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A tandem allylic alcohol isomerization–aldol condensation catalyzed by Rh and Ru complexes

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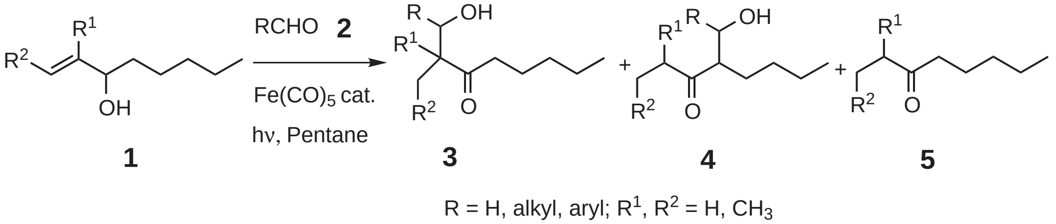
Abstract—Allylic alcohols react with aldehydes, in an atom economy aldol-type reaction, in the presence of catalytic amounts of various rhodium and ruthenium complexes. This reaction occurs with total regiocontrol under mild conditions, but varying amounts of ketone derived from the competing isomerization reaction are also observed. © 2001 Elsevier Science Ltd. All rights reserved.

Developing the synthetic potential of enol/enolate intermediates derived from allylic alcohols employing transition metal catalysts is a promising, yet relatively less explored approach for C–C bond formation.[1] Bosnich et al. have shown that Rh catalyzed isomerization of allylic alcohols results in the formation of enols which could be detected by NMR and also trapped in an *ene*-type reaction.[1] In a different approach, Motherwell et al. have established that allylic lithium alkoxides can be isomerized to lithium enolates in the presence of transition metal catalysts (Rh and Ni) and can be further engaged in aldol reactions.[2] However, this attractive strategy has some drawbacks due to the stoichiometric amount of base required to generate the lithium alcoholates. Therefore, a major improvement would be to perform such a reaction directly from allylic alcohols under neutral conditions. We have recently demonstrated for the first time that a variety of allylic alcohols of the general structure **1** can be isomerized and trapped in situ by aldehydes **2** to furnish aldol products **3** in the presence of catalytic amounts of $Fe(CO)_5$ upon irradiation (Scheme 1).[3] Nevertheless, small amounts of regioisomers **4** as well as ketones **5** were also encountered.

While this novel aldol-type reaction is the first step towards a complete atom economy process under neutral conditions, the scope of the reaction can be further improved in terms of regiocontrol and circumventing the need for photochemical activation. Further, as $Fe(CO)_5$ is not amenable to extension for asymmetric catalysis, we explored the possibility of employing other transition metal complexes for this purpose.

We have screened many different catalytic systems and present here the preliminary results demonstrating that several Ru and Rh based catalysts (**6**–**11**) are able to perform the tandem isomerization–aldolization reaction.

While various rhodium and ruthenium catalysts are known to isomerize allylic alcohols to saturated



Scheme 1.

Keywords: allylic alcohols; aldols; catalysts; rhodium; ruthenium.

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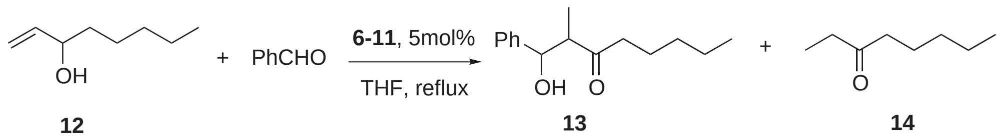
ketones,[4] $Rh(PPh_3)_3Cl$[5] and $Ru(PPh_3)_3Cl_2$ are themselves inactive. However, we have shown that after their reaction with an organolithium agent (e.g. *n*-BuLi), an active catalyst was generated which could bring about this transformation.[6] *We were further pleased to find that in the presence of an aldehyde*, *such activated rhodium and ruthenium catalysts could readily effect an aldol-type reaction on an allylic alcohol* (Scheme 2).

We first tried $(PPh_3)_3RhH$ **6** generated under the conditions reported by Boons.[5] Refluxing a THF solution of allylic alcohol **12** with benzaldehyde in the presence of catalytic amounts (5 mol%) of catalyst **6** (Table 1, entry 1) afforded diastereoisomeric mixtures[7] of aldol **13** (54%) along with ketone **14** (29%). To verify the structure of the catalytic species involved in the process we prepared **6** following an alternative procedure[8] and have obtained a comparable result (entry 2). According to the literature,[9] the reaction of Wilkinson's catalyst with an activator that does not contain any β-hydrogen, like MeLi, PhLi, MeMgBr or PhMgBr, affords $(PPh_3)_3RhPh$ **7** or $(PPh_3)_3RhMe$ **8** after the displacement of chlorine. These two catalysts were prepared from Grignard and organolithium reagents. The resulting catalysts were engaged in an aldol-type reaction with benzaldehyde and octen-3-ol (entries 3–6) to furnish adducts **13** in fair yields (56–68%) and a low diastereoselectivity (*syn*/*anti* 0.6:1). Nevertheless, it has to be noticed that the reaction rate is far slower when the catalyst is prepared from Grignard reagent.

Though known catalysts **6**, **7** and **8** have been isolated in a pure form,[9b,9c,10] it proved to be far more convenient to prepare and use them in situ since they are very



6 : $Rh(PPh_3)_3H$ **9** : $Ru(PPh_3)_3HCl$
7 : $Rh(PPh_3)_3Ph$ **10** : $Ru(PPh_3)_3PhCl$
8 : $Rh(PPh_3)_3Me$ **11** : $Ru(PPh_3)_3MeCl$

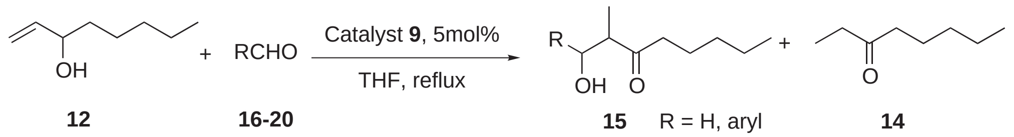
Scheme 2.

Table 1.

Entry	Catalyst	Catalyst preparation	Additive	Time	Conv. (%)[a]	**13** (Yield %)	**13** (*syn:anti*)	**14** (Yield %)
1	**6**	$[Rh(PPh_3)_3Cl$– 1 equiv. ^{n}BuLi]		25 min	100	54	40:60	29
2	**6**	$[Rh(PPh_3)_3Cl$– 1 equiv. LDA]		90 min	100	62	34:66	29
3	**7**	$[Rh(PPh_3)_3Cl$– 1 equiv. PhLi]		35 min	100	63	37:63	27
4	**7**	$[Rh(PPh_3)_3Cl$– 1 equiv. PhMgBr]		8 h	80	[b]	41:59	19
5	**8**	$[Rh(PPh_3)_3Cl$– 1 equiv. MeLi]		35 min	100	56	39:61	37
6	**8**	$Rh(PPh_3)_3Cl$– 1 equiv. MeMgBr]		10 h	94	[b]	42:58	26
7	**8**	$[Rh(PPh_3)_3Cl$– 1 equiv. MeLi]	$MgBr_2$	36 h	100	69	43:57	23
8	**6**	$[Rh(PPh_3)_3Cl$– 1 equiv. ^{n}BuLi]	LiBr	7 h	25	[b]	42:58	21
9	**6**	$[Rh(PPh_3)_3Cl$– 1 equiv. ^{n}BuLi]	$LiBF_4$	7 h	72	[b]	44:56	27
10	**9**	$[Ru(PPh_3)_3Cl_2$– 1 equiv. ^{n}BuLi]		30 min	100	62	55:45	17
11	**9**	$[Ru(PPh_3)_3Cl_2$– 1 equiv. LDA]		90 min	100	51	58:42	34
12	**10**	$[Ru(PPh_3)_3Cl_2$– 1 equiv. PhLi]		40 min	100	75	55:45	14
13	**11**	$[Ru(PPh_3)_3Cl_2$– 1 equiv. MeLi]		40 min	100	73	51:49	13
14		$[Ru(PPh_3)_3Cl_2$– 1 equiv. K_2CO_3]		90 min	100	45	70:30	50

[a] Conversions are based on transformation of compound **12** to aldols **13** and have been calculated from ^1H NMR of the crude mixture.

[b] The reaction could not be completed and an inseparable mixture of **12** and **13** was isolated. So, isolated yields for **13** could not be obtained and are not given.

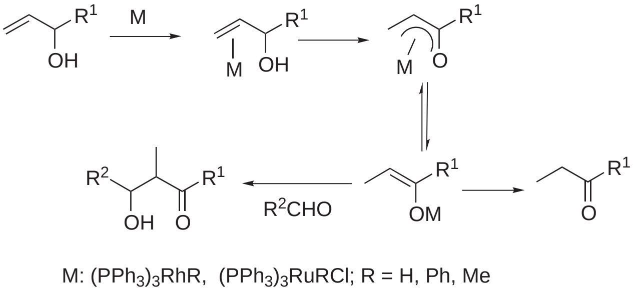


Scheme 3.

Table 2.

Entries	Aldehyde	Time (min)	**15** (Yield %)	**15** (*syn:anti*)	**14** (Yield %)
1	**16** *p*-ClPhCHO	35	72	56:44	9
2	**17** *p*-NO_2PhCHO[a]	120	46	59:41	31
3	**18** *p*-OCH_3PhCHO	30	31	57:43	57
4	**19** 5-Acetoxymethyl-2-furaldehyde	45	27	60:40	55
5	**20** HCHO (anhyd.)	30	26	–	52

[a] 10 mol% of the catalyst was used.



Scheme 4.

sensitive towards oxygen and moisture. This leads to the unavoidable presence of magnesium or lithium salts in the reaction mixture. To evidence any eventual effect of these salts on the aldol reaction we have conducted some experiments in the presence of added salts (entries 7–9). The addition of 5% $MgBr_2$ to a catalyst solution prepared from Wilkinson's catalyst and an organolithium reagent has an influence on the kinetics (the rate of the reaction being slower) and the conversion[11] (entry 7). The addition of 5% LiBr has a critical effect on the reactivity as the conversion is very low (only 25% after 7 hours) in this case (entry 8). It is noteworthy that the use of a less coordinating counter anion (BF_4^-) instead of Br^- increases the conversion (entry 9).

We also explored the extension of this reaction to ruthenium catalysts. By analogy, we propose that the chlorine of $(PPh_3)_3RuCl_2$ is replaced by a H, Ph or Me group, when the organolithium reagent is *n*-BuLi, PhLi or MeLi, respectively, to give new transition metal complexes **9**[12]–**11** (entries 10–13) of the general formula $(PPh_3)_3RuRCl$, (R = H, Ph, CH_3). In the presence of these catalysts, the aldol products **13** were isolated in 51–75% yield with modest but reverse diastereoselectivity (*syn*/*anti* 1.2:1).[13] When $(PPh_3)_3RuCl_2$ was activated according to the conditions described by Bäckvall,[4a] a decrease in yield of the aldol along with a slight increase of the diastereoselectivity was observed (entry 14). In each case the ketone **14** was also isolated (13–50 yield%).[14]

Preliminary screening with ruthenium catalyst **9** indicated that the reaction could be extended to other aldehydes **16**–**20** and in each case aldol products were obtained in moderate yields (Scheme 3, Table 2). In the case of aldehyde **17** the reaction was slow and did not readily go to completion.

The mechanism of the reaction will require further studies. However, by analogy with iron carbonyl-mediated reactions, it is possible to consider a process via π-oxa allyl intermediates and/or η^1-oxygen bound rhodium/ruthenium enolates, which can either be trapped by an aldehyde or just undergo a tautomerization to give the saturated ketone (Scheme 4). There is ample literature precedence for π-oxa-η^1 equilibria, the later depending on the ligands and the metal.[15] Further, η^1-oxygen bound rhodium enolates have already been prepared by another route and have also been engaged in catalytic aldol reactions.[16]

In conclusion, though preliminary, our studies have established that allylic alcohol **12** reacts with aldehydes in the presence of rhodium and ruthenium catalysts **6**–**11** to give aldol adducts with complete atom economy. Though the stereoselectivity and the scope of this reaction need to be improved, *it is noteworthy that with this family of catalysts no regioisomeric aldol could be detected in the crude reaction mixture as opposed to the iron carbonyl mediated reaction.*[3] Such catalysts are easy to prepare and the reaction occurs under mild conditions. Our route is distinctly different from the one reported by Motherwell as no lithium alcoholate is involved in the process.[2] Extension to other systems as well as asymmetric synthesis are under active study in the laboratory.

Acknowledgements

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12. (a) Catalyst **9** can be prepared by the procedure described by Wells,[12b] nevertheless the catalytic solution prepared in this way did not perform the isomerization–aldol condensation probably due to the large excess of triethylamine used in this preparation; (b) Hudson, B.; Webster, D. E.; Wells, P. B. *J. Chem. Soc., Dalton* **1972**, 1204–1207.
13. **Representative experimental procedure**. To a stirred suspension of $(PPh_3)_3RuCl_2$ (48 mg, 0.05 mmol, 5 mol%) in 5–10 ml of dry THF, under an atmosphere of nitrogen, was added one equivalent (32 μL, 0.05 mmol) of *n*-BuLi (1.6 M solution in hexane) at room temperature. A wine red solution was quickly formed and this mixture was allowed to react for about 10–15 min before adding a degassed mixture of the allylic alcohol **14** (154 μL, 1 mmol) and freshly distilled benzaldehyde (122 μL, 1.2 mmol) in dry THF (5–7 mL). The reaction mixture was heated at reflux and the progress of the reaction was monitored by thin-layer chromatography. Upon consumption of the starting material, the reaction mixture was cooled to ambient temperature and THF removed under reduced pressure. The crude reaction mixture was purified by column chromatography (silica gel, pentane:ether, 9:1) to initially afford ketone **16** (22 mg, 17%). Upon further elution (pentane:ether, 4:6), a diastereomeric mixture of aldol products **15** (145 mg, 62%) was obtained. All the diastereoisomeric mixtures of aldol products gave satisfactory ^{1}H and ^{13}C NMR spectra and satisfactory high resolution mass measurements.
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