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# A Ruthenium-Catalyzed Approach to the Friedländer Quinoline Synthesis

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In a modification of the Friedländer reaction, 2-aminobenzyl alcohol is oxidatively cyclized with a variety of ketones to yield substituted quinolines. Of all the ruthenium catalysts that were tested for this reaction, the second-generation Grubbs' catalyst gives the highest quinoline yield, in combination with KO*t*Bu as a base. The presence of a hydrogen acceptor is required to regenerate the catalyst. Also the reaction mechanism is discussed, and the results show that there are possibly two different pathways towards quinolines.

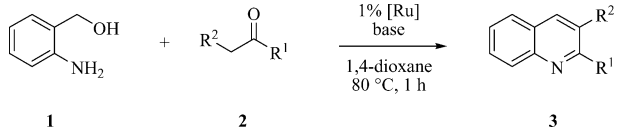


## Introduction

The synthesis of nitrogen-containing heterocycles, such as quinoline, is the subject of extensive research in organic chemistry, because the quinoline scaffold is present in many biologically active compounds. Applications of quinolines in medicinal chemistry include the use as antimalarial,[1,2] antiinflammatory,[3] antiasthmatic,[4] antibacterial,[5] antihypertensive[6] and tyrosine kinase inhibitory agents.[7] Quinoline based polymers are currently investigated for applications as thermally stable transparent materials in the fields of electronics, optoelectronics and nonlinear optics.[8,9]

Many traditional methods, such as the Skraup, Doebner–von Miller, Conrad–Limpach, and Pfitzinger syntheses, suffer from harsh reaction conditions, low stereoselectivity or consist of multiple steps, resulting in low overall yields, limiting their applicability.[1] The Friendländer method is generally considered to be the most versatile method of synthesis although its full potential is inhibited due to the use of unstable aminobenzaldehydes.

Besides these conventional named reactions, several organometal-catalyzed approaches have recently been developed for the synthesis of the quinoline nucleus. Ruthenium complexes catalyze the reaction of aniline with allyl alcohols,[10] triallylamines,[11] allylammonium chlorides[11] and even alkylamines.[12] Substituted quinolines were synthesized by Arisawa, Theeraladanon et al. via ring closing metathesis of α,ω-dienes derived from 2-isopropenylaniline.[13–15] Other researchers reported the use of Pd,[16–19] Ni,[20] Rh,[21,22] and Co[23,24] complexes for transition-metal mediated quinoline synthesis. A modified Friedländer protocol (Scheme 1) has been developed by Cho and coworkers.[25]




1 2 3

Scheme 1. The modified Friedländer quinoline synthesis.

Instead of using the unstable 2-aminobenzaldehyde as a starting product it is generated in situ via a catalytic transfer hydrogenation reaction, involving the oxidation of 2-aminobenzyl alcohol. $RuCl_2(=CHPh)(PCy_3)_2$, commonly known as the first-generation Grubbs' catalyst, was reported to be the best catalyst for this reaction.[25] Other metal complexes that have been successfully employed for the modified Friedländer reaction include $CuCl_2/O_2$,[26] Pd/C,[27] $RuCl_2(DMSO)_4$,[28–31] $IrCl_3$ and $[IrCl(cod)]_2$.[32]

Given our experience in ruthenium-based catalysis, this remarkable activity for hydrogen transfer reactions of the first-generation Grubbs' catalyst prompted us to further investigate the potential of similar ruthenium complexes. Here we present a comprehensive overview of our results.

## Results and Discussion

In a previous communication,[33] we have compared several ruthenium complexes based on the first and second generation Grubbs' catalyst and the ruthenium dimer $[RuCl_2(p\text{-cymene})]_2$ **8** (Figure 1) for the reaction between 2-aminobenzyl alcohol (**1**) and acetophenone (**2a**, $R^1$ = Ph, $R^2$ = H) which was chosen as a model reaction. The most important results are summarized in Table 1. Although the ruthenium dimer precursor **8** was ineffective, the inclusion of a phosphane ligand (complexes **9a** and **9b**) proved to be

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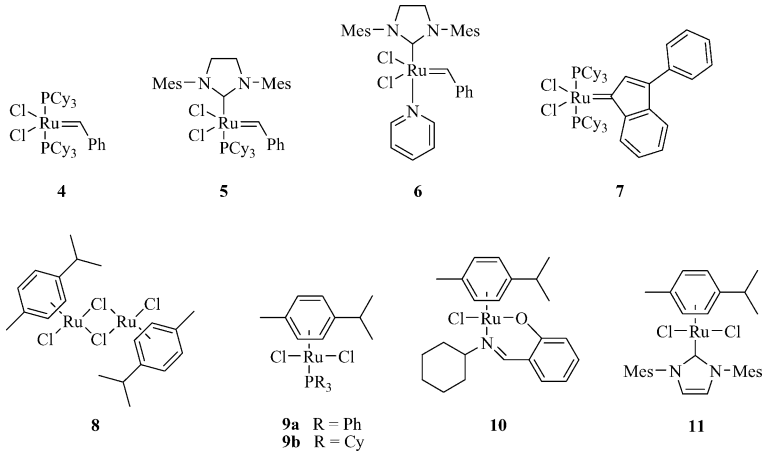



Figure 1. Catalysts tested for the modified Friedländer synthesis.

beneficial. The conversion increased from 15% to 53% for **9b**, whereas the use of an N,O-bidentate Schiff base ligand in complex **10** did not improve the catalytic activity.

Table 1. Ruthenium-catalyzed synthesis of quinolines from **1** and acetophenone (**2a**, $R^1$ = Ph, $R^2$ = H).[a]

| Entry | Catalyst | % Yield |
|---|---|---|
| 1 | **4** | 74 |
| 2 | **5** | 100 |
| 3 | **6** | 53 |
| 4 | **7** | 32 |
| 5 | **8** | 15 |
| 6 | **9a** | 40 |
| 7 | **9b** | 53 |
| 8 | **10** | 14 |
| 9 | **11** | 26 |

[a] Reaction conditions: **1** (1 mmol), **2a** (2 mmol), catalyst (0.01 mmol) and KOH (1 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields determined by GC.

We have shown that catalyst **5** was superior to **4**. The replacement of a phosphane ligand by an N-heterocyclic carbene (NHC) ligand clearly improved catalytic activity, resulting in 100% conversion for **5** after 1 hour compared to 74% for **4**. This might be attributed to the higher σ-donating ability of the NHC ligand, making it more suitable to stabilize the [$RuH_2$] species with a presumably higher oxidation state compared to the original catalyst. Variation of the NHC ligand through replacement of one mesityl group by aliphatic groups, such as methyl or cyclohexyl, decreased the quinoline yield.[33]

Based on the conclusions of our previous report, a series of new complexes (**6**, **7** and **11**) was screened for the modified Friedländer reaction. It is remarkable that, when the phosphane ligand in **9a** or **9b** is replaced by an NHC ligand, in complex **11**, the conversion does not further increase but drops to 26%. Even more remarkable is the relatively low conversion achieved with **6** while it is similar to **5** in structure. We are currently unable to explain this peculiar behaviour but apparently, the presence of at least one phosphane ligand is required to achieve good yields. Replacing the benzylidene ligand of **4** with a bulkier indenylidene ligand in complex **7** decreases the conversion.

When the reaction is monitored over time (Figure 2), it is revealed that the yields after one hour are not necessarily final yields. The catalysts are still active after one hour of reaction. Complex **5** reaches full conversion after 60 minutes, **4** after 90 minutes and also **9a** and **9b** eventually reach full conversion after 6 and 5 hours, respectively.

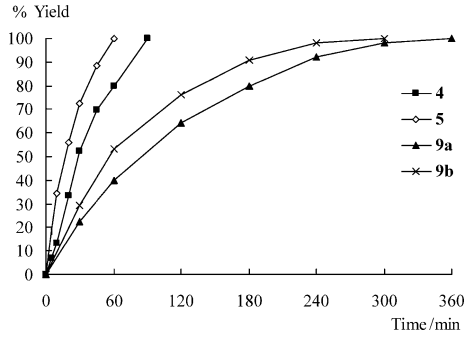
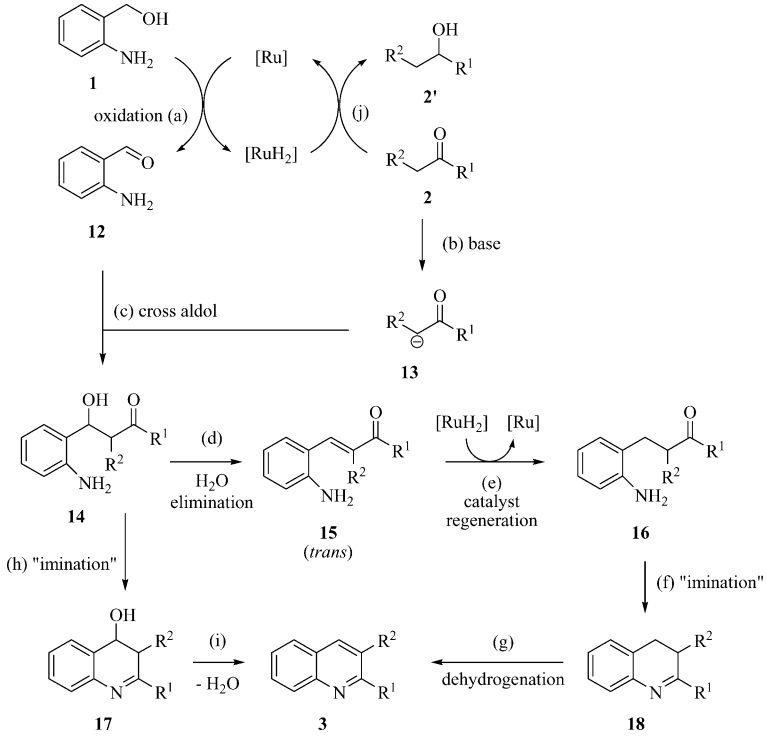



Figure 2. Monitoring of the reaction over time with different Ru complexes. Reaction conditions: **1** (1 mmol), **2a** (2 mmol), catalyst (0.01 mmol) and KOH (1 mmol) in dioxane (3 mL) at 80 °C.

From the results in Table 2, it becomes clear that not only the catalyst determines the reaction rate, also the base is important. The role of the base is to abstract an α-proton of the ketone, so it can undergo a cross-aldol reaction with 2-aminobenzaldehyde [see steps (a), (b) and (c) in Scheme 2]. The p$K_a$ value of the α-proton is approximately 16 for **2a**. Typically, KOH is used by most other researchers and although KOH is insoluble in dioxane, it is seldomly specified under which conditions it is added.[25,31,32] When large pellets are used, the conversion after one hour is only 8% but this can be increased to 67% with KOH powder. An even higher conversion of 74% is achieved when KOH is added as a 4 M solution in methanol. This is probably caused by the increased solubility. As an added advantage, this not only results in a higher yield, it is also much more practical. Unless otherwise stated, for all experiments in this manuscript, KOH was added as a 4 M solution in methanol (1 mmol, 250 μL).




Scheme 2. Proposed reaction mechanism.

Table 2. Influence of the base on quinoline synthesis with **4**.[a]

| Entry | Base (1 mmol) | p$K_a$[b] | % Yield |
|---|---|---|---|
| 1 | KOH (pellets) | 15.7 | 8 |
| 2 | KOH (powder) | 15.7 | 64 |
| 3 | KOH (4 M in MeOH) | 15.7 | 74 |
| 4 | NaOH (powder) | 15.7 | 38 |
| 5 | NaOH (4 M in MeOH) | 15.7 | 48 |
| 6 | NaOEt (powder) | 15.9 | 74 |
| 7 | KO*t*Bu (powder) | 17.0 | 98 |
| 8 | LiHMDS (0,5 M in toluene) | ≈26[c] | 27 |
| 9 | Triethylamine | 10.6 | 0 |
| 10 | DBU | 12.8 | 0 |
| 11 | 0.4 mmol KOH (4 M in MeOH) | 15.7 | 67 |
| 12 | 2.0 mmol KOH (4 M in MeOH) | 15.7 | 73 |

[a] Reaction conditions: **1** (1 mmol), **2a** (2 mmol), **4** (0.01 mmol) and base (1 mmol, except for entries 11 and 12) in dioxane (3 mL) at 80 °C for 1 h. Yields determined by GC. [b] p$K_a$ values of the protonated form of the base. [c] in THF.

The yield is substantially lower when NaOH is used, either as powder (entry 4) or as a 4 M solution in MeOH (entry 5). This may be explained by the smaller size of the sodium cation, resulting in a lower solubility. It is, however, surprising that a cation change from potassium to sodium leads to such a big difference. Sodium ethoxide (entry 6) has approximately the same base strength as NaOH, yet a higher yield, comparable to KOH, is achieved. Again, the higher solubility of NaOEt because of the aliphatic ethyl group can explain these results. Another common base, KO*t*Bu, has a higher basic strength, which is reflected in the higher quinoline yield (entry 7). Not only the basic strength is important, as is evidenced by entry 8. Lithium bis(trimethylsilyl)amide (LiHMDS) has a p$K_a$ of approximately 26, but only 27% quinoline yield is obtained. Both bases have a non-nucleophilic character, but maybe LiHMDS is too aggressive and deactivates the catalyst. Grubbs et al. have also shown the exchange of the chloride ligands with the *tert*-butoxy group, which implies that, when KO*t*Bu is used, a different catalytic center may be formed.[34,35]

Organic bases such as triethylamine (entry 9) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, entry 10) have the advantage of being readily soluble in dioxane, but their low basicity prevents them from being effective bases for this reaction. Although the proton abstraction is base-catalyzed, an equimolar ratio of base and **1** gives the best results, as can be deducted from entries 3, 11 and 12. A higher concentration of base does not further improve the yield. Figure 3

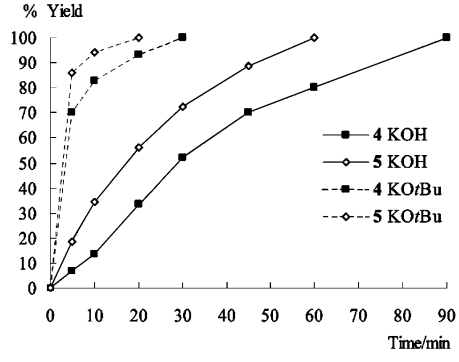



Figure 3. KOH vs. KO*t*Bu. Reaction conditions: **1** (1 mmol), **2a** (2 mmol), catalyst **4** or **5** (0.01 mmol) and base (1 mmol) in dioxane (3 mL) at 80 °C.

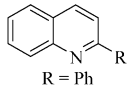
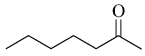
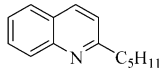
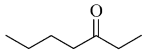
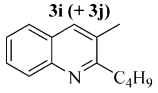
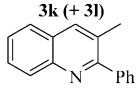
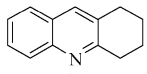
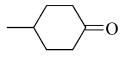
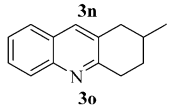
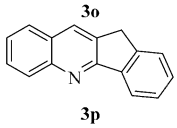
  

illustrates the effect of the base even better. With KO*t*Bu and **5**, full conversion is reached already after 20 minutes, compared to 60 minutes for KOH.

The determination of the turn-over number (TON) for the model reaction of **1** with **2a** in the presence of KO*t*Bu and **5** was carried out by lowering the catalyst concentration and measuring the maximum yield. A catalyst loading of 0.1% still results in full conversion within 1 h. With a catalyst loading of 0.01%, a maximum yield of 85% is observed after 5 h, meaning a TON as high as 8500 was achieved, showing the potential of this catalytic system. The calculation of the turn-over frequency (TOF) at the beginning of the reaction (after the first 5 minutes), fully quantifies the difference between the catalytical systems. With KOH, complex **4** has a TOF of 1.7 $min^{-1}$ (measured after 20 min because of the observed induction period), while that of **5** is twice as large (3.8 $min^{-1}$). Using KO*t*Bu the TOF increases spectacularly to 14.0 and 17.0 respectively for **4** and **5**.

To assess the scope of the modified Friedländer reaction, **1** was treated with a variety of ketones in the presence of **4** and **5** and both KOH and KO*t*Bu were used as base. The results are shown in Table 3. From these results, it is obvious that the second generation outperforms the first generation Grubbs' catalyst. For almost all ketone substrates, a higher quinoline yield was obtained for **5** compared to **4**. The stronger base KO*t*Bu gives better results than KOH for almost all ketones. The only two exceptions are acetone (entry 8) and 1-indanone (entry 14) were KOH is the preferred base in combination with **5**. The reaction is inhibited by substrates with strong electron withdrawing groups like $NO_2$ (entry 7). Entries 9 and 10 illustrate that a mixture of two quinolines is formed when two α-protons are available in an asymmetric ketone, a problem that is avoided with symmetric ketones (entries 12 and 13). The ratio of **3i/3j** and **3k/3l** is the same for **4** and **5** as can be expected since the only action of the catalyst is the oxidation of **1** (this is not entirely true, as will be explained in the discussion of

Table 3. Ruthenium-catalyzed synthesis of quinolines from **1** and ketones.[a]

| | | | % Yield | | | |
|---|---|---|---|---|---|---|
| | | | **4** | | **5** | |
| Entry | Ketone | Quinoline | KOH[b] | KO*t*Bu | KOH[b] | KO*t*Bu |
| 1 |  R = Ph |  R = Ph **3a** | 75[c] | 98 | 100[d] | 100 |
| 2 | R = 2-$MeC_6H_4$ **(2b)** | R = 2-$MeC_6H_4$ **3b** | 31 | 98 | 66 | 100 |
| 3 | R = 3-$MeC_6H_4$ | R = 3-$MeC_6H_4$ **3c** | 63 | 97 | 91 | 100 |
| 4 | R = 4-$MeC_6H_4$ | R = 4-$MeC_6H_4$ **3d** | 64 | 100 | 86 | 100 |
| 5 | R = 2-$MeOC_6H_4$ | R = 2-$MeOC_6H_4$ **3e** | 38 | 100 | 87 | 100 |
| 6 | R = 4-$MeOC_6H_4$ | R = 4-$MeOC_6H_4$ **3f** | 47 | 96 | 74 | 95 |
| 7 | R = 4-$NO_2C_6H_4$ | R = 4-$NO_2C_6H_4$ **3g** | 0 | 0 | 0 | 0 |
| 8 | R = Me | R = Me **3h** | 65 | 76 | 100 | 68 |
| 9 |  |  **3i (+ 3j)** | 34 (8)[e] | 61 (21)[e] | 76 (18)[e] | 65 (22)[e] |
| 10 |  |  **3k (+ 3l)** | 21 (7)[f] | 65 (25)[f] | 51 (15)[f] | 62 (23)[f] |
| 11 |  |  **3m** | 72 | 100 | 87 | 100 |
| 12 |  |  **3n** | 72 | 97 | 100 | 100 |
| 13 |  |  **3o** | 78 | 100 | 100 | 100 |
| 14 |  |  **3p** | 17 | 21 | 30 | 22 |

[a] Reaction conditions: **1** (1 mmol), **2** (2 mmol), catalyst (0.01 mmol) and base (1 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields determined by GC. [b] From ref.[33] [c] Isolated yield: 65%. [d] Isolated yield: 94%. [e] Value in parentheses is the yield of 3-butyl-2-methylquinoline (**3j**). [f] Value in parentheses is the yield of 2-ethyl-3-propylquinoline (**3l**).

the reaction mechanism). There is however a small but notable difference between KOH and KO*t*Bu. With 2-heptanone, the ratio of **3i/3j** is 4.2 for KOH and 2.9 for KO*t*Bu, meaning there is a higher selectivity with KOH. With 3-heptanone the difference is less pronounced (3 vs. 2.6).

The GC spectra did not only show unreacted starting products **1** and **2** and the quinoline, but also one peak which in many cases almost completely overlapped with the ketone peak. This peak was identified as the alcohol equivalent **2′** of the ketone **2**. This alcohol is the result of hydrogenation of the ketone by the [$RuH_2$] complex, resulting in the regeneration of the catalyst. Exactly for this reason, two equivalents of ketone were used to perform the reaction: one equivalent for the reaction and the other equivalent as a hydrogen acceptor for the regeneration of the catalyst. The use of other hydrogen acceptors was examined by using only one equivalent of the ketone **2b** vs. **1**, instead of 2 equivalents (Table 4). With 1 equivalent of benzophenone (compared to **1**), full conversion is reached after 70 minutes. Increasing the amount of benzophenone to 2 equivalents, is slightly counterproductive. An other common hydrogen acceptor, 1-dodecene, was less effective and the use of nitrobenzene resulted in unwanted side-products, but no quinoline.

Table 4. Effect of a hydrogen acceptor on quinoline synthesis.[a]

| Entry | Additive | % Yield[b] |
|---|---|---|
| 1 | – | 51 (71) |
| 2 | benzophenone (1 mmol) | 91 (100) |
| 3 | benzophenone (2 mmol) | 83 (100) |
| 4 | nitrobenzene (1 mmol) | 0[c] |
| 5 | nitrobenzene (2 mmol) | 0[c] |
| 6 | 1-dodecene (1 mmol) | 52 |
| 7 | 1-dodecene (2 mmol) | 72 |

[a] Reaction conditions: **1** (1 mmol), **2b** (1 mmol), **5** (0.01 mmol) and KOH (1 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields determined by GC. [b] The value of the maximum yield, achieved after 90 minutes, is indicated in parentheses. [c] No quinoline was formed, but the GC spectrum showed many other unidentified compounds.

When the reaction is carried out without hydrogen acceptor, a maximum yield of 71% is achieved. The ketone peak has completely disappeared on the GC spectrum and a new peak of the alcohol has appeared, accounting for approximately 0.30 mmol. This is, however, in contradiction with the previous statement of catalyst regeneration, as with a 1:1 ratio, 0.50 mmol of the alcohol and a maximum yield of only 50% is to be expected. This means that there must be an alternative pathway that allows for catalyst regeneration.

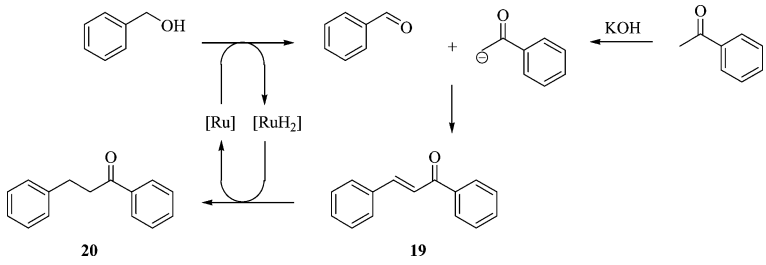
A plausible reaction mechanism for the modified Friedländer synthesis is presented in Scheme 2. First, in step (a), **1** is oxidized to 2-aminobenzaldehyde (**12**) by the ruthenium catalyst that is hydrogenated to a hydrido-ruthenium complex. Under basic conditions, the aldehyde and the ketone undergo a cross aldol reaction to form **14** in steps (b) and (c). Step (j) shows how the catalyst is regenerated by a hydrogen transfer reaction in which ketone **2** is reduced to the alcohol **2′**. This role can also be fulfilled by another hydrogen acceptor, e.g. benzophenone. In step (h), the aldol product **14** can cyclize via imine condensation ("imination") and subsequent $H_2O$ elimination in step (i) leads to the quinoline.

In an alternative pathway, shown in steps (d)–(g), a base-catalyzed $H_2O$ elimination of **14** results in the *trans* enone **15**. The *cis* product is not likely to be formed due to steric hindrance. Compound **15** is then hydrogenated by a [$RuH_2$] species, representing a second method to regenerate the catalyst. Imine condensation and subsequent dehydrogenation lead to the desired quinoline **3**.

Proof that the conversion of **15** to **16** occurs, is found when benzyl alcohol is reacted with acetophenone in dioxane in the presence of **4** and KOH (Scheme 3). Instead of the expected chalcone **19**, 3-phenylpropiophenone **20** is formed, which means that the double bond of chalcone is hydrogenated by the [$RuH_2$] complex, regenerating the catalyst in the process. Similar coupling reactions have been performed by Cho et al. and it were in fact these findings that led them to the modified Friedländer method.[25,36,37]

One could argue that also the oxidation of methanol to formaldehyde could be the reason of the reduction of ketone **2**. When the reaction is carried out with KOH powder in the absence of methanol, the alcohol **2′** is still formed, albeit in slightly smaller quantities. This means that methanol oxidation certainly contributes to the formation of **2′**, but not exclusively and not to a major extent.

Theoretically, the order of steps (a) and (f) could be reversed, i.e. first a condensation reaction between the amine and the ketone to form an imine, followed by the catalytic oxidation and cross aldol reaction. This is, however, not observed. The reaction of **1** with **2a** in basic media did not lead to imines. To exclude the possibility of [Ru]-catalyzed imine formation, aniline was treated with **2a** in the presence of **4** under standard reaction conditions used for the experiments, but again, no imines were formed. The interested




Scheme 3. Ru-catalyzed coupling between benzyl alcohol and acetophenone.

reader can find an excellent article by Muchowski and Maddox, dealing with the mechanism of the Friedländer synthesis.[38]

## Conclusions

In summary, we have shown that the first and second generation Grubbs' catalysts are efficient catalysts for the oxidative cyclization of 2-aminobenzyl alcohol with a variety of ketones, leading to quinolines. The best results are achieved with the second generation catalyst, in combination with KO*t*Bu as base. A TON as high as 8500 was observed. A sacrificial hydrogen acceptor is required for the regeneration of the catalyst. Benzophenone is a fine choice, but an extra equivalent of ketone also works perfectly. In the discussion on the reaction mechanism, the experimental results seem to indicate that there are probably two different pathways involved in this modified Friedländer reaction.

## Experimental Section

All synthetic procedures were performed under argon atmosphere on a vacuum line using standard Shlenck techniques. Solvents were dried and distilled prior to use. Ethyl acetate for column chromatography was of Rotisolv® Pestilyse® quality (Roth). Compounds **4** (Aldrich), **5** (Aldrich), **7** (Umicore), **8** (Aldrich) and all other chemicals were obtained from commercial sources and used as received. Compounds **6**,[35] **9a+b**,[39,40] and **11**[41] were prepared according to literature procedures. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Unity-300 Spectrometer. GC measurements were performed on a Finnigan TraceGC Ultra with an Ultra Fast Column Module (UFC-1, 100% dimethyl polysiloxane, 0.32 mm × 5 m, 0.25 μm film thickness, helium carrier gas, 5 mL/min).

**The synthesis of 10** is achieved in three steps: (a) synthesis of the Schiff base (SB), (b) formation of the thallium salt of the Schiff base, and (c) reaction of the Tl salt with $[RuCl_2(p\text{-cymene})]_2$ to afford **10**. The procedure is analogous to that of similar Ru–Schiff base complexes previously published by our group.[42]

(a) Cyclohexylamine (5.4 mL, 47 mmol) and salicyladehyde (5.0 mL, 47 mmol) were dissolved in 25 mL THF. The solution was allowed to reflux at 60 °C for 4 h, then cooled down to room temperature and dried on $MgSO_4$. After filtration, the solvent was evaporated in vacuo, affording the Schiff base as a viscous yellow oil in good yields (6.7 g, 70%). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 13.81 (s, 1 H, OH), 8.31 (s, 1 H, CH=N), 7.25 (t, 1 H, arom. H), 7.20 (d, 1 H, arom. H), 6.93 (d, 1 H, arom. H), 6.83 (t, 1 H, arom. H), 3.19 (m, 1 H, N-CH), 1.80–1.20 (m, 10 H, cyclohexyl H) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 162.5, 161.8, 132.2, 131.4, 119.2, 118.6, 117.3, 67.7, 34.5 (2 C), 25.8, 24.6 (2 C) ppm.

(b) The Schiff base (0.72 g, 3.53 mmol) was treated with thallium(I) ethoxide (250 μL, 3.53 mmol) in 1 mL THF at room temperature. A yellow precipitate of the Tl salt of the Schiff base started to form after a few minutes. After 1 h, the solvent was evaporated under reduced pressure and the crude product was used in the next step without further purification.

(c) A solution of $[RuCl_2(p\text{-cymene})]_2$ **8** (1.08 g, 1.76 mmol) in 25 mL THF was added to the Schiff base (SB) thallium salt and the mixture was stirred at room temperature. A grey precipitate of TlCl started to form almost immediately. After 4 h, the solvent volume was reduced to 1 mL and the mixture was purified by column chromatography (Silica gel 60, 70–230 mesh, Merck). The red band containing the catalyst was collected and the solvent volume was reduced to 1 mL. Upon addition of hexane (10 mL), a red precipitation formed, that was filtered, washed with hexane (2 × 5 mL) and dried in vacuo to afford the pure compound **10** in good overall yield (1.17 g, 70%). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.76 (s, 1 H, CH=N), 7.15 (t, 1 H, SB aryl H), 6.96 (d, 1 H, SB aryl H), 6.92 (d, 1 H, SB aryl H), 6.43 (t, 1 H, SB aryl H), 5.46 (d, 1 H, *p*-cymene aryl H), 5.40 (d, 1 H, *p*-cymene aryl H), 5.30 (d, 1 H, *p*-cymene aryl H), 5.07 (d, 1 H, *p*-cymene aryl H), 4.23 (m, 1 H, N-CH), 2.80 [m, 1 H, *p*-cymene C*H*$(CH_3)_2$], 2.50–1.25 (m, 10 H, cyclohexyl H), 2.16 (s, 3 H, ar-$CH_3$), 1.23, 1.15 [both d, 3 H, CH(C*H*$_3)_2$] ppm. $^{13}$C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 165.4, 161.6, 134.5, 134.3, 123.0, 120.6, 114.3, 102.4, 97.0, 83.9, 83.3, 82.7, 80.7, 76.3, 36.0, 35.1, 30.9, 26.5 (2 C), 25.9, 22.8, 22.1, 18.6 ppm. $C_{23}H_{30}ClNORu$ (473.01): calcd. C 58.40, H 6.39, N 2.96; found C 58.44, H 6.25, N 2.84.

**General Procedure for Quinoline Synthesis:** A mixture of **1** (1 mmol), **2** (2 mmol, unless otherwise stated), base (1 mmol, KOH: 250 μL of a 4 M solution in MeOH, other bases in their original form) and Ru catalyst (0.01 mmol) in 3 mL of 1,4-dioxane (Aldra-SORB™, Aldrich) was placed in a 7 mL screw-capped vial and allowed to react at 80 °C for 1 h. The catalyst and inorganic salts were removed from the reaction mixture by filtration through a short silica gel column (ethyl acetate). The reported quinoline yields were determined by GC. To isolate the quinoline, the resulting solution was concentrated and passed through a second silica gel column (ethyl acetate/hexane mixture, 1:4). The solvent was evaporated and the resulting product was dissolved again in a minimal amount of ethyl acetate. A pale yellow precipitate formed upon addition of HCl (4 N solution in dioxane, Aldrich), which was filtered and suspended in an aqueous 1 M NaOH solution (15 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2 × 15 mL) and after evaporation of the combined $CH_2Cl_2$ phases, the quinoline was obtained in good yield (typically 5–10% lower than GC yields).

All quinolines were fully characterized with $^1$H and $^{13}$C NMR spectroscopy. Spectroscopic data of **3a**–**d**, **3f**–**j**, **3m** and **3n** has previously been reported[30,43] and our data was in accordance with those results. Yields were determined from the optimized reaction with **5** and KO*t*Bu.

**2-(4-Methoxyphenyl)quinoline (3e):** Pale yellow oil, 0.2094 g, 89%. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.15 (m, 2 H), 7.90–7.80 (m, 3 H), 7.71 (m, 1 H), 7.52 (m, 1 H), 7.42 (m, 1 H), 7.13 (m, 1 H), 7.03 (m, 1 H), 3.87 (s, 3 H) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 157.5, 157.4, 148.6, 135.3, 131.8, 130.6, 130.0, 129.9, 129.5, 127.7, 127.3, 126.4, 123.7, 121.5, 111.7, 55.9 ppm. $C_{16}H_{13}NO$ (235.28): calcd. C 81.68, H 5.57, N 5.95; found C 81.74, H 5.85, N 5.75.

**2-Butyl-3-methylquinoline (3k):** Pale yellow oil, 0.1116 g, 56%. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.01 (m, 1 H), 7.82 (d, 1 H), 7.70 (m, 1 H), 7.60 (m, 1 H), 7.44 (m, 1 H), 2.98 (m, 2 H), 2.48 (s, 3 H), 1.76 (m, 2 H), 1.50 (m, 2 H), 1.04 (m, 3 H) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 161.5, 145.6, 134.7, 128.5, 127.2, 126.4, 126.2, 125.6, 124.5, 35.2, 30.0, 22.0, 18.2, 13.0 ppm. $C_{14}H_{17}N$ (199.29): calcd. C 84.37, H 8.60, N 7.03; found C 84.09, H 8.60, N 6.68.

**2-Ethyl-3-propylquinoline (3l):** Pale yellow oil, 0.0417 g, 21%. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.01 (m, 1 H), 7.82 (d, 1 H), 7.70 (m, 1 H), 7.60 (m, 1 H), 7.44 (m, 1 H), 2.97 (m, 2 H), 2.66

(m, 2 H), 1.76 (m, 2 H), 1.39 (m, 2 H), 0.98 (m, 3 H) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 162.0, 145.5, 133.8, 132.6, 127.8, 127.4, 127.3, 126.2, 125.8, 33.3, 27.8, 22.5, 13.0, 12.6 ppm. $C_{14}H_{17}N$ (199.29): calcd. C 84.37, H 8.60, N 7.03; found C 84.09, H 8.60, N 6.68.

**2-Methyl-1,2,3,4-tetrahydroacridine (3o):** White solid, 0.1815 g, 92%. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.98 (d, 1 H), 7.9 (s, 1 H), 7.61 (d, 1 H), 7.52 (t, 1 H), 7.34 (t, 1 H), 3.20–2.90 (m, 3 H), 2.50 (dd, 1 H), 1.98 (m, 1 H), 1.90 (m, 1 H), 1.52 (m, 1 H) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 159.3, 146.9, 135.2, 130.8, 128.7, 127.4, 127.1, 125.8, 38.0, 33.4, 31.7, 29.3, 21.9 ppm. $C_{14}H_{15}N$ (197.28): calcd. C 85.24, H 7.66, N 7.10; found C 84.98, H 7.88, N 7.03.

**11*H*-Indeno[1,2-*b*]quinoline (3p):** White solid, 0.0326 g, 15%. $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 8.31 (s, 1 H), 8.19 (m, 2 H), 7.83 (m, 1 H), 7.70 (m, 1 H), 7.61 (m, 1 H), 7.51 (m, 3 H), 4.05 (s, 2 H) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 161.9, 148.3, 145.3, 140.6, 134.9, 131.4, 130.2, 129.9, 129.4, 129.1, 128.0, 127.8, 125.9, 125.7, 122.3, 34.3 ppm. $C_{16}H_{11}N$ (217.27): calcd. C 88.45, H 5.10, N 6.45; found C 88.55, H 5.12, N 6.31.

**Synthesis of 3-Phenylpropiophenone (20): 4** (0.0082 g, 0.01 mmol), benzyl alcohol (0.1081 g, 1 mmol), acetophenone (0.1201 g, 1 mmol) and KOH powder (0.0561 g, 1 mmol) in 3 mL of dioxane were placed in a screw-capped vial and allowed to react for 1 h at 80 °C. The mixture was passed through a silica gel column (ethyl acetate) and the solvent was evaporated. **19** was obtained as an orange solid (0.1984 g, 94%). $^1$H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.95 (d, 2 H), 7.55 (t, 1 H), 7.44 (t, 2 H), 7.24–7.36 (m, 5 H), 3.30 (t, 2 H), 3.07 (t, 2 H) ppm. $^{13}$C NMR (300 MHz, $CDCl_3$, 25 °C): $\delta$ = 199.5, 141.6, 137.1, 133.3, 128.9 (2 C), 128.8 (2 C), 128.7 (2 C), 128.3 (2 C), 126.4, 40.7, 30.4 ppm.

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