doi:10.2533/chimia.2014.231 Chimia 68 (2014) 231–234

Benign Synthesis of Indoles from Anilines and Epoxides: New Application for Ruthenium Pincer Catalysts

Angèle Monney[§], Miguel Peña-López, and Matthias Beller*

[§]SCS-Metrohm Foundation Award for best oral presentation

Abstract: For the first time, ruthenium pincer complexes such as Ru-MACHO-BH were successfully used as catalysts in the domino-synthesis of indoles from anilines and epoxides. Following previously optimised procedures, a variety of indoles were produced in an atom-efficient manner with water and hydrogen as the only stoichiometric side-products. The β-amino alcohol, resulting from the ring-opening of the epoxide with the aniline derivative, undergoes dehydrogenation, followed by condensation with excess aniline and the final intramolecular cyclisation affords the desired indole. Ru-MACHO-BH showed similar catalytic activity than our previously reported *in situ* prepared catalyst ($Ru_3(CO)_{12}$/dppf) without further optimisation of the reaction conditions.

Keywords: Alcohol dehydrogenative activation · Anilines and epoxides · Indole synthesis · Ru-MACHO-BH · Ruthenium pincer catalyst

Introduction

With the increasing demand for more sustainable chemical transformations, the development of new catalytic reactions allowing for the synthesis of valuable, complex molecules from cheap and abundant feedstock has become an important topic of today's research. In this regard in recent years, the 'hydrogen autotransfer' methodology – also called 'hydrogen borrowing' – has become a powerful tool for the benign construction of C–C and C–N bonds using alcohols as coupling reagents.[1] Such transformations are generally achieved using suitable transition-metal catalysts and ligands, with water (and possibly hydrogen gas) as the only stoichiometric waste. In the last decade, considerable advances have been made in the design of efficient catalytic systems based mainly on ruthenium and iridium capable of activating otherwise unreactive substrates.[2]

Of particular interest is the use of pincer complexes with cooperative (non-innocent) ligands which show high activity notably in the dehydrogenative activation of alcohols.[2e,2p,3] In this respect, our group has recently made use of ruthenium(II) complexes bearing aliphatic non-innocent PNP pincer ligands, such as commercially available Ru-MACHO (**1a**, Scheme 1), in a variety of catalytic (de)hydrogenation reactions. For example, ethyl acetate was efficiently produced from ethanol using very small quantities of catalyst **1a** along with a catalytic amount of base, reaching a TON >15000 at only 90 °C (reaction (a), Scheme 1).[4] This industrially important reaction allows for a cost-efficient synthesis of EtOAc with the co-production of valuable hydrogen. With the increasing demand for alternative fuels, we also focused on the production of hydrogen from alcohols.[5] For the first time aqueous-phase methanol dehydrogenation and reforming was achieved at temperatures below 100 °C using homogeneous catalyst **1c** in the presence of a base (reaction (b), Scheme 1).[5b] Excellent catalyst turnover numbers (>350000) and turnover frequencies (4700 h^{-1}) were observed with low levels of contaminant CO gas (<10 ppm). A base-free bi-catalytic system was also developed and H_2 was produced with a TON >4700 using the synergistic combination of **1b** with $Ru(H)_2(dppe)_2$.[5a] On the other hand, complex **1b** catalysed efficiently the hydrogenation of oxalic acid esters into either alkyl glycolate or ethylene glycol in high yield and excellent selectivity with high catalyst TONs (5700) and TOFs (360 h^{-1}) at 120 °C under 60 bar of H_2 (reaction (c), Scheme 1).[6] Other groups also reported the use of this type of complex as catalyst for (de)hydrogenation reactions. Hence, Gusev's group reported the use of various osmium and ruthenium pincer complexes in dehydrogenation reactions.[7] Catalyst **1d** was active in the transfer hydrogenation of various ketones with either *iso*-propanol or ethanol as hydrogen donors (reaction (d), Scheme 1). In addition, Ding and co-workers developed an elegant catalytic hydrogenation of cyclic carbonates using **1a** as catalyst under relatively mild conditions (reaction (e), Scheme 1).[8] Notably the hydrogenation of ethylene carbonate – a product of the omega process where CO_2 is reacted with ethylene oxide – generates methanol and ethylene glycol, two important bulk chemicals. The catalytic hydrogenation of esters using Ru-MACHO (**1a**) was reported by Takasago International Corporation – patent holder of this catalyst (reaction (f), Scheme 1).[9] Importantly a large-scale hydrogenation of methyl (*R*)-lactate was performed without loss of optical purity (<1% loss). Ikariya and co-workers described the selective hydrogenation of fluorinated esters using **1a** as catalyst (reaction (g), Scheme 1).[3a] Here again, hydrogenation of a chiral substrate – (*R*)-2-fluoropropionate – proceeded smoothly without serious loss of enantiomeric excess. Simultaneously, Lazzar and Cassani reported the hydrogenation of perfluoro methyl esters using **1a** at 40 °C under 10 bar H_2 (reaction (g), Scheme 1).[10]

*Correspondence: Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e.V. an der Universität Rostock
Albert-Einstein-Strasse 29a
D-18059 Rostock, Germany
Tel.: +49 381 1281 113
E-mail: matthias.beller@catalysis.de

Despite this handful of exciting reports and unlike other well-known aromatic pincer complexes,[2e,3b,3c,3e] aliphatic pincer complexes **1** have not been examined for dehydrogenative activation of easily available substrates to produce more complex, valuable building blocks for organic synthesis. Therefore we decided to explore the catalytic activity of such complexes in the synthesis of indoles *via* a so-called domino reaction.

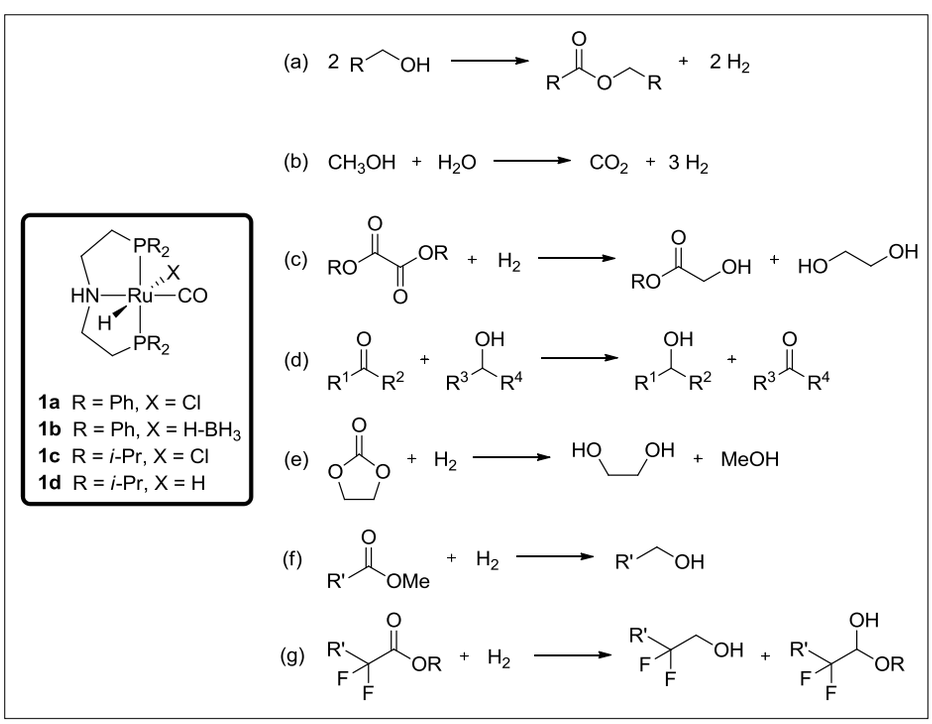
Results and Discussion

Most recently, our group described the synthesis of indoles from anilines and epoxides using an *in situ* prepared ruthenium catalyst.[11] This domino reaction includes the ring-opening of an epoxide (**3**–**5**) with an aniline derivative (**2**), followed by a ruthenium-catalysed cyclisation to give the indole product (**6**–**8**, Scheme 2). The latter step is thought to proceed through the dehydrogenation of the formed β-amino alcohol **I** to give intermediate **II**, which condenses with excess aniline to give the imine **III** before intramolecular cyclisation provides the desired indole product. A screening of catalyst precursors and ligands and optimisation of the conditions led to the efficient transformation of aniline (1.2 equiv.) and cyclohexene oxide into the desired 1,2,3,4-tetrahydrocarbazole using commercially available $Ru_3(CO)_{12}$ (1 mol%), 1,1'-bis(diphenylphosphino) ferrocene (dppf, 3 mol%) and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, 10 mol%) in 1,4-dioxane at 150 °C for 22 h in a sealed tube. Using these conditions, various aniline derivatives were reacted with cyclohexene oxide to afford the corresponding indole products in moderate to good yields. However, when the epoxide was changed to styrene oxide, only traces of product were observed under the same conditions. After careful investigation of the reaction conditions, it was found that activation of the ring-opening step using a catalytic amount of $Zn(OTf)_2$ (2 mol%) prior to the Ru-catalysed cyclisation allowed the reaction to proceed smoothly to the desired indole derivatives. With this sequential procedure, various substituted anilines and epoxides were successfully transformed into the corresponding indoles.

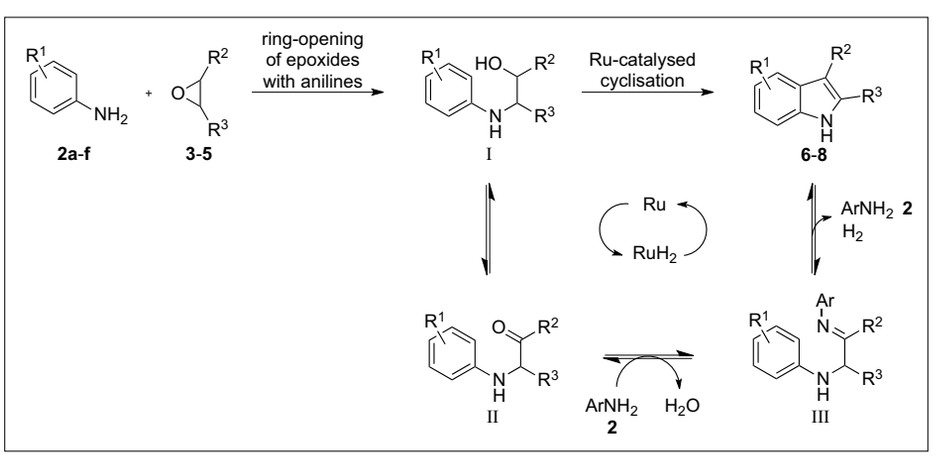
In the present work we studied the catalytic activity of Ru-MACHO-BH (**1b**, Scheme 1) in the reaction of anilines and epoxides to give indoles using our previously optimised conditions. The one-step reaction of aniline (**2a**, Table 1) and cyclohexene oxide (**3**, Table 1) in the presence of 3 mol% **1b** and 10 mol% *p*-TsOH·H_2O in 1,4-dioxane at 150 °C for 22 h in a sealed tube (conditions **A**, Table 1) produced the desired indole **6a** in 86% isolated yield (Table 1, entry 1). Extending the reaction time to 30 h allowed the reaction to proceed to completion and a yield of 98% was obtained (Table 1, entry 2), matching our best result previously reported. A lower catalyst loading (1 mol% **1b**) led to a slower reaction and **6a** was isolated in a 45% yield along with about 50% of the ring-opening intermediate **I** (Table 1, entry 3), which supports our proposed mechanism. In the absence of *p*-TsOH·H_2O, no indole product was observed and only intermediates **I** and **II** were isolated in about 30% and 17% yield, respectively (Table 1, entry 4), demonstrating the importance of the additive not only in the ring-opening process but also in the ruthenium-catalysed cyclisation.

To expand the scope of this reaction, different substituted anilines (**2b**–**2f**) were also reacted with cyclohexene oxide (**3**) under conditions **A** and the desired indoles (**6b**–**6f**) were obtained in moderate to good yields (Table 1, entries 5–9). Interestingly, in the case of *para*-substituted anilines (**2b**, **2d** and **2e**), the obtained isolated yields using Ru-MACHO-BH as catalyst were higher than when using our previously reported *in situ* prepared catalyst ($Ru_3(CO)_{12}$/dppf). Considering that no further optimisations were performed on the present catalytic system, these results demonstrate the high activity of catalyst **1a** and even better yields could be expected if the conditions were to be customised. On the other hand, the *ortho*-substituted anilines (**2c** and **2f**) reacted in a less efficient manner than with our previous system and only moderate yields were observed. Presumably, the bulky tridentate PNP ligand may cause higher steric hindrance than the bidentate dppf during the aniline coordination.

The higher activity of catalyst **1b** was

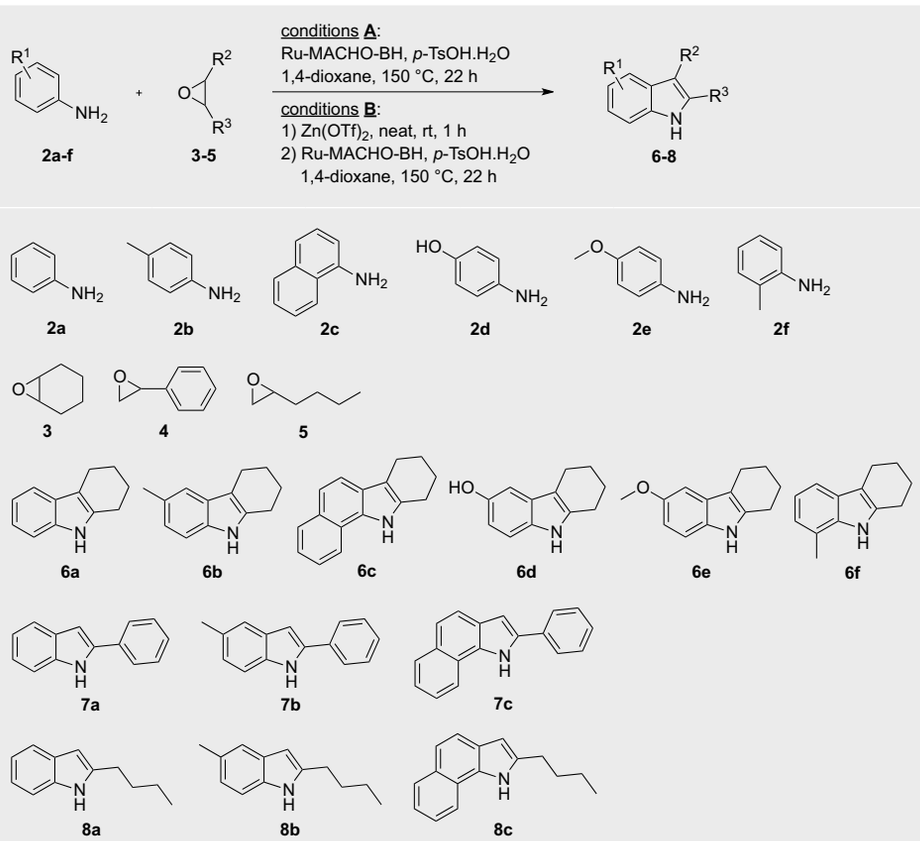


Scheme 1. Catalytic applications of aliphatic pincer complexes **1**.



Scheme 2. Ruthenium-catalysed synthesis of indoles from anilines and epoxides.

Table 1. Ruthenium-catalysed synthesis of indoles from anilines and epoxides.



entry	aniline	epoxide	conditions[a]	product	yield[b]
1	**2a**	**3**	**A**	**6a**	86%
2[c]	**2a**	**3**	**A**	**6a**	98%
3[d]	**2a**	**3**	**A**	**6a**	45%[e]
4[f]	**2a**	**3**	**A**	**6a**	0%[g]
5	**2b**	**3**	**A**	**6b**	82%
6	**2c**	**3**	**A**	**6c**	55%
7	**2d**	**3**	**A**	**6d**	79%
8	**2e**	**3**	**A**	**6e**	80%
9	**2f**	**3**	**A**	**6f**	64%
10	**2a**	**4**	**A**	**7a**	36%[h,i]
11	**2a**	**5**	**A**	**8a**	53%[j]
12	**2a**	**4**	**B**	**7a**	35%[k]
13	**2a**	**5**	**B**	**8a**	62%[l]
14	**2b**	**4**	**B**	**7b**	55%[m]
15	**2b**	**5**	**B**	**8b**	78%
16	**2c**	**4**	**B**	**7c**	23%
17	**2c**	**5**	**B**	**8c**	88%[n]

[a]Conditions **A**: aniline (1.2 mmol), epoxide (1.0 mmol), Ru-MACHO-BH (3 mol%), *p*-TsOH·H_2O (10 mol%), 1,4-dioxane (1 mL), 150 °C, 22 h; Conditions **B**: 1) aniline (1.2 mmol), epoxide (1.0 mmol), $Zn(OTf)_2$ (2 mol%), neat, rt, 1 h, 2) Ru-MACHO-BH (3 mol%), *p*-TsOH·H_2O (10 mol%), 1,4-dioxane (1 mL), 150 °C, 22 h. [b]Isolated yield after column chromatography. [c]Reaction run for 30 h. [d]Reaction run with 1 mol% of Ru-MACHO-BH. [e]Ring-opening product **I** isolated in about 50% yield (*cis*/*trans* 1:1). [f]Reaction run in the absence of *p*-TsOH·H_2O. [g]Ring-opening product **I** isolated in about 30% yield (*cis*/*trans* 1:1) and dehydrogenation product **II** isolated in 17% yield. [h]As a mixture of 2-phenylindole and 3-phenylindole in a 36:64 ratio. [i]Ring-opening product **I** isolated in 46% yield. [j]Ring-opening product **I** isolated in 31% yield. [k]Ring-opening product **I** isolated in 56% yield. [l]Ring-opening product **I** isolated in 15% yield. [m]Ring-opening product **I** isolated in 40% yield. [n]As a mixture of 2-phenylindole and 3-phenylindole in a 44:56 ratio.

also observed when aniline (**2a**) was reacted with styrene oxide (**4**) instead of cyclohexene oxide, although the selectivity was poor. More specifically, a 36:64 mixture of 2-phenylindole (**7a**) and 3-phenylindole was obtained in 36% yield along with 46% of the corresponding intermediate **I** (Table 1, entry 10). Notably, using the $Ru_3(CO)_{12}$/dppf system, only 22% of the desired indole were isolated.[11] Better selectivity was observed when reacting 1,2-epoxyhexane (**5**) with aniline. The desired 2-butylindole (**8a**) was isolated as single isomer in 53% yield along with 31% of the corresponding intermediate **I** (Table 1, entry 11).

In contrast with our previous report,[11] the use of a sequential reaction procedure (conditions **B**, Table 1) involving the preliminary zinc-catalysed aminolysis of the epoxide with the aniline derivative did not lead to a significant improvement of the yields. In the case of the reaction of aniline (**2a**) with styrene oxide (**4**), the selectivity problem was resolved using the sequential procedure, but the yield remained the same (Table 1, entry 12 *vs* entry 10). A slightly improved but still moderate yield was obtained when reacting aniline with 1,2-epoxyhexane (**5**) giving 62% of the desired indole (Table 1, entry 13 *vs* entry 11). This sequential procedure was also applied in the reactions of *p*-toluidine (**2b**) or 1-naphthylamine (**2c**) with either styrene oxide (**4**) or 1,2-epoxyhexane (**5**) producing the corresponding indoles in low to moderate yields in the case of **4** (Table 1, entries 14 and 16) and in good yields in the case of **5** (Table 1, entries 15 and 17).

In conclusion, we demonstrated a new catalytic application of the aliphatic pincer complex Ru-MACHO-BH (**1b**) to give indoles from easily available anilines and epoxides. This straightforward one-step reaction allowed for the efficient synthesis of biologically relevant heterocycles. In general, good isolated yields were obtained using **1b**, similar to an *in situ* prepared catalyst based on $Ru_3(CO)_{12}$ and dppf.[11] It should be noted that no further optimisations were performed on this new catalytic system and that improved yields could be expected if the conditions were to be customised. Such a new application of commercially available ruthenium complex **1b** shows the extent of this catalyst's activity and opens new opportunities for the use of pincer catalysts in more complex reactions.

Experimental Section

General Information

Unless otherwise stated, all reactions were conducted under an argon atmosphere with exclusion of moisture from

reagents and glassware using standard Schlenk techniques for the manipulation of air sensitive compounds. Reaction temperatures refer to external bath temperatures. TLCs were carried out on silica gel 60 F_{254} (layer thickness 0.2 mm) and components were located by observation under UV light. Purifications by column chromatography were performed on silica gel (230–400 mesh) using 4–10% ethyl acetate/heptane as eluent. NMR spectra were recorded at room temperature on Bruker spectrometers (Fourier 300, AV 300 or AV 400) using residual solvent signal as internal standard (7.26 ppm (^{1}H) and 77.0 ppm (^{13}C) in chloroform). Unless otherwise stated, commercial reagents were used as received without purification. All synthesised compounds were fully characterised and reported in our previous paper.[11]

General Procedure for the Ruthenium-catalysed Synthesis of Indoles from Anilines and Epoxide Using Conditions A (One-step Procedure)

In a glass pressure tube (25 mL) under an argon atmosphere, Ru-MACHO-BH (**1b**, 17.6 mg, 0.03 mmol), *p*-toluenesulfonic acid monohydrate (19.0 mg, 0.10 mmol), the aniline (**2a**–**f**, 1.2 mmol) and the epoxide (**3**–**5**, 1.0 mmol) were dissolved in 1,4-dioxane (1 mL). The pressure tube was then closed and the resulting mixture was stirred at 150 °C for 22 h. After cooling down to room temperature, the crude mixture was directly purified by column chromatography (SiO_2, EtOAc/heptane 96:4) to afford, after concentration and high-vacuum drying, the corresponding indoles (**6**–**8**) in the reported yields.

General Procedure for the Ruthenium-catalysed Synthesis of Indoles from Anilines and Epoxides Using Conditions B (Sequential Reaction Procedure)

In a glass pressure tube (25 mL) under an argon atmosphere, $Zn(OTf)_2$ (7.3 mg, 0.02 mmol), the aniline (**2a**–**c**, 1.2 mmol) and the epoxide (**4**, **5**, 1.0 mmol) were stirred at room temperature for 1 h. Ru-MACHO-BH (**1b**, 17.6 mg, 0.03 mmol) and *p*-toluenesulfonic acid monohydrate (19.0 mg, 0.10 mmol) were then added and dissolved in 1,4-dioxane (1 mL). The pressure tube was closed and the resulting mixture was stirred at 150 °C for 22 h. After cooling down to room temperature, the crude mixture was directly purified by column chromatography (SiO_2, EtOAc/heptane 96:4) to afford, after concentration and high-vacuum drying, the corresponding indoles (**7**, **8**) in the reported yields.

Received: January 16, 2014

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