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Ring-Opening Reactions

Ruthenium-Catalyzed Synthesis of Indoles from Anilines and Epoxides

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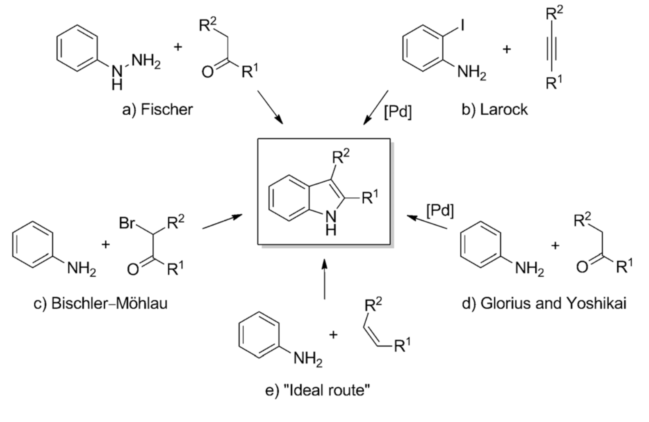
Abstract: A general synthetic route to indoles from readily available anilines and epoxides by using ruthenium catalysis is described. This straightforward transformation allows a variety of indoles to be obtained in good yields by using $[Ru_3(CO)_{12}]$/1,1′-bis(diphenylphosphino)ferrocene as the catalytic system. Water and hydrogen are formed as the only stoichiometric by-products, making this process highly atom efficient.

The indole moiety constitutes one of the most important heterocycles in nature. It is present in many natural products, pharmaceutical agents, and agrochemicals,[1] and binds to many receptors with high affinity.[2] Despite the significant number of powerful methodologies for the synthesis of indoles,[3] the development of new, efficient, versatile, and regioselective strategies is still a field of great interest.

To date, the Fischer indole synthesis from aryl hydrazines and carbonyl compounds represents the most general synthetic route due to its operational simplicity and acceptance of a wide range of compatible functional groups (Scheme 1 a).[4] However, the common instability and toxicity of hydrazines has led to the development of alternative syntheses starting from less expensive and more available reagents, such as anilines. For example, the Bischler–Möhlau synthesis allows the preparation of indoles from anilines and α-haloketones,[5] whereas the more recently developed Larock procedure makes use of modified aniline derivatives, such as *ortho*-haloanilines, in the presence of palladium catalysts (Scheme 1 b and c).[6]



Scheme 1. Traditional syntheses of indoles.

More recently, Glorius and co-workers have developed a palladium-catalyzed oxidative cyclization of *N*-aryl enamines derived from anilines and ketones to afford the corresponding indoles (Scheme 1 d).[7] Alternatively, the research groups of Yoshikai,[8] Jiao,[9] Cacchi,[10] Zhao,[11] and Liang[12] have explored the use of different metals, oxidants, and reaction conditions to improve the substrate scope. From our point of view, the ideal synthesis of indoles would be one that involves the direct connection of anilines with C2 fragments, such as alkenes or alkynes (Scheme 1 e).[13] Herein, we propose the use of epoxides, which are easily available from olefins, for the synthesis of indoles through metal-catalyzed dehydrogenation reactions.

Over the last two years, the synthesis of heterocycles by sequential dehydrogenative coupling processes has been developed by several research groups. Interestingly, the groups of Kempe and Milstein published the iridium- and ruthenium-catalyzed synthesis of pyrroles and pyridines from secondary alcohols and 1,2- or 1,3-aminoalcohols, respectively.[14] At the same time, our research group reported the ruthenium-catalyzed three-component synthesis of pyrroles by using benzylic ketones, vicinal diols, and amines.[15] Based on this work, we considered the synthesis of indoles by using a similar dehydrogenative methodology, starting from anilines and epoxides. To the best of our knowledge, only two precedents exist for such transformations.[16] Unfortunately, several limitations, such as the requirement for high temperatures, high catalyst loading, and high amine/epoxide ratios, meant that only a small number of indoles could be prepared in low and moderate yields. Notably, the reactions of anilines with related substrates, such as diols,[17] alkanolammonium chlorides,[18] or 1,2-dibromoalkanes,[19] proceeded in most cases under harsh conditions, but proved to lack versatility.

In agreement with well-known "hydrogen autotransfer" processes,[20] the indole synthesis should proceed by the following domino sequence (Scheme 2). First, the ring opening of the epoxide with the aniline provides the corresponding 1,2-aminoalcohol **A**. This intermediate is transformed into the final indole through ketone **B** by ruthenium-catalyzed dehydrogenation, followed by condensation with aniline to give the imine **C**. Subsequent intramolecular cyclization provides the desired

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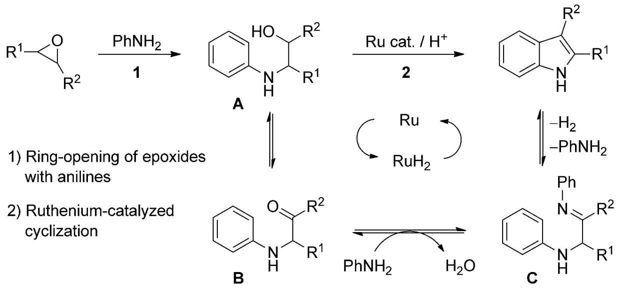
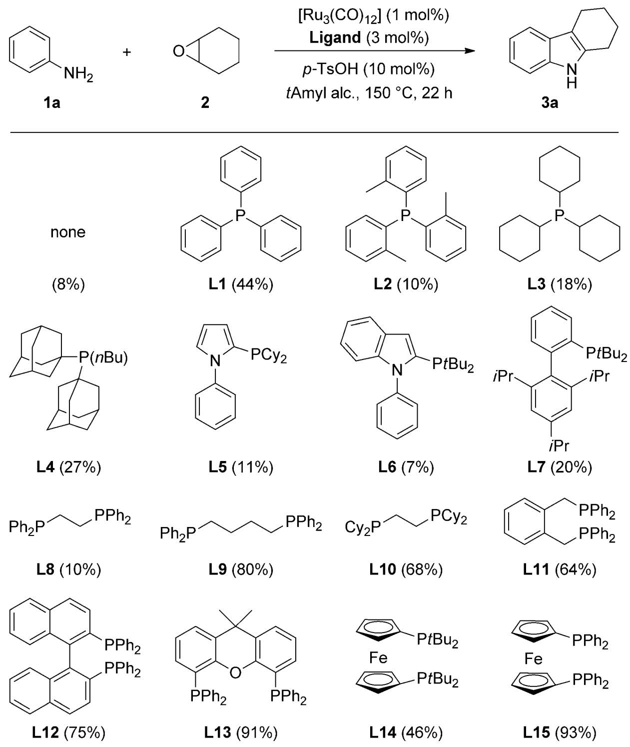


Scheme 2. Ruthenium-catalyzed synthesis of indoles from anilines and epoxides.



Scheme 3. Screening of ligands for the ruthenium-catalyzed synthesis of 1,2,3,4-tetrahydrocarbazole (**3a**) from aniline and cyclohexene oxide. The yield was determined by GC using hexadecane as an internal standard.

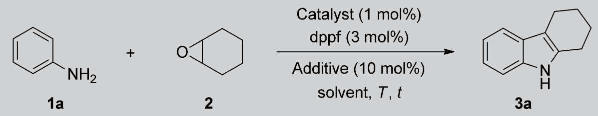
product. Advantageously, water and hydrogen would be the only by-products of this synthesis, and the aniline is used in catalytic amounts in the second step of this transformation. With these premises in mind, we present herein a general study into the ruthenium-catalyzed synthesis of indoles from anilines and epoxides.

Based on previous studies from our group,[21] the research started by analyzing the effect on the reaction of different phospine ligands in combination with [$Ru_3(CO)_{12}$] as the ruthenium source, a highly active catalytic system for several amination reactions. For this purpose, we chose, as a model transformation, the reaction of aniline (**1a**, 120 mol%) with cyclohexene oxide (**2**, 100 mol%) in the presence of [$Ru_3(CO)_{12}$] (1 mol%), a ligand (3 mol%), and *para*-toluenesulfonic acid monohydrate as an additive in *tert*-amyl alcohol at 150 °C (Scheme 3).

Initially, we observed that the reaction under ligand-free conditions only provided traces of the corresponding product, whereas the use of different monodentate ligands (**L1**–**L7**) gave the 1,2,3,4-tetrahydrocarbazole (**3a**) in moderate to low yields (7–44%, Scheme 3). Gratifyingly, bidentate ligands, such as 1,4-bis(diphenylphosphino)butane (dppb, **L9**, 80%), BINAP (**L12**, 75%), and Xantphos (**L13**, 91%), improved the product yield considerably, but the most effective phosphine was found to be 1,1′-bis(diphenylphosphino)ferrocene (dppf, **L15**). In this case, the desired indole was obtained in 93% yield (Scheme 3). It is important to note that in some cases small amounts of the corresponding diamine were formed, which is derived from the reduction of the proposed intermediate imine **C** (Scheme 2).

After this first approach, we explored different reaction conditions to improve the efficiency of the catalytic system. In this way, several catalyst precursors, including $RuCl_3{\cdot}H_2O$, [{$RuCl_2Ph$}$_2$], [{$RuCl_2$(*para*-cymene)}$_2$], [RuHCl(CO)(PPh_3)$_3$], and even [{IrCl(cod)}$_2$] (cod = 1,5-cyclooctadiene), were tested in combination with dppf and *p*-TsOH (*p*-Ts = *para*-tosyl) as an additive, but in all cases the 1,2,3,4-tetrahydrocarbazole (**3a**) was formed in lower yields (67–78%, Table 1, entries 1–5). Next, we studied the effect of different additives that are necessary both for the

Table 1. Optimization of the reaction conditions for the synthesis of **3a**.[a]



Entry	Catalyst	Additive	Solvent	Yield [%][b]
1	$RuCl_3{\cdot}H_2O$	*p*-TsOH	*tert*-amyl alcohol	73
2	[{$RuCl_2Ph$}$_2$]	*p*-TsOH	*tert*-amyl alcohol	67
3	[{$RuCl_2$(*para*-cymene)}$_2$]	*p*-TsOH	*tert*-amyl alcohol	78
4	[RuHCl(CO)(PPh_3)$_3$]	*p*-TsOH	*tert*-amyl alcohol	75
5	[{IrCl$_2$(cod)}$_2$]	*p*-TsOH	*tert*-amyl alcohol	67
6	[$Ru_3(CO)_{12}$]	–	*tert*-amyl alcohol	–
7	[$Ru_3(CO)_{12}$]	*para*-toluic acid	*tert*-amyl alcohol	–
8	[$Ru_3(CO)_{12}$]	$Zn(OTf)_2$	*tert*-amyl alcohol	21
9	[$Ru_3(CO)_{12}$]	$SnCl_2{\cdot}2\,H_2O$	*tert*-amyl alcohol	59
10	[$Ru_3(CO)_{12}$]	$Al(OTf)_3$	*tert*-amyl alcohol	63
11[c]	[$Ru_3(CO)_{12}$]	*p*-TsOH	*tert*-amyl alcohol	79
12	[$Ru_3(CO)_{12}$]	*p*-TsOH	DMF	4
13	[$Ru_3(CO)_{12}$]	*p*-TsOH	DMSO	39
14	[$Ru_3(CO)_{12}$]	*p*-TsOH	toluene	95
15	[$Ru_3(CO)_{12}$]	*p*-TsOH	1,4-dioxane	99
16[d]	[$Ru_3(CO)_{12}$]	*p*-TsOH	1,4-dioxane	77
17[e]	[$Ru_3(CO)_{12}$]	*p*-TsOH	1,4-dioxane	29
18[f]	[$Ru_3(CO)_{12}$]	*p*-TsOH	1,4-dioxane	82
19[g]	[$Ru_3(CO)_{12}$]	*p*-TsOH	1,4-dioxane	81
20[h]	[$Ru_3(CO)_{12}$]	*p*-TsOH	1,4-dioxane	65

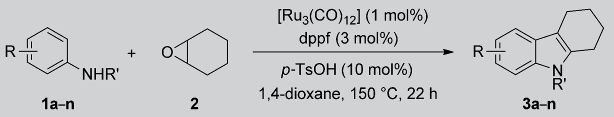
[a] Unless otherwise specified, all reactions were carried out with aniline (1.2 mmol), cyclohexene oxide (1.0 mmol), the catalyst (0.01 mmol), dppf (0.03 mmol), and an additive (0.10 mmol) in a solvent (1 mL) at 150 °C for 22 h. [b] GC yields with hexadecane as the internal standard. [c] *p*-TsOH (0.05 mmol). [d] Reaction temperature: 140 °C. [e] Catalyst (0.005 mmol) and ligand (0.015 mmol). [f] Reaction time: 18 h. [g] Ratio of aniline/epoxide = 1.1:1. [h] Reaction without an argon atmosphere.

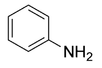
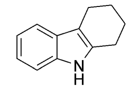
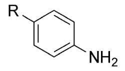
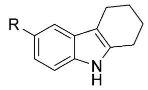
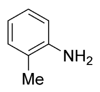
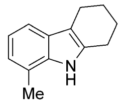
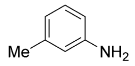
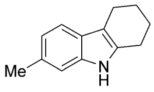
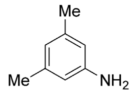
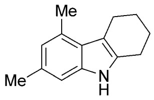
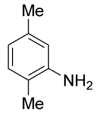
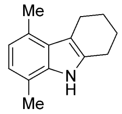
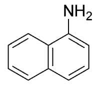
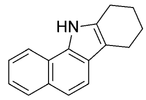
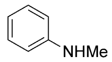
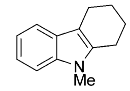
ring opening of the epoxide and the cyclization step. We observed no reaction in the absence of *p*-TsOH. Carboxylic acids such as *para*-toluic acid or other Lewis acids [$Zn(OTf)_2$, $SnCl_2 \cdot 2H_2O$, $Al(OTf)_3$] resulted in low to moderate yields, whereas the use of only 5 mol% of *para*-toluenesulfonic acid resulted in a higher yield (79%, Table 1, entries 6–11). Reactions in DMF and DMSO did not provide the corresponding indole in good yields, but this domino sequence can be performed effectively in toluene and 1,4-dioxane, and in the last case **3a** was obtained in 99% yield (Table 1, entries 12–15). For further optimization, we analyzed other critical parameters, and found that decreasing the temperature, catalyst loading, reaction time, and ratio of amine to epoxide all resulted in lower yields, whereas the reaction without the protection of an argon atmosphere took place in a moderate 65% yield (Table 1, entries 16–20). Thus, after this exhaustive screening of reaction conditions, we selected the reaction with [$Ru_3(CO)_{12}$] (1 mol%), dppf (3 mol%), and *p*-TsOH (10 mol%) in 1,4-dioxane at 150 °C for 22 h as the best catalytic system.

To expand the scope of this methodology, our next step was to check the reactivity of different substituted anilines in the reaction with cyclohexene oxide under the previously optimized conditions. We found that amines containing electron-donating groups, such as *para*-toluidine (**1b**), *para*-anisidine (**1c**), and 4-aminophenol (**1d**), provided the corresponding indoles **3b**–**d** in good yields (67–79%, Table 2, entries 2, **b**–**d**). The reactions with the electron-poor 4-fluoroaniline and 4′-aminoacetophenone also took place efficiently (61–63%, Table 2, entries 2, **e** and **f**), whereas 4-dimethylaminoaniline resulted in **3g** in a moderate 43% yield (Table 2, entry 2, **g**). Unfortunately, the desired product was not observed for the reaction of strongly electron-deficient anilines such as 4-nitroaniline (Table 2, entry 2, **h**). On the other hand, the sterically hindered 2-toluidine gave the corresponding tetrahydrocarbazole **3i** in excellent yield (83%, Table 2, entry 3), and the reaction of 3-toluidine provided a mixture of regioisomers with the major product in 68% yield (Table 2, entry 4). Different substituted dimethylanilines afforded the expected indoles in similarly good yields (71–75%, Table 2, entries 5 and 6), whereas the reaction with naphthylamine allowed isolation of the tetracyclic compound **3m** in 79% yield (Table 2, entry 7). Additionally, this reaction can be performed with secondary amines, such as *N*-methylaniline, obtaining in this case the corresponding N-protected indole **3n** in 60% yield (Table 2, entry 8).

To demonstrate the general applicability of this catalytic system for the synthesis of indoles, our protocol was tested in the reaction with different epoxides. Unfortunately, the ruthenium-catalyzed reaction of aniline with styrene oxide (**4**), under the previously developed conditions, afforded the 2-phenylindole (**5a**) in only a low yield (22%, Table 3, entry 1). At this point, we considered that the strongly acidic conditions, required for the cyclization step, might not be suitable for the ring opening of more sensitive epoxides. In fact, we observed that the aminolysis of cyclohexene oxide with aniline, catalyzed by *para*-toluenesulfonic acid, gave an 85% yield, but the same experiment with styrene oxide led to only traces of the desired aminoalcohol. In the latter case, we found different byproducts resulting from the elimination of water and secondary reactions of the corresponding enamine.

Table 2. Ruthenium-catalyzed synthesis of substituted 1,2,3,4-tetrahydrocarbazoles from anilines and cyclohexene oxide.[a]

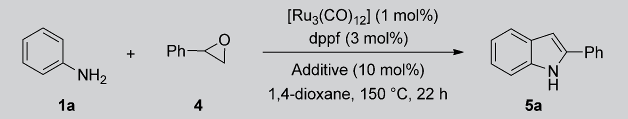


Entry	Aniline		Product		Yield [%][b]
1		**1a**		**3a**	85
2					
	R = Me	**1b**	R = Me	**3b**	79
	OMe	**1c**	OMe	**3c**	68
	OH	**1d**	OH	**3d**	67
	F	**1e**	F	**3e**	63
	Ac	**1f**	Ac	**3f**	61
	NMe_2	**1g**	NMe_2	**3g**	43
	NO_2	**1h**	NO_2	**3h**	–
3		**1i**		**3i**	83
4		**1j**		**3j**	68[c]
5		**1k**		**3k**	71
6		**1l**		**3l**	75
7		**1m**		**3m**	79
8		**1n**		**3n**	60

[a] Unless otherwise specified, all reactions were carried out with the amine (1.2 mmol), cyclohexene oxide (1.0 mmol), [$Ru_3(CO)_{12}$] (0.01 mmol), dppf (0.03 mmol), and *p*-TsOH (0.10 mmol) in 1,4-dioxane (1 mL) at 150 °C for 22 h. [b] Yield of the isolated product. [c] The minor regioisomer was formed in 17% yield.

To solve this problem, we turned our attention to the use of new additives that should allow the amination of epoxides in a more effective manner.[22] First, we analyzed the reaction by using different Lewis acids, which are known to be catalysts in the ring opening of epoxides with anilines. However, the ruthenium-catalyzed reaction of aniline with styrene oxide in

Table 3. Additive screening for the ruthenium-catalyzed synthesis of 2-phenylindole (**5a**) from aniline and styrene oxide.



Entry	Additive	Yield [%][a]
1	p-TsOH	22
2	$Zn(OCl_4)_2{\cdot}6H_2O$	9
3	$Zn(OTf)_2$	12
4	$Al(OTf)_3$	29
5	$SnCl_2{\cdot}2H_2O$	36
6	$Zn(OCl_4)_2{\cdot}6H_2O$/p-TsOH	41
7	$Zn(OTf)_2$/p-TsOH	43
8	$Zn(OCl_4)_2{\cdot}6H_2O$/p-TsOH[b]	68
9	$Zn(OTf)_2$/p-TsOH[b]	79
10	$Zn(OTf)_2$/p-TsOH[b,c]	74

[a] GC yields with hexadecane as the internal standard. [b] Sequential reaction: aniline (1.2 mmol), styrene oxide (1.0 mmol), and zinc salt (0.02 mmol) were stirred without a solvent at RT for 1 h. This was followed by addition of $[Ru_3(CO)_{12}]$ (0.01 mmol), dppf (0.03 mmol), p-TsOH (0.10 mmol), and 1,4-dioxane (1 mL) and stirring at 150 °C for 22 h. [c] Ring-opening reaction was performed at 80 °C.

the presence of 10 mol% of $Zn(OCl_4)_2{\cdot}6H_2O$, $Zn(OTf)_2$, $Al(OTf)_3$, or $SnCl_2{\cdot}2H_2O$ in 1,4-dioxane provided 2-phenylindole in low yields (9–36%, Table 3, entries 2–5). Although these additives have been shown to be effective in the amination of epoxides, they are not acidic enough to carry out the cyclization of the intermediate species. For this reason, we combined zinc salts (effective in the first step of the reaction) with a strong acid, in this case, *para*-toluenesulfonic acid. Nevertheless, the one-pot reaction of aniline with styrene oxide in the presence of zinc perchlorate or triflate (2 mol%) and *p*-TsOH (10 mol%) in 1,4-dioxane at 150 °C took place in a slightly improved 41 and 43% yield, respectively (Table 3, entries 6 and 7).

Performing the sequential reaction of the zinc-catalyzed ring opening followed by the ruthenium-catalyzed dehydrogenative coupling increased the yield. Hence, treatment of an aniline and an epoxide with zinc perchlorate in the absence of a solvent at room temperature for 1 h, with subsequent addition of $[Ru_3(CO)_{12}]$, dppf, *p*-TsOH, and 1,4-dioxane, and heating at 150 °C overnight, afforded the desired 2-phenylindole (**5a**) in 68% yield as the only regioisomer (Table 3, entry 8). The yield was further improved by the use of zinc triflate instead the zinc perchlorate (79%, Table 3, entry 9), but higher temperatures in the first step did not result in better reactivity (Table 3, entry 10). The regioselectivity of this reaction is explained by the better stabilization of the benzylic carbocation than the less substituted carbon atom of the epoxide ring.[22f]

Next, we explored the reactivity of different anilines with styrene oxide (**4**) by following the developed sequential methodology. For this purpose, we chose to use *para*-toluidine (**1b**), 1-naphthylamine (**1m**), and *N*-methylaniline (**1n**), obtaining the corresponding 2-phenylindoles (**5b**, **m**, and **n**) regioselectively in good yields (68–89%, Table 4, entries 2–4).

Finally, the reactivity of different epoxides, including aromatic and aliphatic derivatives, was studied. The reaction of four selected anilines (**1a**, **b**, **m** and **n**) with 4-(chlorophenyl)oxirane (**6**) provided the corresponding indoles **10a**, **b**, **m** and **n** with the *para*-chlorophenyl group in the 2-position as the major products (71–86%, Table 4, entries 5–8). It is important to note that the same reaction, under the conditions described in the Table 2 with *p*-TsOH as the only additive, resulted in very low yields. As in the case of the styrene oxide, the regioselectivity is controlled by the stabilization of the tertiary carbocation.

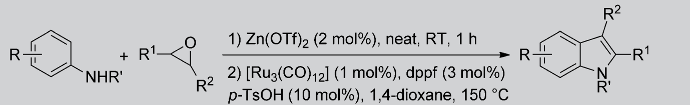
Encouraged by these results, we were intrigued about the reactivity of an aliphatic epoxide. To our delight, the zinc-catalyzed ring opening of 1,2-epoxyhexene (**7**) with aniline and *para*-toluidine at room temperature, followed by ruthenium-catalyzed cyclization in the presence of *p*-TsOH as an additive, took place efficiently to give the corresponding 2-butyl indoles **11a** and **b** in good yields (71–74%, Table 4, entries 9 and 10). However, the same reaction with 1-naphthylamine provided the desired indole **11m** in an excellent yield, but as a mixture of isomers (84%, 45:55, Table 4, entry 11), probably due to the higher steric hindrance caused by the naphthyl group during the ring opening of the epoxide. Analogously, the treatment of the epoxide with an N-protected amine **1n** under the standard conditions also afforded a mixture of indoles in 43% yield. In this case, the 3-substituted compound was obtained as the major product (24:76, Table 4, entry 12).

After this study with monosubstituted epoxides, we examined the use of the optimized conditions with internal epoxides. The reaction of different anilines with cyclopentene oxide (**8**) in the presence of *p*-TsOH took place in very low yields, although this substrate appears similar to the cyclohexene derivative. Nevertheless, the sequential transformation with aniline (**1a**), *para*-toluidine (**1b**), and *N*-methylaniline (**1n**) proceeded in better yields (46–52%, Table 4, entries 13, 14, and 16), whereas the more electron-rich 1-naphthylamine (**1m**) provided the corresponding tetracyclic indole **12m** in an excellent 84% yield (Table 4, entry 15).

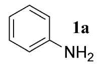
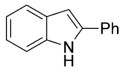
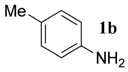
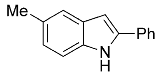
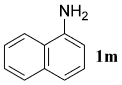
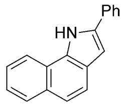
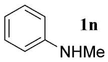
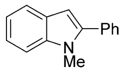
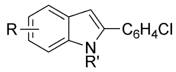
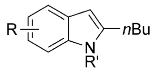
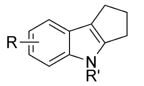
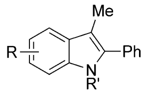
Finally, we analyzed the reactivity of the asymmetric 1-phenylpropylene oxide (**9**). In this case, reactions with selected amines proceeded effectively under the previously developed sequential conditions, affording the desired indoles regioselectively in moderate to good yields (46–76%, Table 4, entries 17–20). The major regioisomer observed in all cases proved to be the 2-phenyl-substituted indole.

In summary, we have developed a general ruthenium-catalyzed synthesis of indoles from readily available reagents, that is, anilines and epoxides. This atom-efficient transformation allowed us to obtain a variety of indoles in good yields in the presence of the commercially available $[Ru_3(CO)_{12}]$/dppf catalytic system. The use of a sequential addition procedure and non-sensitive additives in substoichiometric amounts makes the protocol convenient and easy to use. Water and hydrogen are formed as the only stoichiometric by-products. Our results show that anilines and epoxides are valuable reagents for the synthesis of heteroarenes through metal-catalyzed reactions.

Table 4. Ruthenium-catalyzed synthesis of indoles from anilines and epoxides by using a sequential reaction.[a]



1a–n **4–9** **5–13**

Entry	Aniline	Epoxide	Product[b]		Yield [%][c]
1	 **1a**	**4**		**5a**, 99:1	77
2	 **1b**			**5b**, 98:2	68
3	 **1m**			**5m**, 91:9	76
4	 **1n**			**5n**, 97:3	89
5	aniline (**1a**)	**6**		**10a**, 99:1	71
6	*para*-toluidine (**1b**)			**10b**, 98:2	77
7	1-naphthylamine (**1m**)			**10m**, 90:10	77
8	*N*-methylamine (**1n**)			**10n**, 98:2	86
9	aniline (**1a**)	**7**		**11a**, 97:3	74
10	*para*-toluidine (**1b**)			**11b**, 98:2	71
11	1-naphthylamine (**1m**)			**11m**, 45:55	84[d]
12	*N*-methylamine (**1n**)			**11n**, 24:76	43[d]
13	aniline (**1a**)	**8**		**12a**	51
14	*para*-toluidine (**1b**)			**12b**	46
15	1-naphthylamine (**1m**)			**12m**	84
16	*N*-methylamine (**1n**)			**12n**	52
17	aniline (**1a**)	**9**		**13a**, 99:1	76
18	*para*-toluidine (**1b**)			**13b**, 91:9	65
19	1-naphthylamine (**1m**)			**13m**, 93:7	63
20	*N*-methylamine (**1n**)			**13n**, 95:5	46

[a] Unless otherwise specified, all reactions were carried out in a sequential manner: initially, the amine (1.2 mmol), epoxide (1.0 mmol), and zinc salt (0.02 mmol) were stirred without a solvent at RT for 1 h. This was followed by addition of $[Ru_3(CO)_{12}]$ (0.01 mmol), dppf (0.03 mmol), *p*-TsOH (0.10 mmol), and 1,4-dioxane (1 mL) and stirring at 150 °C for 22 h. [b] The regioisomeric ratio by GC-MS is given, generally with 2-substituted indoles as the major product. [c] Yield of the isolated major regioisomer. [d] Yield of the mixture of regioisomers, in these cases, with 3-butyl indoles as the major products.

Experimental Section

General information

Unless otherwise stated, all of the reactions were conducted under an argon atmosphere with exclusion of moisture from the reagents and glassware by using standard techniques for the manipulation of air-sensitive compounds. Reaction temperatures refer to external bath temperatures. TLC was effected on silica gel 60 F_{254} (layer thickness: 0.2 mm) and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid or *para*-anisaldehyde followed by heating. Column chromatography was performed on silica gel (230–400 mesh) by using 10% ethyl acetate/heptane as the eluent. NMR spectra were performed on a Bruker Avance 400 spectrometer by using the residual solvent signal as an internal standard [chloroform: $\delta = 7.26$ ppm (^{1}H), 77.0 ppm (^{13}C)]. All measurements were carried out at room temperature unless otherwise stated, and DEPT was used to assign the types of carbon atom. Mass spectra were, in general, recorded on an AMD 402/3 or an HP 5989A mass-selective detector. Gas chromatography was performed on an HP 6890 chromatograph with an HP5 column. Infrared spectra were taken on a Bruker Vector 22 with attenuated total reflectance (ATR). Unless otherwise stated, commercial reagents were used as received.

General procedure for the ruthenium-catalyzed synthesis of indoles from anilines and cyclohexene oxide

In a glass pressure tube (25 mL) under an argon atmosphere, $[Ru_3(CO)_{12}]$ (6.4 mg, 0.01 mmol), 1,1′-bis(diphenylphosphino)ferrocene (16.6 mg, 0.03 mmol), *para*-toluenesulfonic acid monohydrate (19.0 mg, 0.10 mmol), the amine (**1a**–**n**, 1.2 mmol), and cyclohexene oxide (**2**, 100 μL, 1.0 mmol) were dissolved in 1,4-dioxane (1 mL). Next, the pressure tube was closed and the resulting mixture was stirred at 150 °C in an oil bath for 22 h. After cooling to room temperature, the crude mixture was directly purified by flash column chromatography on silica gel, eluting with 10% ethyl acetate/heptanes, to afford, after concentration and high-vacuum drying, the corresponding indoles (**3a**–**n**) in the reported yields.

General procedure for the ruthenium-catalyzed synthesis of indoles from anilines and epoxides by using a sequential reaction

In a glass pressure tube (25 mL) under an argon atmosphere, $Zn(OTf)_2$ (7.3 mg, 0.02 mmol), the amine (**1a**–**n**, 1.2 mmol), and the epoxide (**4**–**9**, 1.0 mmol) were stirred at room temperature for 1 h. After this time, $[Ru_3(CO)_{12}]$ (6.4 mg, 0.01 mmol), 1,1′-bis(diphenylphosphino)ferrocene (16.6 mg, 0.03 mmol), and *para*-toluenesulfonic acid monohydrate (19.0 mg, 0.10 mmol) were added and dissolved in 1,4-dioxane (1 mL). Next, the pressure tube was closed and the resulting mixture was stirred at 150 °C in an oil bath for 22 h. After cooling to room temperature, the crude mixture was directly purified by flash column chromatography on silica gel, eluting with 10% ethyl acetate/heptanes, to afford, after concentration and high-vacuum drying, the corresponding indoles (**5**–**13**) in the reported yields.

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Keywords: anilines · epoxides · indole synthesis · ring-opening reactions · ruthenium catalysis

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