ChemComm

New rhodium-catalyzed amination reactions†‡

Harald Trauthwein,[a] Annegret Tillack[b] and Matthias Beller*[b]

[a] *Aventis Research and Technologies, Industriepark Höchst, 65926 Frankfurt, Germany*
[b] *Institut für Organische Katalyseforschung an der Universität Rostock e.V., Buchbinderstr. 5-6, 18055 Rostock, Germany. E-mail: matthias.beller@ifok.uni-rostock.de*

Received (in Basel, Switzerland) 17th May 1999, Accepted 1st September 1999

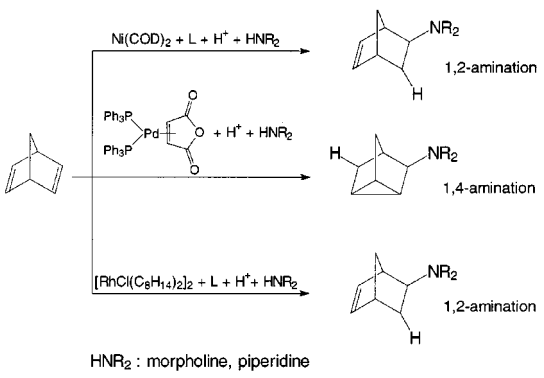
New transition metal-catalyzed reactions of norbornadiene with secondary amines are reported.

The development of efficient protocols for the construction of carbon–nitrogen bonds is of interest owing to the fundamental importance of amines as natural products, pharmacological agents, fine chemicals, and dyes.[1] Regarding the various possibilities to form C–N bonds, the catalytic hydroamination of olefins is the most atom economic process.[1]

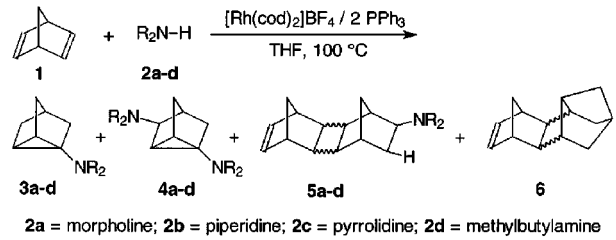
In addition, a wide variety of olefins and amines are both inexpensive and readily available starting materials. Hence, considerable efforts have been undertaken to develop metal-catalyzed hydroamination processes.[2] Among the first transition metal catalysts for hydroamination were Rh salts, *e.g.* $RhCl_3$ introduced by Du Pont.[3] Although a number of Rh complexes catalyze the reaction of ethylene with secondary amines with yields of up to 70%, other olefins do not react. Interestingly, Brunet *et al.*[4] demonstrated later, that $[Rh(PEt_3)_2Cl]_2$ catalyzes both the oxidative amination and the hydroamination of styrene with aniline. Recently, we became interested in catalytic hydroaminations. Our approach to this problem was based on the use of cationic Rh complexes in order to enhance the reactivity of the resulting catalysts. Indeed, a mixture of $[Rh(cod)_2]^+BF_4^-$/2 PPh_3 catalyzes the reaction of aromatic olefins with secondary amines.[5] Surprisingly, no hydroamination takes place, but a rare example of intramolecular oxidative amination is observed to yield *N*-(2-arylethenyl)amines and arylethane in good yields. Here, we describe the first extensions of this methodology to aliphatic olefins, especially norbornadiene (nbd).

The addition of nucleophiles H–X to nbd yields, in general, tricyclic pseudo-1,4-addition products (Scheme 1). This reaction is catalyzed by both acids and Pd complexes.[6]

Adaptation of our previously reported procedure for the oxidative amination of styrene with morpholine to nbd yields, under standard conditions (2.5 mol% $[Rh(cod)_2]^+BF_4^-$, 5 mol% PPh_3, THF reflux), three new amination products **3a**, **4a** and **5a** in 25, 33 and 31% yield, respectively[7] (Scheme 2, Table 1). Furthermore, small amounts (< 3%) of hydrodimerization **6** and hydrooligomerization products were observed. The structure of **3a** and **4a** was unambiguously proved by ^1H and ^{13}C NMR spectroscopy and MS, *e.g.* the ^{13}C NMR spectrum of **3a** exhibit one quaternary, two different secondary and two tertiary carbon centers of the nortricyclene group and two signals of the morpholino ring, while the ^{13}C NMR spectrum of **4a** exhibits one quaternary, four different tertiary and two secondary carbon centers of the nortricyclene group and four signals of the two morpholino rings. **5a** has been identified by GC–MS. Interestingly, **4a** is obtained as a pure diastereomer, where the two morpholino rings point away from each other.



Scheme 1 Known addition of amines to nbd.



Scheme 2 Rh-catalyzed reaction of morpholine with nbd.

Table 1 Reaction of morpholine with norbornadiene

Entry	Catalyst (mol%)	Solvent	Olefin: amine	Yield **3a**[a] (%)	Yield **4a**[a] (%)
1	2.5	THF	4:1	25	33
2	5	THF	4:1	43	14
3	10	THF	4:1	47	5
4	2.5	THF	10:1	7	46
5	2.5	THF	1:2	32	7
6	2.5	Toluene	4:1	3	88

[a] The yield (referred to amine) was determined by GC using an internal standard.

Concerning **3a** and **4a** it is noteworthy that, unlike in previously published amination procedures of nbd, at least one amine is bound directly to one of the C atoms of the cyclopropyl ring. This structural motif can only be explained by a *pseudo*-1,3-addition mode to nbd.[8] To the best of our knowledge *pseudo*-1,3-additions of nucleophiles H–Nu (Nu = NR_2, OR, SR, *etc.*) to nbd have not been reported previously.

Next, we modified the reaction conditions in order to improve the selectivity of the amination reaction. In a series of reactions carried out on 5 mmol scale the amount of catalyst, reaction temperature, solvent and olefin to amine ratio was varied. Reactions employing a larger amount of catalyst (5, 10 mol%) gave significantly higher yields of **3a** (up to 47%) while the yield of the diaminated product **4a** is decreased to only 5%. Use of a ten-fold excess of norbornadiene to morpholine resulted in a drastic decrease of **3a** (7%), but **4a** is obtained in 46%. Consistently at lower amine to olefin ratio the yield of **4a** is

† Dedicated to Professor Dirk Walther on the occasion of his 60th birthday.
‡ Considered as Part 7 of the series Anti-Markovnikov-reactions; for part 6 see M. Beller, H. Trauthwein, M. Eichberger, C. Breindl and T. E. Müller, *Eur. J. Inorg. Chem.*, 1999, 1121.

This journal is © The Royal Society of Chemistry 1999

increased. The use of toluene at higher reaction temperature appeared to be especially suitable for the formation of the diaminated product **4a** (88%).

Analogous to morpholine we reacted other secondary amines and aniline with nbd in the presence of 5 mol% $[Rh(cod)_2]^+BF_4^-$ and 10 mol% PPh_3 in THF in a glass pressure tube at 100 °C (Table 2). While aniline gave only non-aminated dimerization products of nbd, all secondary amines gave a total yield of amination products of 84–99%.

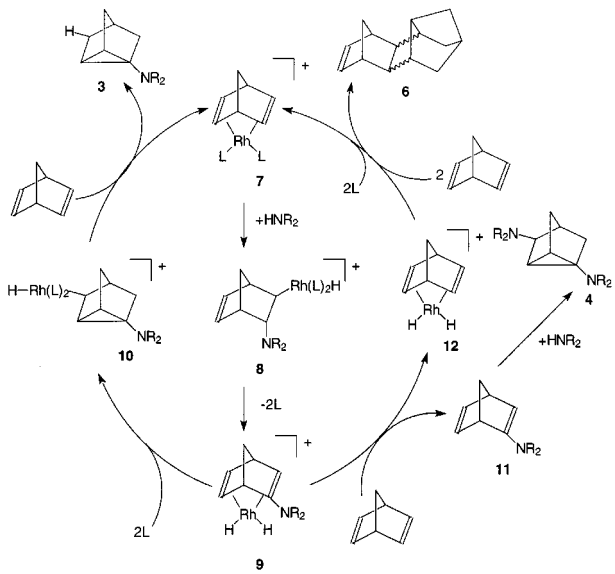
Table 2 Reaction of norbornadiene with amines[a]

Entry	Amine	Yield amines[b] (%)	Yield **3**[c] (%)	Yield **4** (%)
1	Morpholine **2a**	91	43	14[c]
2	Piperidine **2b**	99	52	17[d]
3	Pyrrolidine **2c**	84	52	10[d]
4	*n*-Butylmethylamine **2d**	90	46	13[d]

[a] Ratio of nbd:amine = 4:1, 5 mol% $[Rh(cod)_2]BF_4/2PPh_3$ relative to amine, 20 h reflux in THF. [b] Overall yield of amination products (**3** + **4** + **5**). [c] The yield (referred to amine) was determined by GC using an internal standard. [d] The yield (referred to amine) was determined by GC by percentage area.

The major product under these conditions were the mono-amination products **3b**–**d**. However, in all cases significant amounts of 2,5-bis(*N*-amino)tricyclo[2.2.1.$0^{2,6}$]heptane **4b**–**d** and aminated nbd dimers were formed.

Here, we describe the first example of the catalytic *pseudo*-1,3-addition of nucleophiles (amines) to nbd. In general, amination of nbd with amines proceeds in high yield but with only moderate selectivity. Although the reaction has not been fully optimized, yields of 2-(*N*-morpholino)tricyclo-[2.2.1.$0^{2,6}$]heptane **3a** of *ca.* 50% were obtained in THF at 100 °C. On the other hand a high yield (88%) of 2,5-bis(*N*-morpholino)tricyclo[2.2.1.$0^{2,6}$]heptane **4a** was obtained in toluene at 140 °C. While little mechanistic work has been conducted on the new amination reaction at this time, we propose that the reaction occurs by a catalytic cycle shown in Scheme 3.



Scheme 3 Proposed mechanism for the Rh-catalyzed amination of nbd.

Olefin exchange of cyclooctadiene by nbd will give the corresponding nbd complex **7**. Here, the double bonds are activated for a nucleophilic attack of the amine leading to **8**. Alternatively, **8** may be formed by insertion of the olefin into the Rh–N bond of a hydridoamidorhodium species. Although this mechanism seems unlikely owing to the stereochemistry required for the following β-hydride elimination, it has been shown that cationic Rh complexes are able to activate N–H bonds under similar conditions.

β-Hydride elimination would form the Rh–dihydride complex with a chelating enamine ligand **9**. Stepwise hydrogen transfer with concurrent double bond shift would give the Rh alkyl complex **10**. Subsequently, reductive elimination yields **3**. On the other hand ligand exchange of the enamine with nbd would yield **11** and **12**. It is known in the literature[9] that **11** reacts with amines to give **4**. While it is easy to explain the improved yield of **4** with increased olefin to amine ratio owing to the increased ligand exchange with nbd, we do not understand the influence of the catalyst concentration. In addition it is obvious that higher reaction temperatures (140 °C, toluene) favor the ligand exchange, hence yielding **4** predominantly. The occurrence of the hydrodimerization product **6** confirms the existence of Rh–hydride species.

Regarding the synthetic value of this new method, it is important to note that a number of aliphatic polycyclic amines such as amantadine, memantine, venritidine, carmantadine, oxphaman and amantocillin are interesting pharmacologically active compounds.[10] New analogs may be prepared by our method.

In conclusion, we have developed a new type of Rh-catalyzed amination. Here, nbd is aminated in an unusual *pseudo*-1,3-addition mode. Both mono- as well as di-aminated products are accessible as major products.

This work is supported by the Deutsche Forschungsgemeinschaft (BE 1931/3-1).

Notes and references

1 For leading reviews of hydroamination, see: M. Beller and T. Müller, *Chem. Rev.*, 1998, **98**, 675; D. M. Roundhill, *Chem. Rev.* 1992, **92**, 1; J.-J. Brunet, D. Neibecker and F. Niedercorn, *J. Mol. Catal.*, 1989, **49**, 235.

2 Recent examples: R. Dorta, P. Egli, F. Zürcher and A. Togni, *J. Am. Chem. Soc.*, 1997, **119**, 10 857; J.-J. Brunet, *Gazz. Chim. Ital.*, 1997, **127**, 111; V. M. Arrenodo, S. Tian, F. E. McDonald and T. J. Marks, *J. Am. Chem. Soc.*, 1999, **121**, 3633.

3 D. R. Coulson, *Tetrahedron Lett.*, 1971, **12**, 429.

4 J.-J. Brunet, D. Neibecker and K. Philippot, *J. Chem. Soc., Chem. Commun.*, 1992, 1215; *Tetrahedron Lett.*, 1993, **34**, 3877; J.-J. Brunet, G. Commenges, D. Neibecker and K. Philippot, *J. Organomet. Chem.*, 1994, **469**, 221.

5 M. Beller, M. Eichberger and H. Trauthwein, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2225; M. Beller, M. Eichberger and H. Trauthwein, *Catalysis of Organic Reactions*, ed. F. Herkes, Marcel Dekker, New York, 1998; M. Beller, H. Trauthwein, M. Eichberger, J. Herwig, T. E. Müller and O. Thiel, *Eur. J. Chem.*, 1999, **5**, 1306; M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, T. E. Müller and A. Zapf, *J. Organomet. Chem.*, 1998, **566**, 277; M. Beller, H. Trauthwein, M. Eichberger, C. Breindl and T. E. Müller, *Eur. J. Inorg. Chem.*, 1999, 1121.

6 L. Schmerling, J. P. Luvisi and R. W. Welak, *J. Am. Chem. Soc.*, 1956, **78**, 2819; J. Kiji, S. Nishimura, S. Yoshikawa, E. Sasakawa and J. Furukawa, *Bull. Chem. Soc. Jpn.*, 1974, **47**, 2523.

7 *General procedure:* 89.3 mg $[Rh(cod)_2]BF_4$ (0.22 mmol) and 115.4 mg PPh_3 (0.44 mmol) were mixed in 10 ml THF. Subsequently, 0.38 ml morpholine (4.40 mmol) and 1.92 ml nbd (17.6 mmol) were added at room temp. The reaction was heated to reflux for 20 h before being cooled to room temp. After removal of the solvent *in vacuo*, the residue was dissolved in 20 ml CH_2Cl_2 and extracted three times with 5% HCl. NaOH was added to the combined aqueous phases until a pH of 9 was reached. The aqueous phase was then extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was distilled off. The products were obtained after column chromatography ($CHCl_3$–MeOH = 30:1). Isolated yields: **3a**: 32% (252 mg); **3b**: 40% (312 mg); **3c**: 37% (266 mg); **3d**: 34% (268 mg); **4c**: 4% (23 mg).

8 We term this reaction of amines with norbornadiene a pseudo-1,3-addition in agreement with literature for 1,4-addition reactions.

9 A. G. Cook, M. L. Absi and V. K. Bowden, *J. Org. Chem.*, 1995, **60**, 3169.

10 G. D. Diana and F. Pancic, *Angew. Chem.*, 1976, **88**, 458; E. X. Albuquerque, A. T. Eldefrawi, M. E. Eldefrawi, N. A. Mansour and M.-C. Tsai, *Science*, 1978, **199**, 788; Negwer, *Organic-chemical Drugs and their Synonyms*, Fachinformationszentrum Chemie, Berlin.

Communication 9/03920A