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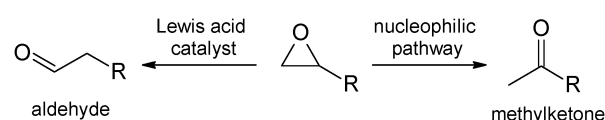
Selective rearrangement of terminal epoxides into methylketones catalysed by a nucleophilic rhodium–NHC–pincer complex†

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An efficient Rh^I–NHC–pincer catalyst for the highly regioselective Meinwald rearrangement of monoalkylated epoxides into methylketones under mild conditions is presented. The nucleophilic epoxide opening is assisted by Lewis acids.

Epoxides are widely used as substrates in organic synthesis,¹ as they can be transformed under ring opening into various functional groups. One well-documented reaction is the so-called Meinwald rearrangement, *i.e.* the rearrangement into aldehydes or ketones usually catalysed by Lewis acids.² Selectivity is determined by formation of the most stable carbenium intermediate followed by an alkyl or hydride shift.³ Therefore, aldehydes are the major product when using terminal epoxides. A number of Lewis acid catalysts¹ are known for internal epoxides^{3,4} while catalysts for the rearrangement of monoalkyl-substituted terminal epoxides are less common. Only a few catalysts are known to selectively convert monoalkylated epoxides into methylketones, *e.g.* Pd(OAc)₂,^{5a,b} MnI₂ or Co₂(CO)₈ (ref. 5c). In those cases a nucleophilic ring opening can explain the inverse product selectivity. In the following, we describe the first rhodium catalysed Meinwald rearrangement of terminal epoxides to methylketones (Scheme 1).

In 2006 we reported the highly nucleophilic character of rhodium–pincer-complex **1**⁶ that is caused by the two electron-donating N-heterocyclic carbene moieties (Fig. 1).⁷ Therefore, complex **1** seems to be a promising candidate for catalysing the nucleophilic epoxide rearrangement. Initially, we carried out the reaction with various epoxides in the presence of



Scheme 1 Rearrangement of terminal epoxides (Meinwald reaction).

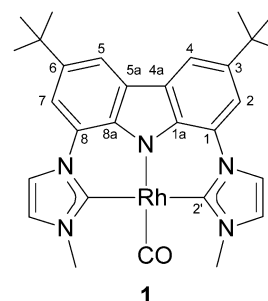


Fig. 1 The highly nucleophilic NHC–pincer rhodium complex **1**.

10 mol% of pure complex **1**, but no reaction could be achieved. However, upon addition of a stoichiometric amount of lithium chloride in tetrahydrofuran a rearrangement product was detected in low yields.

Using dichloromethane or acetonitrile suppresses the rearrangement to the methylketone and results in formation of new organometallic species (*vide infra*),⁸ while benzene improved the reaction rate remarkably. In addition, lithium salts of weakly coordinating anions such as lithium tetrakis(pentafluorophenyl)borate or lithium bis(trifluoromethanesulfonimide) (LiNTf₂) led to very high reaction rates at 60 °C (see ESI† for optimisation details).

As strong Lewis acids can act as catalysts for the epoxide rearrangements themselves, we checked their individual reactivity towards 1,2-epoxyhexane, but none of the Lewis acid additives used catalyses the rearrangement on its own, not even at elevated temperatures of up to 120 °C in thf and 80 °C in benzene. We then optimised the amount of catalyst, lithium salt additive as well as the reaction temperature by analysing

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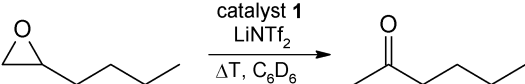
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† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra and crystallographic data. CCDC 1018408 (**4a**) and 1018409 (**4b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc07154a



Table 1 Optimisation of the reaction conditions: influence of catalyst loading and temperature on the reaction^a

					
Entry	T [°C]	1 [mol%]	LiNTf ₂ [mol%]	Time [min]	Yield ^{b,c} [%]
1	25	10	10	100	3
2	40	10	30	100	7
3	60	10	10	100	51
4	60	10	30	100	94
5	60	10	50	100	98
6	80	10	10	100	98
7	60	1	30	120	18
8	60	5	20	120	95

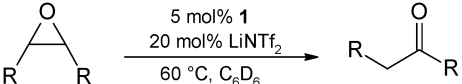
^a Reaction conditions: **1** (10 mol%), 1,2-epoxyhexane (35 μ L), 0.5 mL benzene, 100 min, all reactions were carried out using a *J. Young* NMR tube. ^b The ketone was the only observed reaction product. ^c Yield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

the reaction mixture after 100 min (Table 1). The rearrangement proceeded almost quantitatively after this time when using 30–50 mol% of LiNTf₂ and 10 mol% of **1** (Rh : Li = 1 : 3–1 : 5) at 60 °C (entries 3–5) or only 10 mol% of the Li additive at 80 °C (entry 6), but already at room temperature or 40 °C slow rearrangement is observed (entries 1 and 2). Reducing the catalyst loading to 1 mol% decreases the reaction rate affording only 18% of the methylketone after 2 h (entry 7). Good results are still achieved using 5 mol% of **1** and 20 mol% LiNTf₂ at 60 °C (95% yield after 2 h; entry 8). All experiments with 1,2-epoxyhexane gave the methylketone as the sole rearrangement product; the respective aldehyde was never detected.

The best results for this reaction have been reported by Kagan as well as Kulawiec with a combination of Pd(OAc)₂ and PBu₃ that resulted in the selective formation of the ketone at 120 °C in toluene without the use of any additive.^{5a,b} Using SmI₂, MnI₂ or Co₂(CO)₈ also formed the corresponding ketones with a selectivity of above 95% and reaction times between 2 h (MnI₂, 70 °C) and 24 h (Co₂(CO)₈, 40 °C, MeOH), but only yields between 70–80% were obtained.^{5c} To probe the nucleophilic effect of our rhodium catalyst, we then tested commercially available Wilkinson catalyst [Rh(PPh₃)₃Cl] and [Rh(μ -Cl)(COD)]₂ under our optimized conditions (100 min, 60 °C, benzene, 30 mol% LiNTf₂) with 1,2-epoxyhexane, but observed only inferior results (Table 2). About 35% of the methylketone could be obtained when heating the reaction mixture with [Rh(PPh₃)₃Cl] at 85 °C for 60 h. In the case of [Rh(μ -Cl)(COD)]₂ no catalytic activity was observed applying these conditions.







As a first substrate scope, we found that propylenoxide is rearranged to acetone in excellent yields (Table 3, entry 1), whereas styrene oxide gave a mixture of acetophenone and 2-phenylacetaldehyde at 60 °C in a 3 : 2 ratio in an only overall 10% yield after 2 h (entry 3). A blank test revealed that LiNTf₂ itself reacts with styrene oxide leading exclusively to the aldehyde at 60 °C. This side reaction can be suppressed completely when lowering the temperature to 30 °C, however, only 5% of acetophenone were obtained after 16 h (entry 4). Using LiCl as a

Table 2 Comparison of catalyst **1** with other rhodium complexes and literature examples of other metal catalysts

					
Entry	Catalyst	Amount [mol%]	Temp. [°C]	Time [h]	Yield [%]
1	1	10	60	2	98 ^{a,b,c}
2	Rh(PPh ₃) ₃ Cl	10	60	2	0 ^{a,b,c}
3	Rh(PPh ₃) ₃ Cl	10	85	60	35 ^{a,b,c}
4	[Rh(μ -Cl)(COD)] ₂	10	60	2	0 ^{a,b,c}
5	[Rh(μ -Cl)(COD)] ₂	10	85	60	0 ^{a,b,c}
6 ^{5c}	Co ₂ (CO) ₈ (ref. 5c)	4	40	24	71
7 ^{5a,b}	Pd(OAc) ₂ , PBu ₃ (ref. 5a and b)	5–10	120	3	88

^a Reaction conditions: LiNTf₂ (30 mol%), 60 °C, C₆D₆ (0.5 mL), all reactions were carried out in a *J. Young* NMR tube with 1,2-epoxyhexane (35 μ L) as substrate. ^b The ketone was observed as sole reaction product. ^c Yield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

Table 3 Rhodium catalyzed Meinwald rearrangement of epoxides into methylketones

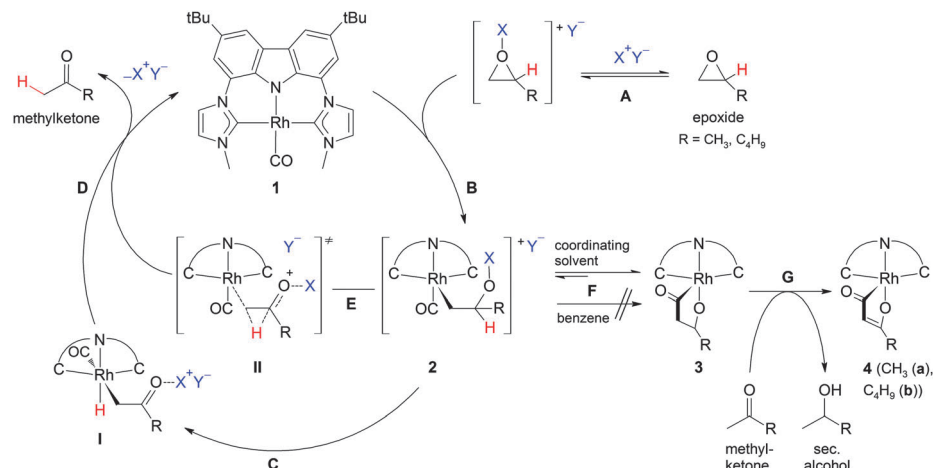
Entry	Substrate	Product	Time [h]	Yield ^{a,b} [%]
1		Acetone	3	93
2		2-Hexanone	2	95
3		Acetophenone: 2-phenylacetaldehyde	2	6 : 4
4		Acetophenone	16	5 ^c
5		Cyclohexanone	24	80 ^d
6		No ketone traces of aldehyde	24	0

^a Reaction conditions: **1** (5 mol%), LiNTf₂ (20 mol%), 60 °C, all reactions were carried out in a *J. Young* NMR tube in C₆D₆ (0.4 mL). ^b Yield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard. ^c At 30 °C. ^d At 80 °C.

Lewis acid additive (60 °C) did not lead to any rearrangement product. Cyclohexene oxide, a 1,2-disubstituted epoxide, can be rearranged to cyclohexenone in 80% yield (80 °C, entry 5). As expected 2,2-dimethyloxirane did not rearrange into a ketone as the reaction is blocked by the additional methyl substituent (entry 6). Traces of the aldehyde were formed due to Lewis-acidic epoxide opening by LiNTf₂ (blank test).

A nucleophilic mechanism for the Meinwald reaction was suggested for Co₂(CO)₈ in methanol that involves *in situ* formation of the nucleophile [Co(CO)₄][–] as well as cationic [Co(MeOH)₆]⁺ to activate the epoxide upon coordination.^{5c–e} Therefore, a plausible mechanism for our 16 e[–] rhodium





Scheme 2 Proposed reaction pathway for the conversion of monoalkyl-substituted epoxides to methylketones catalyzed by **1**.

complex **1** starts with preactivation of the epoxide by the Lewis acid additive (Scheme 2, (A)) followed by a nucleophilic attack of the Rh^I centre at the most electrophilic side of the epoxide which is also the least hindered one. In C₆D₆ Rh^{III} intermediate **2** (B) is obtained which was confirmed by *in situ* formation of **2** in a stoichiometric reaction at RT. The metal bound CO ligand was identified by its ¹³C NMR chemical shift of $\delta = 207$ ppm and an IR stretching frequency (benzene) at 2046 cm⁻¹.⁹ Subsequent β -hydride migration (C) could lead to the Rh^{III} hydrido complex **I** that releases the ketone by reductive elimination (D) under regeneration of Rh^I complex **1**. So far, no metal hydrido complex was observed during reaction, which could be due to a fast reductive elimination process. Alternatively, intermediate **2** could release the product directly by a concerted 1,2-hydride shift-S_Ni reaction *via* transition state **II** (E) to release the product and close the catalytic cycle.

In thf-d₈ however, only formation of **3** upon CO insertion (F) was observed during the NMR spectroscopic monitoring of the catalytic reaction.⁹ The identical product **3** could be synthesized independently by a stoichiometric reaction of **1** with one equivalent of the respective epoxide in the presence of the Lewis acid additive in tetrahydrofuran (room temperature) or acetonitrile (60 °C). The ¹H NMR spectrum of **3** in thf-d₈ solution displays a double set of resonances for the ligand backbone due to the reduced symmetry of the complex (R = CH₃). A doublet at 1.16 ppm is assigned to the methyl group resulting from the reaction of the epoxide with rhodium complex **1**. The other characteristic peaks of the ring-opened epoxide moiety are superimposed by the residual solvent peak (thf-d₈) and epoxide signals, but could be detected by 2D NMR experiments as well as in acetonitrile-d₃. In the ¹³C NMR spectrum (thf-d₈) the doublet at 229.4 ppm (¹J_{RhC} = 43.3 Hz) strongly hints towards a CO insertion and formation of the Rh acyl complex **3**. In addition a ¹³C DEPT-135 experiment confirms the signal for the CH₂ group at 26.1 ppm (²J_{RhC} = 30.0 Hz). Proof that compound **3** is a resting state and can react (partly) back into the catalytic cycle was obtained by removing all volatiles *in vacuo* after generation of **3** and redissolving the residue in

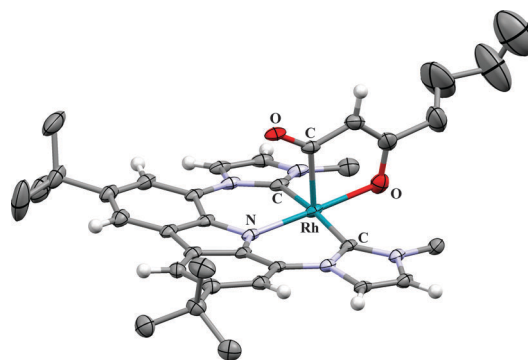


Fig. 2 X-ray crystal structure of the side product **4b** bearing an unsaturated rhodacycle. For reason of better clarity, the anisotropic displacement parameters are given at the 20% probability level and only the hydrogen atoms of sp²-hybridized C-atoms are shown and solvent molecules omitted.⁹

thf-d₈. After 2 d at room temperature the peaks of **3** cannot be detected, whilst the peak of acetone as well as the signals of isopropanol and the poorly soluble yellow species **4a** appear.

The ¹³C DEPT-135 experiment of this species reveals the signal of a CH group at 93.6 ppm; the respective proton signal is found at $\delta_{\text{H}} = 3.96$ ppm. All other peaks also coincide well with the formation of complex **4a** by dehydrogenation (G). Single crystals suitable for X-ray diffraction were obtained from saturated solutions of the reaction mixtures at room temperature. The analyses confirm formation of the unsaturated five-membered rhodacycles in complexes **4a** and **b** (Fig. 2, for **4a** see ESI†). This also explains the formation of isopropanol from acetone during the course of the reaction. Formation of **4** can only be observed after formation of complex **3**. In pure C₆D₆ neither complex **3** nor complex **4** is obtained. However, after generation of **3** (R = CH₃) in thf-d₈, removal of all volatiles *in vacuo* and dissolving of the residue in C₆D₆, the formation of both, complex **1** and acetone as well as formation of complex **4a** is observed. We assume that residual thf-d₈, coordinated to the Li⁺ cation, prevents direct observation of **2** under these conditions.

We showed that terminal epoxides can be transformed into ketones under mild conditions using the strong nucleophilic



rhodium catalyst **1**. To the best of our knowledge this is the most reactive and selective catalyst for this transformation and the first example of a rhodium catalyst yielding the methylketone as product.

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