Letter to the Editor

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A facile route to ruthenium–carbene complexes and their application in furfural hydrogenation

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A number of new *N*-heterocyclic carbene (NHC) ligands were synthesized via a multicomponent reaction, wherein an aldehyde or ketone, a primary amine and an α-acidic isocyanide were reacted, giving the corresponding 2*H*-2-imidazolines. These were easily alkylated with an alkyl halide at position N-3, yielding the final NHC precursors, that were then complexed with Ru *in situ*. The resulting complexes are shown to be active and selective catalysts for the transfer hydrogenation of furfural to furfurol, using isopropanol as the hydrogen source. Importantly, the carbene ligand remains coordinated to the ruthenium center throughout the reaction.

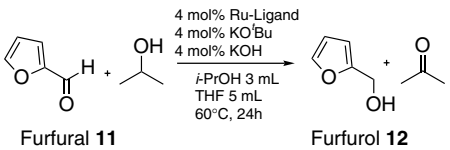
Supporting information may be found in the online version of this article.

Keywords: *N*-heterocyclic carbenes; multicomponent reaction; transfer hydrogenation; homogeneous catalysis

Introduction

One thorny problem in applied organometallic chemistry is setting up a general protocol for ligand synthesis and complex formation.[1,2] This is especially true in the case of carbene complexes,[3,4] where synthesizing ligand backbones from scratch can be a nightmare. This is a pity, since in many cases, and particularly with *N*-heterocyclic carbenes (NHCs), the resulting pre-catalysts are air- and moisture-stable.[5–9] In this communication, we present a simple, straightforward and inexpensive synthesis route to NHCs and demonstrate the application of their ruthenium derivatives in catalytic transfer hydrogenation. The synthesis is based on a so-called multicomponent reaction (MCR).[10–18] Importantly, this approach is general, giving access to a variety of potential carbene ligand structures.

In a typical ligand synthesis (Fig. 1), an aldehyde or ketone **I**, a primary amine **II** and an α-acidic isocyanide **III** were combined in a one-pot reaction to give the corresponding 2*H*-2-imidazoline. This was then easily alkylated with an alkyl halide **IV** at position N-3, giving the final NHC precursor.[10,11] We synthesized 10 different catalyst precursors this way (structures **1**–**10** in Scheme 1), all of which were isolated and characterized. These precursors were then complexed with ruthenium and tested in the transfer hydrogenation of furfural **11** to furfurol **12**, using isopropanol as the sacrificial hydrogen source [equation (1)].[19] The deprotonation was done by mixing equivalent amounts of the imidazolinium precursor and potassium *tert*-butoxide for 30 min at 40 °C. Subsequently, the resulting carbene was coordinated *in situ* to $[RuCl_2(p\text{-cymene})]_2$. The formation of the complex was shown clearly by ^{13}C NMR. Note that characterizing this complex by NMR requires rigorous exclusion of water and oxygen under glove box conditions (see Experimental section and Supporting Information for details). Both reactions were complete within 30 min. An excess of isopropanol, used as both solvent and sacrificial hydrogen donor, was then added, together with 1 equivalent of potassium hydroxide, activating the catalyst. Then, 25 equivalents of furfural were added, the mixture heated to 60 °C and stirred under nitrogen for 24 h. Reaction progress was monitored by GC (see Experimental section for details).



Furfural **11** Furfurol **12** (1)

Table 1 shows the substrate conversion, product selectivity and product yield. In the absence of any carbene ligand, the metal precursor $[RuCl_2(p\text{-cymene})]_2$ already gives 94% conversion, with 84% yield to furfurol after 24 h. Nevertheless, adding a carbene ligand can raise both numbers to >99%. Control experiments showed that the hydrogen transfer reaction is sensitive to the type and amount of base used.[7] The best conversions were obtained with a mix of potassium *tert*-butoxide for deprotonating the imidazolinium precursor, and KOH as a promoter.[20] No reaction occurred in the absence of KOH, and <80% yield was observed when using 0.1 equivalents of KOH with respect to the Ru catalyst.

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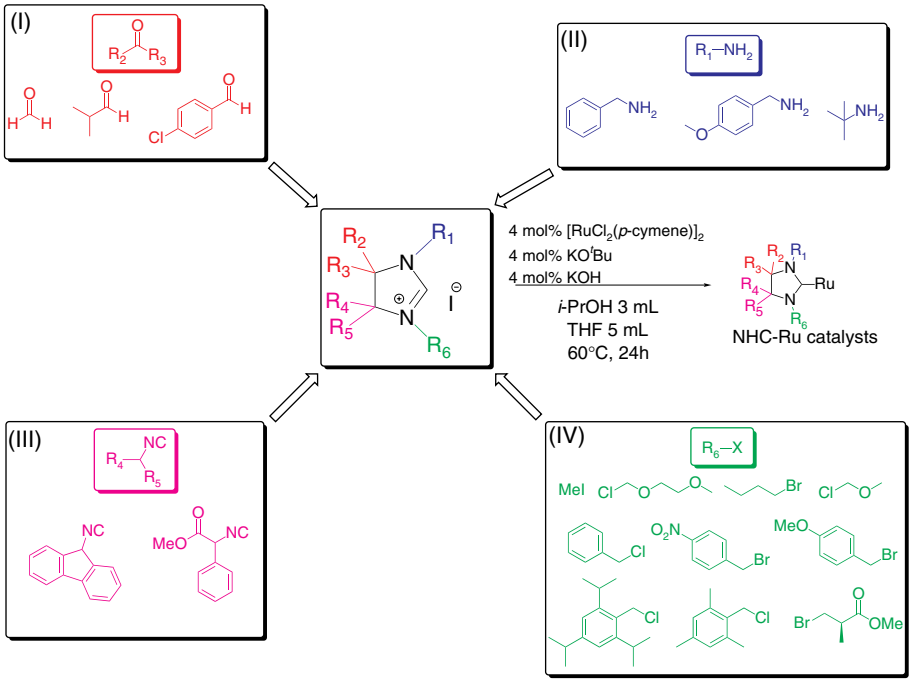
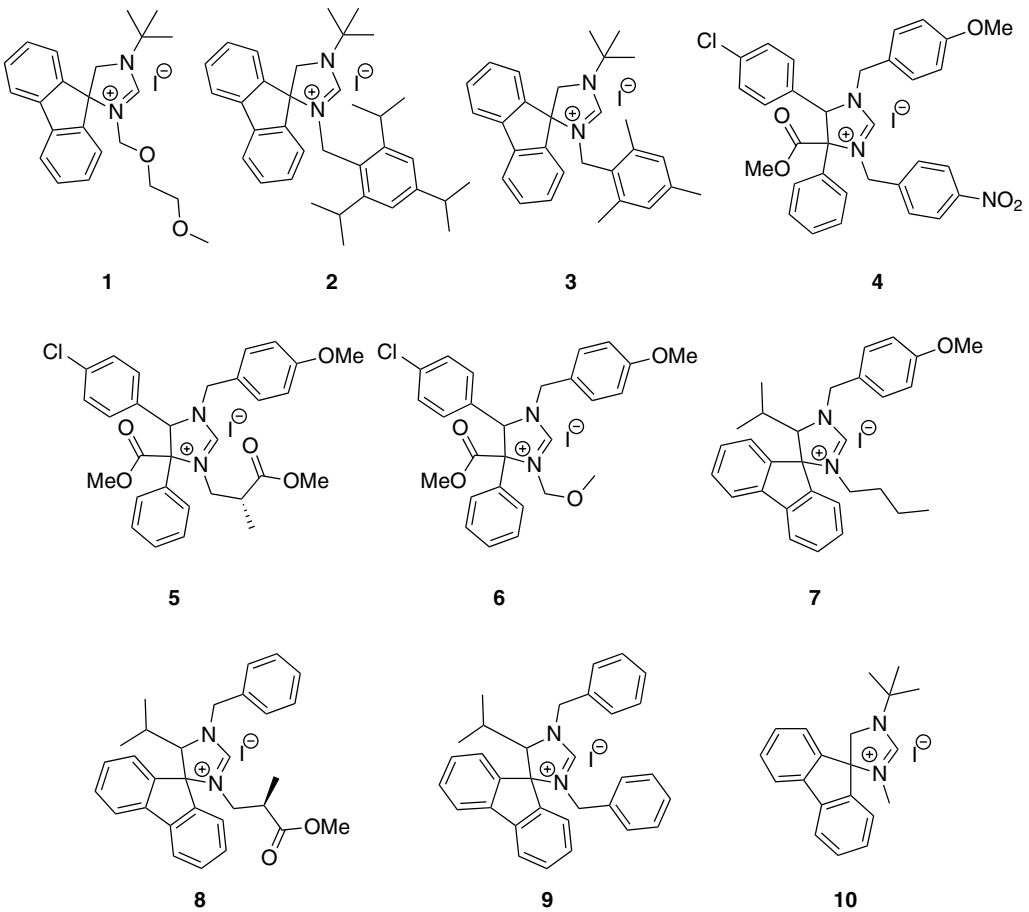


Figure 1. Multicomponent synthesis route to *N*-heterocyclic carbene ligand precursors. Note that only a small selection of the 1080 precursor permutations were synthesized.



Scheme 1. The 10 new *N*-heterocyclic carbene precursors synthesized via the multicomponent route.

Table 1. Ru–carbene catalyzed transfer hydrogenation of furfural to furfurol[a]

Entry	Imidazolinum ligand precursor	Furfural conversion (%)[a]	Furfurol	
			Selectivity (%)[b]	Yield (%)[c]
1	**1**	92.94	99.00	92.01
2	**2**	95.34	98.32	93.74
3	**3**	99.61	99.40	99.01
4	**4**	99.91	98.98	98.89
5	**5**	81.04	99.54	80.67
6	**6**	63.50	98.99	62.86
7	**7**	98.72	98.37	97.11
8	**8**	63.32	99.22	62.83
9	**9**	98.05	99.01	97.08
10	**10**	99.48	98.88	98.37
11	No ligand	94.15	90.10	84.63

[a] Standard reaction conditions: 5 mmol furfural **11**, 0.1 mmol $[RuCl_2(p\text{-cymene})]_2$; 0.2 mmol 2-imidazolinium precursor (structures shown in Scheme 1); 0.2 mmol KO*t*Bu; 0.1 mmol KOH; 5 ml dried THF; 3 ml *i*-PrOH; N_2 atmosphere; 60 °C; 24 h.
[b] Determined dividing the total amount of furfurol **12** by the total amount of products.
[c] Determined by GC analysis using *n*-octane as internal standard.

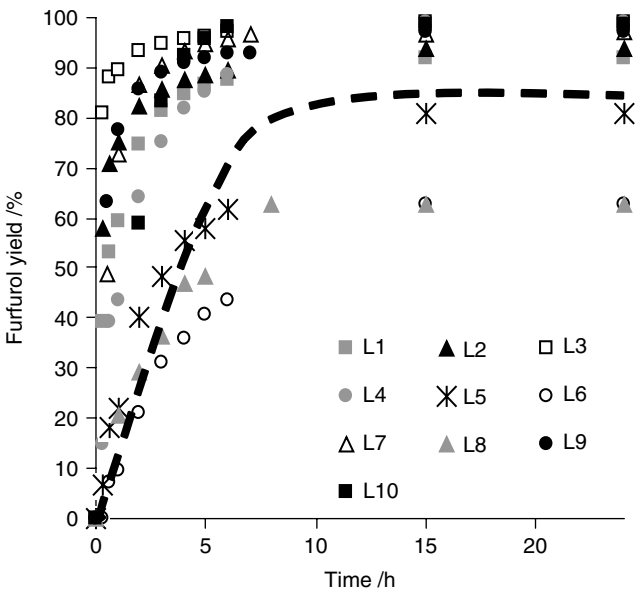
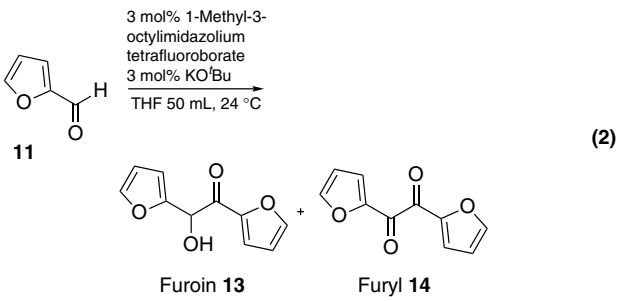


Figure 2. Time-resolved profiles for the Ru-carbene catalyzed hydrogenation of furfural **11** to furfurol **12**. Reaction conditions are as in Table 1. The broken curve shows the blank experiment using $[RuCl_2(p\text{-cymene})]_2$ precursor only (no carbene ligand).

Figure 2 shows the time-resolved profiles for the transfer hydrogenation reaction catalyzed by the 10 different ruthenium–carbene complexes made from the imidazolinium precursors in Scheme 1, where L**n** denotes the ligand prepared using precursor **n**. For comparison, the broken curve shows the yield obtained without a carbene ligand {i.e. using only the $[RuCl_2(p\text{-cymene})]_2$ precursor}. We see that several of the complexes, and especially **2, 3** and **9**, exhibit both fast and highly selective catalysis. Curiously, the catalysts based on precursors **5, 6** and **8** are *poorer* than the carbene-free complex. While a detailed mechanistic analysis is beyond the scope of this preliminary communication, examining the structures in Scheme 1 reveals an interesting relationship: structures **2, 3** and **9** all have the rigid spiro-bicyclic moiety, plus large hindering groups at the N-1 and N-3 positions. A simple molecular mechanics simulation shows that the ruthenium centre in all these three cases is effectively 'hidden', resulting in a narrow reaction pocket.[21] Conversely, structures **5, 6** and **8** all lack the spiro construction and have a small and flexible oxygen-bearing group on the N-3 position. Competitive coordination by this oxygen to the Ru atom may explain the lower conversion obtained with these complexes.[22] Once the furfural coordinates, however, the reaction proceeds with a comparable selectivity to the other complexes.

One question that springs to mind in such systems pertains to the ligand dissociation equilibria. Namely, what is the chance that, in the course of the catalytic cycle, the carbene ligands dissociate from the Ru complex? Happily, we can say that our carbene ligands remain coordinated throughout the cycle. Any free carbene in solution would lead to immediate acyloin condensation, analogous to the reactions reported by Enders *et al.*[23] A series of separate control experiments showed that this acyloin condensation [equation (2), giving roughly 90% furoin **13** and 10% furyl **14**] is very fast under our reaction conditions compared with the transfer hydrogenation reaction. Thus, using a 1 : 1 ligand : metal ratio, we managed to avoid any acyloin condensation, confirming that the carbene ligand remains coordinated to the ruthenium complex throughout the catalytic cycle.



(2)

Theoretically, a reductive elimination of an intermediate (di)-hydride to an imidazole species that does not catalyze acyloin condensation is also possible, but since our reactions are under basic conditions, the base would restore the carbene *in situ*. Thus, any carbene coming off as an H-imidazole would be restored and then catalyze the above acyloin condensation. Since this condensation was not observed, and since a series of control experiments confirmed that neither OH^- nor *t*-BuO^- in itself promotes the acyloin condensation of furfural, we maintain that indeed the Ru remains coordinated to the carbene.

In conclusion, we show that the multicomponent reaction of aldehydes/ketones, primary amines and α-acidic isocyanides opens a facile and effective route to imidazolinium salts. Ruthenium–carbene complexes based on such salts are good transfer hydrogenation catalysts. The fact that the carbene ligand remains coordinated to the ruthenium centre throughout the reaction creates an opportunity for ligand design, and indeed ligands with different peripheral groups show markedly different catalysis effects.[24]

Experimental Section

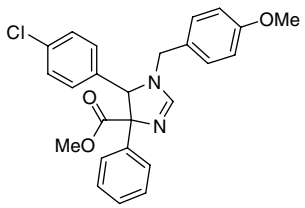
Materials and Instrumentation

GC analysis was performed on an Interscience GC-8000 gas chromatograph with a 100% dimethylpolysiloxane capillary column (VB-1, 30 m × 0.325 mm). Samples for GC analysis were diluted in 1 ml EtOH. GC conditions: isotherm at 60 °C (2 min); ramp at 50 °C min^{-1} to 80 °C; isotherm at 80 °C (3 min); ramp at 1 °C min^{-1} to 90 °C; ramp at 50 °C min^{-1} to 250 °C; isotherm at 250 °C (3 min). ^{1}H NMR spectra were recorded on a Varian Mercury *300* (300 MHz, $CDCl_3$) All reactions were performed under N_2 using standard Schlenk techniques. Unless otherwise noted, all chemicals were purchased from commercial sources and used as received. All products are known compounds and were identified by comparing of their GC retention times and/or NMR spectra to those of authentic samples. Ligand **10** is a known compound, and was synthesized following a published procedure.[17] Ligands **1–9** are new compounds, synthesized using a modified procedure as outlined below. Detailed synthesis procedures and characterization data for these compounds, as well as details of the NMR characterization control experiments, are included in the Supporting Information.

General Procedure for Synthesizing the 2*H*-2-imidazoline Archetypes

Four archetypes of 2*H*-2-imidazolines were synthesized via a three-component Mannich-type reaction. All reactions were performed using a concentration of 1 M of aldehyde, 1 M of amine, and 0.5 M of isocyanide in dry CH_2Cl_2 or MeOH. Na_2SO_4 and the aldehyde were added, at 25 °C, to a stirred solution of the amine. The mixture was stirred for 2 h. The isocyanide was then added and the mixture was stirred at 25 °C for an additional 18 h, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (cyclohexane–EtOAc–Et_3N = 2 : 1 : 0.01, gradient, unless stated otherwise).

Example: 2H-2-imidazoline type A

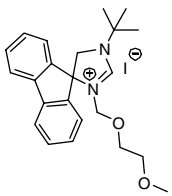


Starting from *p*-methoxybenzylamine (177.9 mg, 1.298 ml, 10.0 mmol), *p*-chlorobenzaldehyde (1.405 g, 10.0 mmol) and methyl 2-isocyano-2-phenylacetate (876 mg, 749 µl, 5.00 mmol) yielded 2*H*-2-imidazoline **A** (339.2 mg, 7.80 mmol, 78%) as 3 : 2 mixture of diastereoisomers as a yellow foam. ^{1}H NMR (250 MHz $CDCl_3$) δ: 7.62–7.60 (m, 2H), 7.37–7.29 (m, 4H), 7.25–7.21 (m, 2H), 7.06–6.97 (m, 7H), 6.94–6.83 (m, 7H), 6.76 (m, 2H), 5.272 (s 1H), 4.729 (s, 1H), 4.35 (d, J = 14.7, 2H), 4.31 (d, J = 14.8, 2H), 3.81–3.25 (m, 4H), 3.811 (s, 3H), 3.767 (s, 3H), 3.728 (s, 3H), 3.256 (s, 3H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 173.82 (C), 170.97 (C), 159.37 (C), 159.26 (C), 156.63 (CH), 155.64 (CH), 142.95 (C), 137.07 (C), 135.22 (C), 134.30 (C), 133.95 (C), 133.24 (C), 129.52 (2 × CH), 129.45 (CH), 129.11 (CH), 128.78 (CH), 128.26 (CH), 127.98 (2 × CH), 127.72 (CH), 127.71 (CH), 127.31 (C), 127.25 (CH), 127.06 (C), 126.53 (2 × CH), 126.49 (CH), 114.22 (CH), 114.11 (CH), 85.30 (C), 84.32 (C), 72.08 (CH_3), 68.63 (CH_3), 55.28 (CH_3), 55.26 (CH_3), 53.05 (CH_3), 48.89 (CH_2), 48.35 (CH_2); IR: 3064.03, 3020.63, 2942.02, 2912.13, 2838.35, 1722.97, 1608.69, 1511.76, 1490.06, 1430.75, 1360.34, 1290.90, 1232.55, 1170.83, 1087.89, 1014.11, 933.58, 695.84638.46; HRMS calculated for $C_{25}H_{24}ClN_2O_3$ (M^+ + H) 435.1470, found 434.1454. The synthesis details and characterization data for archetypes **B, C**, and **D** are provided in the Supporting Information.

Procedure for the Synthesis of 2-Imidazolinium Salts

Reactions were carried out at a concentration of 1 M of imidazoline in acetone. The halide (1 equiv.) was added to a stirred solution of the 2*H*-2-imidazoline and NaI (1 equiv.). The reaction mixture was stirred at rt for 18 h. Then, the reaction mixture was filtrated over celite and concentrated *in vacuo*.

*Example 1: imidazolium iodide **1***



According to general procedure II for the synthesis of 2-imidazolinium salts, the reaction between 2*H*-2-imidazoline **D** (276.2 mg, 1.00 mmol), NaI (149.9 mg, 1.00 mmol) and 1-(chloromethoxy)-2-methoxyethane (123.0 mg, 112.8 µl, 1.00 mmol) afforded 2-imidazolinium iodide **1** (482.1 mg, 0.979 mmol, 98%) as a yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.794 (s, 1H), 7.74 (d, J = 7.2, 2H), 7.69 (d, J = 7.2, 2H), 7.52–7.48 (m, 2H), 7.44–7.40 (m, 2H), 4.832 (s, 2H), 4.291 9s, 2H), 3.44 (t, J = 1.5, 2 H), 3.207 (s, 3 H), 3.16 (t, J = 1.5, 2 H), 1.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.98 (CH), 142.35 (C), 140.12 (C), 130.99 (CH), 129.24 (CH), 124.59 (CH), 120.77 (CH), 76.28 (CH_2), 73.48 (C), 71.12 (CH_2), 68.70 (CH_2), 58.90 (CH_3), 58.57 (C), 57.81 (CH_2), 28.02 (CH_3); IR: 2982.53 (m), 2916.95 (m), 2876.92 (m), 1624.12 (s), 1448.11 (m), 1295.24 (br), 1229.18 (m), 1181.92 (m), 1095.60 (m), 1032.06 (br), 844.85 (m), 767.69 (s), 756.12 (s), 734.42 (s); HRMS calculated for $C_{23}H_{29}N_2O_2$ ($M^+ - I^-$) 365.2197, found 365.2210.

Procedure for Preparing the Ru–Carbene Complexes

A solution of $[RuCl_2(p\text{-cymene})]_2$ (61 mg, 0.1 mmol) was stirred under N_2 in a 25 ml Schlenk tube together with the 2-imidazolinium salt (0.2 mmol), KO*t*Bu (22 mg, 0.2 mmol) and KOH (6 mg, 0.1 mmol) in 5.0 ml dried THF and 3.0 ml *i*-PrOH for 30 min at 40 °C.

*Example: $[RuCl_2(p\text{-cymene})]_2$/**1***

$[RuCl_2(p\text{-cymene})]_2$ (61 mg, 0.1 mmol), 2-imidazolinium salt **1** (73.1 mg, 0.2 mmol), KO*t*Bu (22 mg, 0.2 mmol) and KOH (6 mg, 0.1 mmol) were stirred in 5.0 ml dried THF and 3.0 ml *i*-PrOH for 30 min at 40 °C.

Procedure for Catalytic Transfer Hydrogenation of Furfural

In a 25 ml Schlenk tube under N_2, the catalyst was first prepared according to the above procedure. Furfural **11** (480 mg, 5.0 mmol) and octane (240 mg) were added and the reaction mixture was heated to 60 °C and stirred for 24 h. Periodically, samples were taken out and analyzed by GC.

Procedure for Acyloin Condensation of Furfural 11 to Furoin 13

In a 100 ml Schlenk tube equipment under N_2, 1-methyl-3-octylimidazolium tetrafluoroborate (28 mg, 1 mmol) and KO*t*Bu (122 mg, 1 mmol) were dissolved in 50 ml of dry THF and stirred for 15 min at 24 °C. After addition of distilled furfural **11** (3200 mg, 33 mmol) the reaction mixture was stirred overnight, and quenched with 2 ml formic acid 98%. The solvents were evaporated and the crude product was recrystallized from EtOH (85 ml), to give **13** as a yellow solid (3030 mg, 31.56 mmol, 94%) containing 2-3% of furyl **14** as side product.

Procedure for Characterization of the Ru–Carbene Complex by ^{13}C NMR

In a glovebox, a flame-dried NMR tube containing a solution of imidazolium salt **1** (30.0 mg, 60.8 µmol, 1 equiv.) and $[RuCl_2(p\text{-cymene})]_2$ (37.7 mg, 60.8 µmol, 1 equiv.) in THF (1 ml) was prepared. Subsequently, KO*t*Bu (7.0 mg, 60.8 µmol, 1 equiv.) was added. The resulting reaction mixture was stirred on a vortex mixer for 1 min and subsequently ^{1}H and ^{13}C NMR measurements were performed. In the ^{13}C NMR analysis the C2-Ru signal was observed at 166.07 ppm as a small peak.

Supporting information

Supporting information may be found in the online version of this article.

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