Improved ruthenium catalysts for the modified Friedlaender quinoline synthesis

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Herein we describe an improved ruthenium catalyst for the oxidative cyclization of 2-aminobenzylalcohol with ketones, leading to quinolines *via* a modified Friedlaender synthesis.

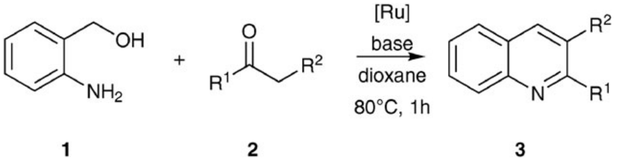
The synthesis of nitrogen-containing compounds, such as quinoline, is the subject of extensive research in organic chemistry because the quinoline skeleton is an important building block of many biologically-active compounds, *e.g.* anti-malarial agents.[1] Conventional routes, such as the Skraup, Döbner–von Miller, Conrad–Limpach, Friedlaender and Pfitzinger syntheses, often require harsh reaction conditions or consist of multiple steps, resulting in low overall yields, limiting their applicability.[1] However, recently, several homogeneous transition metal-catalyzed synthetic methods have been reported.[2–6] A very interesting method has been proposed by Cho and co-workers after their discovery of a remarkable transfer hydrogenation reaction of ketones by alcohols, catalyzed by ruthenium complexes.[7,8] This led to a modified Friedlaender quinoline synthesis (Scheme 1).[9,10]

Instead of using the unstable 2-aminobenzaldehyde as a starting product, it is now *in situ*-generated *via* a catalytic oxidation reaction of 2-aminobenzylalcohol (**1**). In the presence of a base, a cross-aldol reaction between the aldehyde and ketone **2** occurs, followed by a condensation reaction to form the quinoline **3**.†

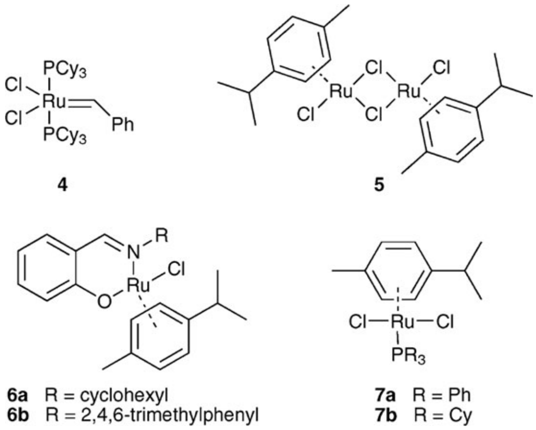
Among the few ruthenium precursors and catalysts that are described in literature, $RuCl_2({=}CHPh)(PCy_3)_2$ (**4**), commonly known as Grubbs' first generation catalyst, gives the highest conversion. However, no extensive research has been done on the systematic modification of different catalytic systems.

Given our experience in the synthesis of ruthenium catalysts for metathesis reactions, we wanted to explore the possibilities of some potentially interesting complexes for the modified Friedlaender synthesis.[11–13]

Of the many ruthenium catalysts that are able to oxidize alcohols, complexes of the type $[RuCl_2(\eta^6\text{-arene})]_2$ are easily accessible. Although these catalysts are not very active themselves, *in situ*-addition of suitable phosphines, or *N*,*O*-bidentate ligands like ethanolamine, greatly improve their activity.[14–16] Furthermore, Schiff base-substituted complexes have been reported as catalytic oxidants.[17,18]



Scheme 1 The modified Friedlaender quinoline synthesis.



Scheme 2 Ruthenium catalysts tested for the modified Friedlaender quinoline synthesis.

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

Catalyst	Yield (%)
4	74
5	15
6a	14
6b	15
7a	40
7b	53
5 + ethanolamine (0.20 mmol)	24
5 + PPh_3 (0.05 mmol)	25
5 + PPh_3 (1 mmol)	19
None	9

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

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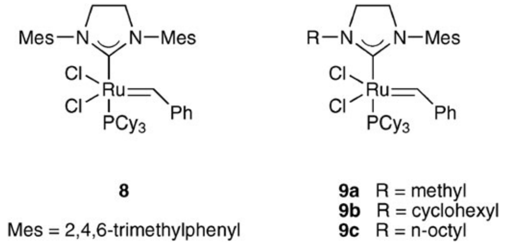
Table 2 Ruthenium-catalyzed synthesis of quinolines from **1** and acetophenone (**2**, R^1 = Ph, R^2 = H)[a]

Catalyst	Yield (%)
4	74
8	100
9a	52
9b	72
9c	75

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

Bearing these considerations in mind, complexes with *N*,*O*-bidentate Schiff base ligands (**6a** and **6b**) and phosphine ligands (**7a** and **7b**) were synthesized from the precursor $[\mathrm{RuCl_2}(\textit{para}\text{-cymene})]_2$ (**5**) (Scheme 2).[11,19,20] The results of the catalytic tests are summarized in Table 1.

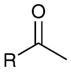
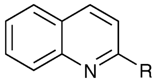
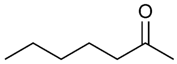
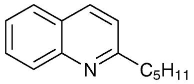
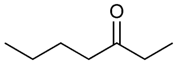
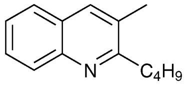
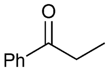
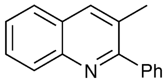
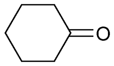
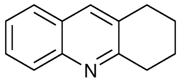
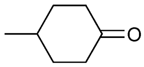
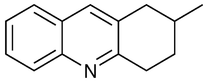
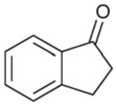
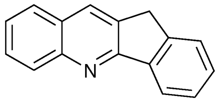
Much to our surprise, the use of *N*,*O*-bidentate ligands showed no significant influence on the catalytic activity (catalyst **5** *vs.* **6a** and **6b**). *In situ*-addition of ethanolamine to **5** resulted in a slightly increased yield (25% compared to 15% after 1 h), but the overall yield remained poor.



Scheme 3 Grubbs' second generation catalyst and analogues.

In situ-addition of $\mathrm{PPh_3}$ also resulted in a small increase in yield, but upon the use of a large excess of $\mathrm{PPh_3}$ the yield diminished again. This is probably due to a saturation effect of the catalyst: the vacant site for accepting hydrogen becomes blocked by excess phosphine. With isolated complex **7b**, a moderate conversion of 53% was achieved. Thus, phosphine ligands clearly have a positive influence on the conversion. These results indicate that the choice of ligands is crucial for this reaction. To further investigate this, we implemented variations on the Grubbs' first generation catalyst in the next set of experiments.

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

Ketone	Quinoline	Yield (%) Catalyst **4**	Yield (%) Catalyst **8**
			
R =	**R** =		
Ph	Ph	74 (65)[b]	100 (94)[b]
2-$\mathrm{MeC_6H_4}$	2-$\mathrm{MeC_6H_4}$	31	66
3-$\mathrm{MeC_6H_4}$	3-$\mathrm{MeC_6H_4}$	63	91
4-$\mathrm{MeC_6H_4}$	4-$\mathrm{MeC_6H_4}$	64	86
2-$\mathrm{MeOC_6H_4}$	2-$\mathrm{MeOC_6H_4}$	38	87
4-$\mathrm{MeOC_6H_4}$	4-$\mathrm{MeOC_6H_4}$	47	73
4-$\mathrm{NO_2C_6H_4}$	4-$\mathrm{NO_2C_6H_4}$	0	0
Me	Me	65	100
		34[c]	76[d]
		21[e]	51[f]
		72	87
		72	100
		78	100
		17	30

[a] Reaction conditions: Aminobenzylalcohol (1 mmol), acetophenone (2 mmol), catalyst (0.01 mmol) and KOH (1 mmol) in dioxane (3 mL) at 80 °C for 1 h. Yields determined by GC. [b] Isolated yields are given in brackets. [c] 8% 3-butyl-2-methylquinoline was also formed. [d] 18% 3-butyl-2-methylquinoline was also formed. [e] 7% 2-ethyl-3-propylquinoline was also formed. [f] 17% 2-ethyl-3-propylquinoline was also formed.

Over the past few years, *N*-heterocyclic carbene (NHC) ligands have received a great deal of attention due to their superior stability and electronic properties.[21,22] This led to the so-called Grubbs' second generation catalyst, several variants of which have been synthesized (Scheme 3).[13] The results are summarized in Table 2.

The replacement of a PCy_3 ligand by H_2-IMes clearly improves catalytic activity. The first generation Grubbs' catalyst reached 74% conversion after 1 h, while the second generation gave complete conversion. This may implicate that the σ-donating character of the ligands influence the activity of the catalyst. Phosphines and H_2-IMes are both good σ-donors, but the superior donor capacity of the latter has been attributed to be the cause of increased catalytic activity for several catalytic systems.[21]

Variation of the NHC ligand through replacement of one Mes group by an aliphatic group decreased the conversion. The bulkiness of the amino side group seems to play an important role, which is evidenced in the series methyl $<$ cyclohexyl $\approx$ *n*-octyl $<$ Mes, where the complex with the bulkiest group shows the highest quinoline yield.

To assess the scope of this reaction, a series of ketones was screened with **4** and **8**. The results are shown in Table 3.

From these results, it is obvious that the second generation Grubbs' catalyst outperformed the first. For all ketone substrates, a higher yield was obtained for catalyst **8** compared to catalyst **4**. Substrates with strong electron withdrawing groups, such as NO_2, inhibit the reaction. When two α-protons are available in an asymmetric ketone, two quinolines will be formed, as illustrated by 2-heptanone and 3-heptanone.

In summary, we have shown that Grubbs' second generation catalyst and its analogues are efficient catalysts for the oxidative cyclization of **1** with ketones to give quinolines. The second generation catalyst **8** proved to be a superior catalyst, even surpassing the first generation catalyst, which had been the best catalyst to date.

Experimental

The general experimental procedure for quinoline synthesis is as follows: A mixture of ketone (2 mmol), **1** (1 mmol), KOH (1 mmol) and Ru catalyst (0.01 mmol) in 3 mL dioxane was placed in a 7 mL screw-capped vial and allowed to react at 80 °C for 1 h. To remove the catalyst and inorganic salts, the reaction mixture was filtered through a short silica gel column (ethyl acetate). Unless otherwise stated, yields were determined by GC. Isolation of the quinoline, as described by Cho and co-workers,[9,10] proved to be problematic: the quinoline could not be separated from the unreacted ketone. To isolate the quinoline, the resulting solution was concentrated and passed through a second silica gel column (ethyl acetate/hexane 1 : 4). The solvent was evaporated and the resulting product was dissolved again in ethyl acetate. The pale yellow precipitate that formed upon addition of HCl (4 M solution in dioxane) was filtered and suspended in an aqueous 1 M NaOH solution. The aqueous phase was extracted twice with CH_2Cl_2 and, after evaporation of the combined CH_2Cl_2 phases, the quinoline was obtained in good yield (typically 5–10% lower than GC yields).

References

† Although the order of the steps could theoretically 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 not observed. The reaction of **1** with acetophenone in basic media (KOH, dioxane, 80 °C, 1 h) gave no imine formation. This is not really unexpected, since imine formation using ketones proceeds very slowly and is typically performed in acidic media. To further illustrate this, the reaction of **1** with acetophenone using a catalytic amount of formic acid (dioxane, 80 °C, 1 h) does not produce detectable amounts of imine either.

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