Rhodium(I)-catalyzed one-pot synthesis of dialkyl ketones from methanol and alkenes through directed sp^3 C–H bond activation of *N*-methylamine†

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The hydroacylation of methanol with alkenes was developed using a catalytic system consisting of Rh(I), 2-amino-4-picoline and benzoic acid; the reaction is speculated to occur by the initial *N*-methylation of 2-amino-4-picoline with methanol, and the subsequent dehydrogenation of the resulting *N*-methylamine, followed by double chelation-assisted hydroimination of alkene with the imine to give dialkyl ketones after hydrolysis.

The activation of C–H bonds by transition metal complexes is a current interest in organic synthesis.[1] In particular, hydroacylation of alkenes or alkynes with aldehydes to produce ketones is quite interesting in terms of atom economy.[2] We have successfully developed a Rh(I)-catalyzed chelation-assisted hydroacylation with a co-catalyst system consisting of rhodium(I) complex and 2-amino-3-picoline as an organic catalyst.[3] This protocol was further applied to the synthesis of ketones from primary alcohols instead of aldehydes.[4] In this reaction, aldehyde may be *in situ* generated from the primary alcohol by transition metal-catalyzed transfer hydrogenation with olefins. Among them, methanol is an interesting substrate since double hydroacylation of alkenes is possible. As expected, dialkyl ketones could be prepared from methanol and alkenes using the chelation-assisted protocol (Scheme 1). To date, there have been few direct methods to prepare dialkyl ketones from simple starting materials.[5] Herein, we wish to report direct rhodium(I)-catalyzed synthesis of dialkyl ketones from methanol and alkenes with a different mechanism from the conventional chelation-assisted hydroacylation mechanism.

In our experiments, when the reaction of methanol and norbornene (**1a**) was carried out in toluene at 150 °C for 24 h in the presence of $(Ph_3P)_3RhCl$ (**2**, 5 mol% based on methanol) and 2-amino-4-picoline (**3**), dinorbornyl ketone **5a** was isolated in a 84% yield after chromatographic isolation (Table 1, entry 1).

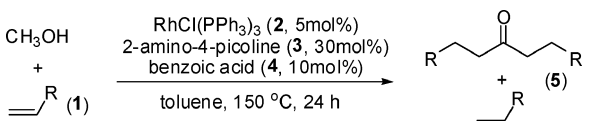
The catalytic activities of various 2-aminopyridine derivatives as chelation-assisted auxiliaries were examined. Among them, 2-amino-4-picoline showed the best catalytic activity, while 2-amino-6-picoline was least active, probably due to the steric hindrance of the 6-methyl group causing difficult coordination of the nitrogen atom in the pyridine group to the metal center. Other catalysts such as $RuH_2(CO)(PPh_3)_3$, $IrCl(CO)(PPh_3)_2$ and $[IrCl(coe)_2]_2$ with PPh_3 were ineffective except for $RhCl(CO)(PPh_3)_2$, which exhibited a similar reactivity to **2**.[6]

The reaction of other terminal alkenes (**1b–f**) with methanol afforded the corresponding dialkyl ketones in good to moderate isolated yields (Table 2).

Two possible mechanisms for this one-pot synthesis of dialkyl ketones from methanol and alkenes can be proposed as shown in Scheme 2. One mechanism involves the formation of formaldehyde (**6**) *in situ* generated from methanol by transfer hydrogenation, followed by condensation of **6** with 2-amino-4-picoline (**3**) leading to the formation of imine **7**. The chelation-assisted hydroimination of alkene **1** with **7** generates aldimine **9**, which may react further with **1** by hydroimination to give ketimine **10**. The hydrolysis of **10** by H_2O, generated from the condensation of **3** and **6**, produces dialkyl ketone **5**. To confirm this mechanism, the reaction of **1** with formaldehyde instead of methanol was carried out under identical reaction conditions, and resulted in no ketone **5** being produced.[7]

This result implies that formaldehyde is not directly involved in this reaction. Another possible mechanism is that the reaction proceeds through the formation of 2-(methylamino)-4-methylpyridine (**8**), which is generated from the reaction of methanol and **3**. There are some reports on this type of *N*-methylation of aromatic amines with methanol on acid media under transition metal catalyst.[8] The subsequent chelation-assisted dehydrogenation of **8** with alkene affords imine **7**, which reacts with alkene **1** to give ketimine **10**.[9] The mechanism of this route can be directly confirmed by stepwise reactions.

In the absence of alkene, *N*-methylated compound **8** was isolated from the reaction of **3** and methanol under the catalyst mixture of **2** and **4** (Scheme 3). Then, the reaction of **8** with alkene **1a** in the presence of **2** (5 mol%), **4** (10 mol%), and H_2O (100 mol%) afforded dialkyl ketone **5a** in 83% isolated yield.[10] Other alkenes **1b–e** were also applied to this dialkylation to give dialkyl ketones **5b–e** in moderate yields. Since alkenes serve as both hydrogen acceptors and



Scheme 1

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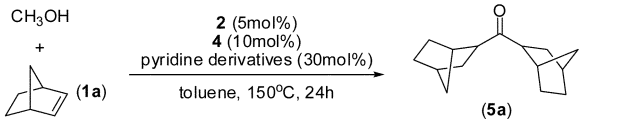
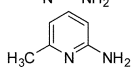
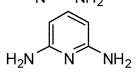
† Electronic supplementary information (ESI) available: Experimental procedures and spectral analyses of reaction products. See DOI: 10.1039/b814166e

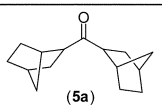
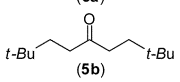
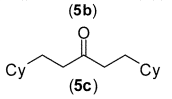
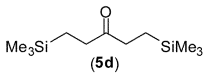
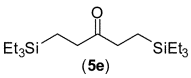
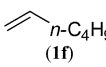
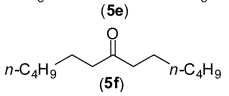
Table 1 Catalytic activities of 2-aminopyridine derivatives[a]



Entry	Pyridine derivatives	Isolated yield of **5a** (%)
1		84
2		48
3		17
4		59
5		48

[a] *Reaction conditions*: 1 mmol of methanol, 6 eq. of norbornene (**1a**), 50 mg toluene mixture at 150 °C (bath temp.) for 24 h.

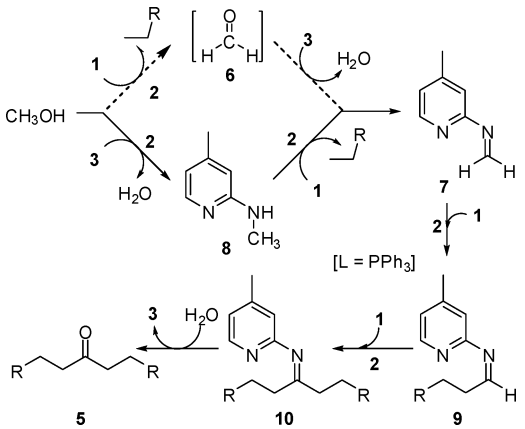
Table 2 Reaction of methanol with various alkenes[a]

Entry	Alkene (**1**)	Product (**5**)	Isolated yield (%) of product (**5**)
1	 (**1a**)	 (**5a**)	85
2	 (**1b**)	 (**5b**)	76
3	 (**1c**)	 (**5c**)	62
4	 (**1d**)	 (**5d**)	72
5	 (**1e**)	 (**5e**)	71
6	 (**1f**)	 (**5f**)	54

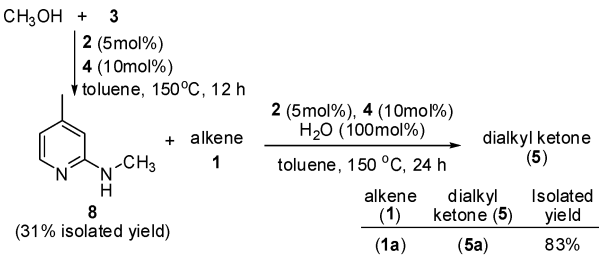
[a] *Reaction conditions*: 1 mmol of methanol, $(PPh_3)_3RhCl$ (**2**, 5 mol%), 2-amino-4-picoline (**3**, 30 mol%), benzoic acid (**4**, 10 mol%), 6 mmol of alkene (**1**), 50 mg toluene mixture at 150 °C (bath temp.) for 24 h.

hydroacylation substrates in this reaction, the amount of alkene required at least three times that of methanol.

For the dehydrogenation of *N*-methylamine by Rh(I) catalyst, we tried to find evidence for the C–H bond activation of the *N*-methyl group in **8**. Despite difficult C–H bond cleavage in the methyl group, there are some reports on the transition metal-catalyzed chelation-assisted sp^3 C–H bond activation of an alkyl[11] methyl group and *N*-methyl group.[12] To identify the C–H bond activation of the methyl group in **8** by Rh(I), **8**-d_3 was prepared and allowed to react with H_2O in the presence of **2** at 130 °C for 24 h (Scheme 4). It was observed that 68% of the deuterium in **8**-d_3 was exchanged with hydrogen of H_2O, as

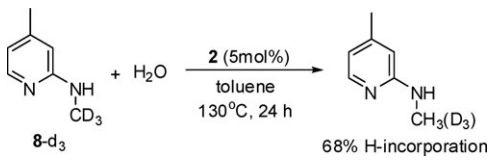


Scheme 2 Mechanism for the synthesis of dialkyl ketone from methanol and 1-alkenes.



alkene (**1**)	dialkyl ketone (**5**)	Isolated yield
(**1a**)	(**5a**)	83%
(**1b**)	(**5b**)	71%
(**1c**)	(**5c**)	50%
(**1d**)	(**5d**)	54%
(**1e**)	(**5e**)	58%

Scheme 3 Stepwise synthesis of dialkyl ketone **5** from methanol and alkene **1** through *N*-methylamine **8** using Rh(I) catalyst.



Scheme 4

determined by ^1H NMR spectra.[13] However, compound **11**-d_3 (Fig. 1) having no coordination site in the proper position did not exhibit any D/H exchange by H_2O under the identical reaction conditions as in Scheme 4. This result shows that the pre-coordination of substrate or organic catalyst is important for the C–H bond activation due to easy access of the metal center to the C–H bond to be cleaved.

Another interesting point to be noted is that the reaction proceeds through the imine **7** because *N*,*N*-dimethyl-2-amino-4-picoline (**12**), which can barely be dehydrogenated to form imine, did not react with alkene to produce dialkyl ketone.

In summary, we developed a technique for the direct synthesis of dialkyl ketones from methanol and alkenes using the catalytic system consisting of Rh(I), 2-amino-4-picoline and

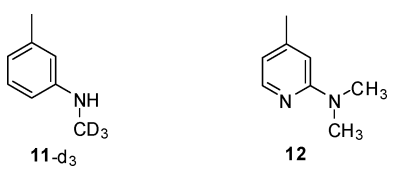


Fig. 1

benzoic acid. The reaction is speculated to occur by the initial *N*-methylation of 2-amino-4-picoline with methanol, followed by dehydrogenation of the resulting *N*-methylamine to afford imine. Then, the double chelation-assisted hydroimination of alkene with imine and hydrolysis of the resulting ketimine produces the dialkyl ketone. Further applications of this protocol to other catalytic systems are currently being studied.

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6 Among various other transition metal complexes examined, only $(Ph_3P)_2(CO)RhCl$ showed a comparable isolated yield (82%) of **5a** under the identical reaction conditions to those in Table 1.

7 In a separate experiment, the reaction of formaldehyde, in the form of paraformaldehyde, with 2-amino-4-picoline in the presence of benzoic acid did not give **7**, but resulted in a stable aminal compound, which did not react with alkene under Rh(I) catalyst **2**. For the stepwise reaction, see ESI†.

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