ChemComm

# High yields of diazabicycloalkanes and oxazabicycloalkanes containing medium and large rings from rhodium-catalysed hydroformylation reactions without the need for high dilution conditions

**David J. Bergmann, Eva M. Campi, W. Roy Jackson* and Antonio F. Patti**

*Department of Chemistry, Monash University, Clayton, Victoria, 3168 Australia.*
*E-mail: w.r.jackson@sci.monash.edu.au*

*Received (in Cambridge, UK) 6th May 1999, Accepted 1st June 1999*

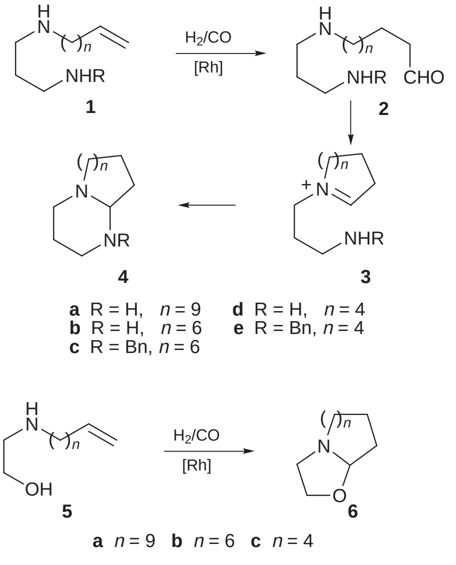
**Rhodium-catalysed reactions of *N*-alkenyl-1,3-diaminopropanes and *N*-alkenylaminoethanols give diazabicycloalkanes and oxazabicycloalkanes containing medium or large rings in excellent yields.**

We have previously reported the preparation of 1,5-diazabicyclo[4.3.0]nonane and 1,5-diazabicyclo[4.4.0]decane in high yield by rhodium-catalysed reactions of appropriate *N*-alkenyl-1,3-diaminopropanes **1** ($n = 1$ or 2) with $H_2$/CO.[1] The reactions presumably involve cyclisation of an initially formed diaminoaldehyde **2** to form an aminopropyl substituted cyclic iminium salt **3** or enamine which subsequently cyclises to give the bicyclic product **4** (Scheme 1). It has been well established that the amino function of an aminoalkene rapidly coordinates to the rhodium atom[2] and as only very low ratios of rhodium to substrate are used (typically 1:100 or greater) it seemed probable that the newly formed aldehyde function should be in close proximity to the rhodium-coordinated amino function and thus cyclisation rather than polymerisation be preferred even for medium and large ring systems. There is indirect evidence that iminium species contained in medium or large rings are susceptible to polymerisation reactions.[3] Thus the possibility that a pendant amino or hydroxy function could be used to trap any such reactive cyclic iminium species was investigated as a general route to the synthesis of bicyclic heterocycles containing medium or large rings.

A series of *N*-alkenyl-1,3-diaminopropanes **1** and *N*-alkenylaminoethanols **5** were thus reacted with $H_2$/CO under a range of conditions and the results are summarised in Table 1.

Excellent yields of compounds **4a** and **6a** containing a thirteen-membered ring fused to six- or five-membered heterocycles were obtained when BIPHEPHOS[4] was used as a ligand in reactions of the primary amine **1a** and the alcohol **5a** (entries 1 and 2). Use of this ligand in hydroformylation reactions has been shown to lead to almost complete regioselectivity for the terminal aldehyde.[1,4,5] The products **4a** and **6a** from these reactions showed no evidence for any compounds containing a methyl-substituted twelve-membered ring which would arise from the products of internal rather than terminal hydroformylation. Reaction of the primary amine **1b** under these conditions led to polymerisation and only a poor yield (28%) of the bicyclic compound containing a ten-membered ring was obtained when the reaction temperature was decreased to 40 °C (entry 3). A reaction of the related secondary amine **1c** however gave an excellent yield of the bicyclic product **4c** using $PPh_3$ as a ligand at 80 °C (entry 4). The product contained *ca.* 10% of compound arising from branched-chain aldehyde. A reaction using BIPHEPHOS with a 1 : 1 ratio of $H_2$/CO gave a complex mixture whose $^1$H NMR spectrum suggested that some hydrogenation of the intermediate iminium species **3** and possibly the substrate **1c** had occurred. Accordingly a reaction was carried out using a 1 : 5 $H_2$/CO gas ratio as this has been shown to minimise the problems associated with substrate hydrogenation.[6] The bicycle **4c** containing a ten-membered ring was now obtained in excellent yield and with > 95% regioselectivity (entry 5). The related aminoethanol **5b** behaved in an identical fashion with excellent yields (*ca.* 93%) of bicyclic compound **6b** containing a ten-membered ring being obtained (entries 6 and 7). Again the reaction involving BIPHEPHOS appeared to be virtually regiospecific.

A reaction of the primary amine **1d** using BIPHEPHOS as ligand at 80 °C gave only polymeric material but a good yield (74%) of the (6,8) bicycle **4d** was obtained when the reaction

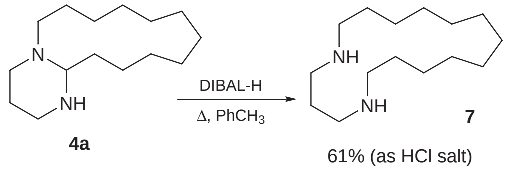


**Scheme 1**

**Table 1** Rhodium-catalysed reactions of *N*-alkenyl-1,3-diaminopropanes **1** and *N*-alkenylaminoethanols **5** with $H_2$/CO[a]

| Entry | Reactant | *n* | R | *T*/°C | Ligand | Ratio $H_2$/CO | Product (ring sizes) | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | 9 | H | 80 | BIPHEPHOS | 1 : 1 | **4a** (6,13) | 80 |
| 2 | **5a** | 9 | — | 80 | BIPHEPHOS | 1 : 1 | **6a** (5,13) | 80 |
| 3 | **1b** | 6 | H | 40 | BIPHEPHOS | 1 : 1 | **4b** (6,10) | 28 |
| 4 | **1c** | 6 | Bn | 80 | $PPh_3$ | 1 : 1 | **4c** (6,10) | 95[c] |
| 5 | **1c** | 6 | Bn | 80 | BIPHEPHOS | 1 : 5 | **4c** (6,10) | 95 |
| 6 | **5b** | 6 | — | 80 | $PPh_3$ | 1 : 1 | **6b** (5,10) | 93[c] |
| 7 | **5b** | 6 | — | 80 | BIPHEPHOS | 1 : 5 | **6b** (5,10) | 93 |
| 8 | **1d** | 4 | H | 50 | BIPHEPHOS | 1 : 1 | **4d** (6,8) | 74 |
| 9 | **1e** | 4 | Bn | 80 | BIPHEPHOS | 1 : 5 | **4e** (6,8) | 95 |
| 10 | **1e** | 4 | Bn | 80 | $PPh_3$ | 1 : 1 | **4e** (6,8) | 14[d] |
| 11 | **5c** | 4 | — | 80 | $PPh_3$ | 1 : 1 | **6c** (5,8) | 92[c] |

[a] Reaction conditions: Substrate (0.5–1 mmol) with substrate: $[Rh(OAc)_2]_2$ : ligand = 200 : 1 : 4 in benzene (5–10 ml) for 20 h with an initial gas pressure ($H_2$ + CO) of 2.76 MPa (400 psi). [b] Isolated yields; products from reactions using BIPHEPHOS as ligand contained > 95% of linear derived material. [c] Containing *ca.* 10% branch-chain derived product. [d] The (6,7) bicyclo compound arising from initial internal hydroformylation was the major product (38%).



**Scheme 2**

temperature was reduced to 50 °C (entry 8). An excellent yield (95%) of almost regiopure material was obtained from a reaction of **1e** using BIPHEPHOS with a 1:5 $H_2$/CO ratio (entry 9). In contrast a reaction using $PPh_3$ as ligand surprisingly gave the (6,7) bicyclo product arising from initial internal hydroformylation as the major product with only a small amount (14%) of the (6,8) compound **4e** (entry 10). However a reaction of the related aminoalcohol **5c** under these conditions gave an excellent yield (92%) of bicyclic products consisting mainly of **6c** together with *ca*. 10% of the methyl-substituted (5,7) compound.

The potential of the bicyclic diamines as precursors of monocyclic diamino compounds was illustrated by ring opening of the (6,13) bicyclic amine **4a** and the related (6,6) compound which was available from previous work.[1] Reactions of these compounds with DIBAL-H in toluene led to formation of 1,5-diazacycloheptadecane **7** and 1,5-diazacyclodecane respectively in good yield (*ca*. 60%) (Scheme 2).[7]

We thank the Australian Research Council for support and provision of a postgraduate award (to D. J. B.) and Johnson Matthey Pty Ltd for a loan of rhodium.

## Notes and references

1 D. J. Bergmann, E. M. Campi, W. R. Jackson, Q. J. McCubbin and A. F. Patti, *Tetrahedron*, 1997, **53**, 17 449.
2 M. E. Krafft, L. J. Wilson and K. D. Onan, *Organometallics*, 1988, **7**, 2528; E. M. Campi, W. R. Jackson, Q. J. McCubbin and A. E. Trnacek, *J. Organomet. Chem*., 1997, **539**, 147.
3 E. M. Campi, W. R. Jackson, Q. J. McCubbin and A. E. Trnacek, *Aust. J. Chem*., 1996, **49**, 219.
4 G. D. Cuny and S. L. Buchwald, *J. Am. Chem. Soc*., 1993, **115**, 2066.
5 G. D. Cuny and S. L. Buchwald, *Synlett*, 1995, 519; I. Ojima, M. Tzamarioudaki and M. Eguchi, *J. Org. Chem*., 1995, **60**, 7078; I. Ojima, D. M. Iula and M. Tzamarioudaki, *Tetrahedron Lett*., 1998, **39**, 4599.
6 T. Rische and P. Eilbracht, *Synthesis*, 1997, 1331.
7 H. Yamamoto and K. Maruoka, *J. Am. Chem. Soc*., 1981, **103**, 4186; R. Alder, E. Heilbronner, E. Honegger, A. B. McEwen, R. E. Moss, E.Olefirowicz, P. A. Petillo, R. B. Sessions, G. R. Weisman, J. M. White and Z.Yang, *J. Am. Chem. Soc*., 1993, **115**, 6580.

*Communication 9/03638E*