brown oil (95 mg) that was purified by FLC (3.6 g of silica gel, 1.5 × 4.5 cm, hexanes–AcOEt–Et_3N = 3 : 2 : 0.05) to afford pure **6** (73 mg, 74%) as a colourless oil.

