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Solvent-Free Chelation-Assisted Catalytic C–C Bond Cleavage of Unstrained Ketone by Rhodium(I) Complexes under Microwave Irradiation

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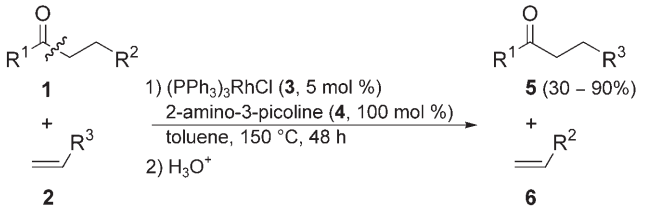
Abstract: A highly efficient C–C bond cleavage of unstrained aliphatic ketones bearing β-hydrogens with olefins was achieved using a chelation-assisted catalytic system consisting of $(Ph_3P)_3RhCl$ and 2-amino-3-picoline by microwave irradiation under solvent-free conditions. The addition of cyclohexylamine catalyst accelerated the reaction rate dramatically under microwave irradiation compared with the classical heating method.

Keywords: C–C bond cleavage; chelation-assistance; microwave heating; Rh(I) complex; solvent-free reaction

C–C bond activation is of current interest to organometallic chemists.[1] However, there have been very few examples of catalytic C–C bond activation in spite of its usefulness in organic synthesis.[2,3] The substrates are confined mainly to ring-strained molecules and specially designed model compounds. In the course of our studies on hydroacylation using 2-amino-3-picoline as a temporary chelating auxiliary,[4] we found a C–C bond activation of an unstrained ketone utilizing a chelation-assisted protocol.[5] For example, ketone **1** reacted with alkene **2** under the cocatalyst system of $(PPh_3)_3RhCl$ (**3**) and 2-amino-3-picoline (**4**) to give an alkyl group-exchanged ketone **5** and alkene **6** [Eq. (1)].[5a]



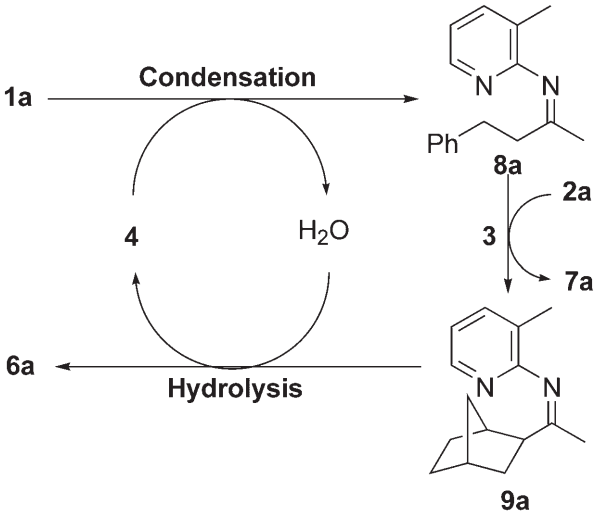
(1)

Because this chelation-assisted C–C bond cleavage is too sluggish, high temperature and long reaction times were required to continue the reaction. Therefore, we were intrigued to use a solvent-free microwave (MW)-accelerated reaction since this method allows easy access to high temperatures.[6]

When the reaction of benzylacetone (**1a**, 1 mmol) and norbonylene (**2a**, 1.2 mmol) was carried out using the cocatalyst system of $(PPh_3)_3RhCl$ (**3**, 5 mol %) and 2-amino-3-picoline (**4**, 20 mol %) at 200 °C for 5 min under MW irradiation[7] in closed vessels (due to the rather low boiling point of the alkene), a 44% yield of 2-acetylnorbonane (**6a**)[8] was obtained along with a 40% yield of styrene, as determined by GC. When the reaction was performed at 200 °C under conventional heating (Δ) inside a thermostatted oil bath, only a 9% yield of **6a** was obtained after the same reaction time with similar ramps in temperatures (Table 1, entries 1 and 2).

The reaction is believed to proceed not through direct C–C bond cleavage of ketone **1a** by Rh(I) complex **3**. Instead, a ketimine intermediate **8a** is initially formed *in situ* from ketone **1a** and 2-amino-3-picoline (**4**) with elimination of H_2O. Chelation-assisted C–C bond cleavage of **8a** by Rh(I) with **2a** produces ketimine **9a** and alkene **7a** (Scheme 1). Subsequent hydrolysis of **9a** with H_2O, previously formed by condensation of **1a** and **4**, leads to ketone **6a**. This type of chelation-assisted strategy was previously applied to hydroacylation reactions in which aldehydes and alkenes were transformed into ketones.[9]

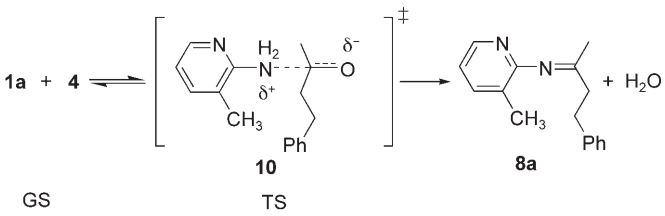
The beneficial result of MW irradiation compared with conventional heating can be explained as follows. In the chelation-assisted catalytic C–C bond activation,



Scheme 1. Mechanism of chelation-assisted C–C bond activation of **1a** with norbonylene (**2a**).

the rate-determining step is supposed to be the condensation (imine formation) between ketone **1a** and 2-amino-3-picoline (**4**). As shown previously for hydroacylation, MW irradiation accelerates the condensation of ketone and 2-amino-3-picoline when compared with classical heating by lowering the energy level of the polar transition state **10** as the polarity of the system is increased during the progress of the reaction from the ground state (GS) towards the transition state (TS) (Scheme 2). It has been reported that the more polar transition state is better stabilized by dipole-dipole electrostatic interactions of MW, resulting in a lowering of the enthalpy of activation.[6a, b]

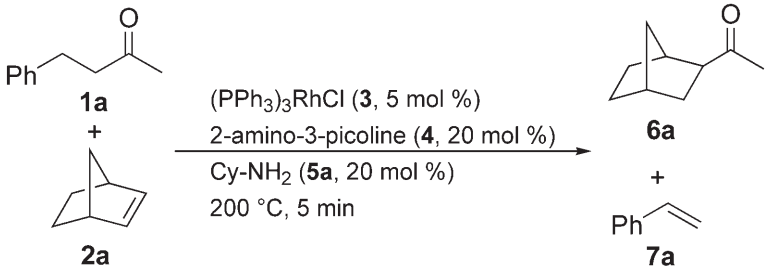
The rate of the overall reaction can be enhanced by the addition of cyclohexylamine. In its presence (**5a**, 20 mol %), the yield of **6a** was increased from 9% to 16% under conventional thermal reaction conditions (Table 1, entries 1 and 3) whereas it increased from 44% to 85% under MW irradiation (entries 2 and 4). Addition of cyclohexylamine (**5a**) might lower the enthalpy of activation from ketone and 2-amino-3-picoline to the corresponding ketimine **8a** by generating an intermediate ketimine **12**. This type of rate enhancement was also developed in chelation-assisted hydroacylation using a transimination protocol.[10] In this case, two transition states are involved as the reaction progresses from the ground state (GS) to the intermediate **8a**. The polarities of these two transition states, TS1 (**11**) and TS2 (**13**) (Scheme 3), are increased when compared with those of starting materials, **1** and **2a**, or intermediate **12**. Moreover, increasing the polarity of the transition state TS1 or TS2 might lower the enthalpy of activation by MW irradiation.



Scheme 2. Increase of the polarity of the system during the progress of the reaction from the ground state (GS) towards the transition state (TS).

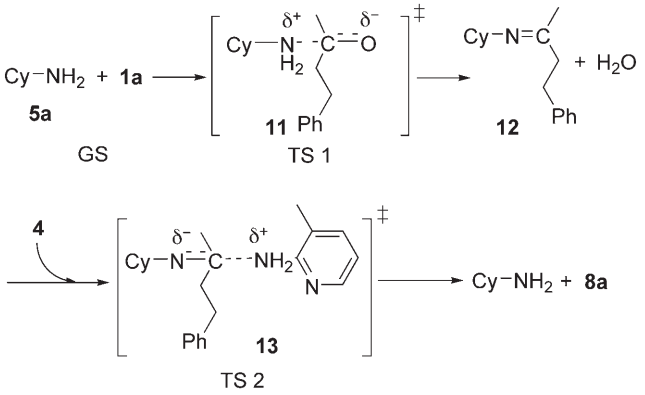
Among the primary amines tested, cyclohexylamine (**5a**) reveals a better reactivity than aniline (**5b**) (Table 2, entries 2 and 3). The reason must be that the more nucleophilic (basic) the amine is, the more polar are the transition states (TS1 or TS2) developed. Another possible hypothesis is that $CyNH_2$ could act as a base to abstract a proton in **4** thereby generating an amide anion **14** more

Table 1. Rh(I)-catalyzed C–C bond activation of **1a** with norbonylene (**2a**).



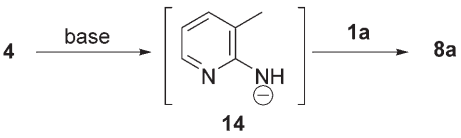
Entry	Cy-NH_2	Activation mode	Yield[a] of **6a** (**7a**)
1	none	Δ	9% (8%)
2	none	MW	44% (40%)
3	20 mol %	Δ	16% (14%)
4	20 mol %	MW	85% (84%)

[a] Yield was determined by GC and the ratio of *exo/endo*-**6a** was *ca.* 7/3.



Scheme 3. Increase of the polarity system during the progress of the reaction from the ground state (GS) towards the transition state (TS).

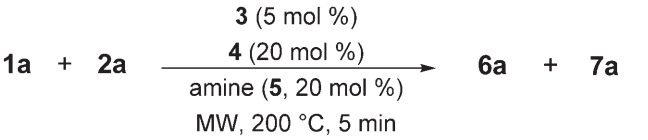
susceptible to the formation of ketimine **8a** than **4** [Eq. (2)].



(2)

To test this hypothesis, secondary and tertiary amines such as **5c**–**5e**, which could not form intermediate ketimes **12** but are stronger bases than $CyNH_2$, were applied in this reaction (entries 4–6). No enhanced reactivity was found with these amines. This result indicates that the enhanced reactivity of cyclohexylamine might be related to the other reaction pathways such as the transimination as shown in Scheme 3, not simply to the basicity, although the exact reason is not clear at the present stage.

Table 2. Rh(I)-catalyzed C–C bond activation of **1a** with additional amine.



Entry	Amine (**5**)	pK_a	Yield[a] of **6a** (**7a**)
1	none	–	42% (38%)
2	Cy-NH_2 (**5a**)	10.7	83% (80%)
3	Ph-NH_2 (**5b**)	4.6	36% (32%)
4	Diethylamine (**5c**)	11.0	44% (35%)
5	Dibutylamine (**5d**)	11.3	30% (25%)
6	Triethylamine (**5e**)	10.8	27% (19%)
7	Pyridine (**5f**)	5.3	16% (20%)

[a] Yield was determined by GC.

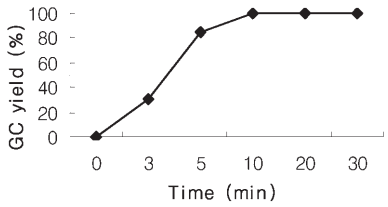


Figure 1. Yield of **6a** from **1a** and **2a** depending on reaction time at 200 °C with catalysts **3** (5 mol %), **4** (20 mol %) and **5** (20 mol %) under MW irradiation.

The reactions of **1a** and **2a** were completed within 10 min (Figure 1). This can be explained considering that the strain energy of norbonylene (**2a**) is partially relieved by forming a less strained 2-acetylnorbonane (**6a**), which might be a driving force in this reaction. The formation of styrene is another driving force in this transformation since the relatively stable, conjugated styrene is generated from the non-conjugated norbonylene.

Other aliphatic ketones bearing β-hydrogens were applied in this reaction, and fairly good yields of C–C bond cleaved products were obtained in 30 min (Table 3, entries 2 and 3). Since the reactions with unstrained olefins like vinylcyclohexane or 1-alkene were sluggish, harsher reaction conditions were required to get moderate yields of C–C bond cleaved products (entries 4–7) such as, for example, a high concentration (100 mol %) of 2-amino-3-picoline and additional benzoic acid (10 mol %). The reason must be that with an unstrained olefin there is no energy gain for relieving the strain energy, unlike with norbonylene. Therefore, a large excess (7 equivs.) of olefin was used to drive the forward reaction.

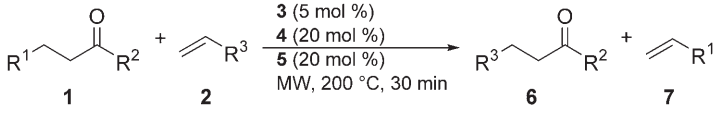
In conclusion, highly efficient C–C bond cleavages of aliphatic ketones bearing β-hydrogens were achieved with olefins using a chelation-assisted catalytic system consisting of $(Ph_3P)_3RhCl$ and 2-amino-3-picoline by MW irradiation under solvent-free conditions. Additional cyclohexylamine catalyst accelerated the reaction rate dramatically, and the rate enhancement was observed under MW irradiation compared with classical heating probably due to a specific non-purely thermal MW effect.

Experimental Section

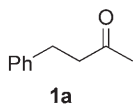
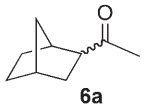
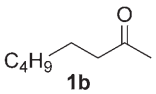
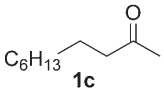
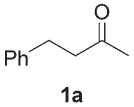
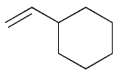
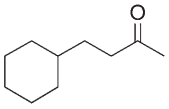
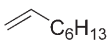
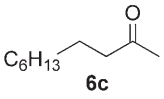
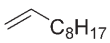
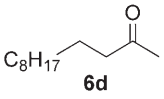
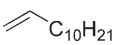
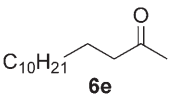
Typical Procedure for the Catalytic C–C Bond Cleavage of Ketone by Wilkinson's Complex under Microwave Irradiation

In a 10-mL thick-wall Pyrex tube, were introduced successively benzylacetone (**1a**, 148 mg, 1 mmol), 2-amino-3-picoline (**4**, 21.6 mg, 0.2 mmol), norbonylene (**2a**, 112.8 mg, 1.2 mmol), and $(Ph_3P)_3RhCl$ (3, 46.3 mg, 0.05 mmol). The reaction vessel was capped with a Teflon septum and installed in the CEM mi-

Table 3. Rh(I)-catalyzed C–C bond activation of various ketones with several alkenes.



1 2 6 7

Entry	1 (Ketone)	2 (Olefin)	6 (Product)	Yield [%][a]
1	 1a	 2a	 6a	100% (*exo/endo* = 72/28)[b]
2	 1b	2a	6a	98%
3	 1c	2a	6a	98%
4[c]	 1a	 2b	 6b	93% (76%)
5[c]	1a	 2c	 6c	71% (52%)
6[c]	1a	 2d	 6d	80% (79%)
7[c]	1a	 2e	 6e	64% (67%)

[a] GC yield based on **1** and values in parenthesis are isolated yields.
[b] The ratio was determined by ^{1}H NMR.
[c] 7 equivs. of olefin were used under 100 mol % **4**, 15 mol % **5**, and 10 mol% benzoic acid.

crowave reactor. The reaction was carried out with internal magnetic stirring for 5 min to ensure homogeneous conditions at 200 °C under microwave irradiation. After cooling, the reaction mixture was filtered through a short column filled with silica and washed with CH_2Cl_2 and ethyl acetate. The filtrate was analyzed by GC and GCD, and determined as 44% of 2-acetylnorbonane (**6a**, *exo*- and *endo*-mixtures) and 40% of styrene (**7a**). A ratio of *exo*- and *endo*-2-acetylnorbonanes was determined by ^{1}H NMR spectroscopy. 2-Acetylnorbonane comprised an *exo* and *endo*-mixtures in a *ca.* 72/28 ratio. When the reaction was carried out with additional cyclohexylamine (**5a**, 20 mol % based on **1a**), 85% of **6a** and 84% of **7a** were determined.

Acknowledgements

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[7] The MW reaction was performed using a CEM Discover monomode reactor with measurement and monitoring of temperature by IR detection and power modulation between 15–300 W.

[8] Since 2-acetylnorbonane (**6a**) is volatile, isolated yields were not accurate, and yields were determined by GC.

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