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Building molecular complexity *via* tandem Ru-catalyzed isomerization / C-H activation

Agnieszka Bartoszewicz, and Belén Martín-Matute*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University,

106 91 Stockholm, Sweden

belen@organ.su.se

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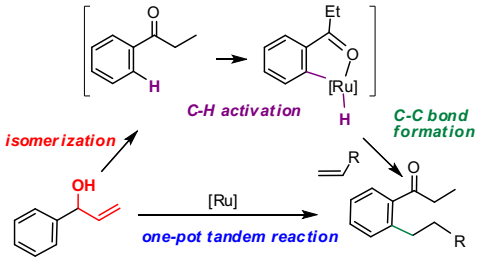
ABSTRACT



A tandem isomerization / C-H activation of allylic alcohols was performed using a catalytic amount of $RuCl_2(PPh_3)_3$. A variety of *ortho* alkylated ketones have been obtained in excellent yields. This tandem process relies on an *in situ* generation of a carbonyl functional group that directs the *ortho* C-H bond activation.

The search for the most atom-economical ways[1] to form C-C bonds is a matter of increasing importance among industrial and academic research groups.[2] One way to achieve clean, cheap and atom-economical processes is to use "low energy" starting materials. For example, the functionalization of a C-H bond rather than a C-X bond is a highly desirable alternative. Hence, the functionalization of C-H bonds has attracted much attention in organic chemistry. In 1993, Murai reported a highly efficient ruthenium-catalyzed coupling reaction of aromatic C-H bonds with olefins.[3] The key feature of this reaction is the assistance by chelation. The reaction is generally applicable, and a variety of coordinating groups containing N or O can be used.[4]

A variety of Ru complexes, such as $RuH_2(CO)(PPh_3)_3$, $Ru(CO)_2(PPh_3)_3$, $Ru(CO)_3(PPh_3)_2$, $RuH_2(PPh_3)_4$, $Ru_3(CO)_{12}$, and $RuH_2(H_2)(CO)(PCy_3)_2$, have been used in aromatic C-H activation.[4] These complexes show very high selectivity and reactivity. On the other hand, they are expensive, and some of them, in particular the hydrides,

(1) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705.

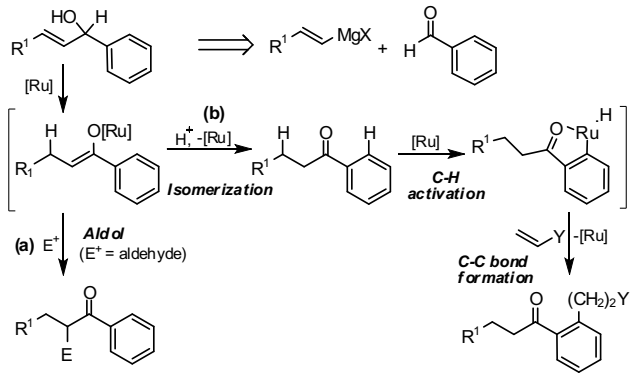
(2) (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995. (b) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J. Ed.; Wiley-VCH: Weinheim, 1998. (c) Brandsma, L.; Vaselevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*, Springer: Berlin, 1998.

(3) (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531. (b) For a review, see: Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834. (c) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Pure App. Chem.* **1994**, *66*, 1527–1534.

(4) For reviews using Ru complexes, see: (a) Park, Y. J.; Jun, C.-H. *Bull. Korean Chem. Soc.* **2005**, *26*, 871–877. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770. (d) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. For other metals, see: (e) Ackermann, L. *Top. Organomet. Chem.* **2007**, *24*, 35–60. (f) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2007**, *24*, 61–84. (g) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (h) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (i) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (j) Bergman, R. G. *Nature* **2007**, *446*, 391–393. (k) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35–41.

are sensitive to moisture and oxygen. Recently, ruthenium complex $[Ru(p\text{-cym})Cl_2]_2$ (**1a**) (*p*-cym = η^6-*p*-cymene). has been used, from which the active Ru dihydride was generated *in situ*, and excellent reactivity was obtained.[5] Furthermore, **1a** is stable and one of the cheapest Ru complexes available. Activations of aromatic C-H bonds not involving chelation have also been reported, but these are less selective, giving mixtures of regioisomers.[4c,6] On the other hand, from a synthetic point of view, the introduction of the directing group may increase the number of synthetic steps, and thus limit the scope of the transformation.

Scheme 1. Tandem Ru-catalyzed (a) isomerization / aldol reaction, and (b) isomerization / C-H activation in one pot.



We have recently developed a very efficient one-pot Ru-catalyzed isomerization/aldol reaction of allylic alcohols (Scheme 1a). Ru enolates are key intermediates in this transformation.[7] In the absence of the electrophile, the Ru-enolate intermediate is converted into the corresponding ketone (Scheme 1b). We envisioned that the transformation of allylic alcohols into ketones could broaden the scope of the aromatic C-H activation processes, since the *in situ* generated carbonyl functional group could assist the cleavage of the *ortho* C-H bond by chelation. Ideally, both processes could be catalyzed by the same Ru complex. In this way, molecular complexity would be achieved in very few steps starting from commercially available aldehydes. In this article, we report a tandem isomerization of allylic alcohols followed by *ortho* C-H bond activation directed by the *in situ* formed carbonyl group using stable ruthenium precursors.

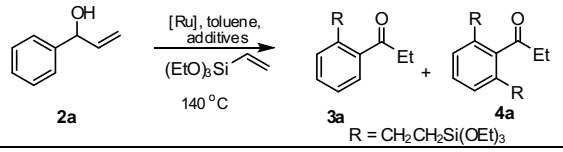
(5) (a) Martinez, R.; Chevalier, R.; Darses, S.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2006**, *45*, 8232–8235. (b) Martinez, R.; Genêt, J.-P.; Darses, S. *Chem. Commun.* **2008**, 3855–3857 (c) Simon, M. C.; Martinez, R.; Genêt, J.-P.; Darses, S. *Adv. Synth. Catal.* **2009**, *351*, 153–157.

(6) Foley, N. A.; Ke, Z.; Gunnoe, T. B.; Cundari, T. R.; Petersen, J. L. *Organometallics*, **2008**, *27*, 3007–3017.

(7) Bartoszewicz, A.; Livendahl, M.; Martín-Matute, B. *Chem. Eur. J.* **2008**, *14*, 10547–10550.

In a systematic study, we found that a number of commercially available Ru complexes efficiently catalyze both the isomerization and the C-H activation (Table 1). We also observed that the isomerization occurs within minutes.

Table 1. Catalyst and Additives Screening.



entry	catalyst	additives (mol %)	time (h)	**3a**+**4a** (%)[a]
1	$RuH_2CO(PPh_3)_3$ (**1b**)	-	2	>99 (92/8)
2	$RuH_2(PPh_3)_4$ (**1c**)	-	2	86 (93/7)
3	$[Ru(p\text{-cym})Cl_2]_2$ (**1a**)	HCO_2Na (30)/ PPh_3 (15)	2	>99 (62/38)
4	$RuCl_2(PPh_3)_3$ (**1d**)	HCO_2Na (30)	2	>99 (67/33)
5	**1d**	-	2	-[b]
6	**1d**	Na_2CO_3 (30)	12	49 (96/4)
7	**1d**	^{t}BuOK (7)	12	-[c]
8	**1a**	Na_2CO_3 (30)/ PPh_3 (15)	12	90 (83/17)
9	**1a**	Na_2CO_3 (30)/ ^{i}PrOH (30)/ PPh_3 (15)	12	>99 (80/20)
10	**1d**	Na_2CO_3 (30)/ ^{i}PrOH (30)	6	100 (83/17)
11	**1d**	HCO_2Na (30)/ $P(p\text{-}MeOC_6H_4)_3$ (7)	2	>99 (67/33)
12	**1d**	HCO_2Na (30)/P^tBu_3 (7)	2	>99 (40/60)

[a]Yield measured by ^{1}H NMR (**3a**+**4a**); in parenthesis, **3a**:**4a** ratio. [b]Propiophenone (**5a**) was produced in 100% yield. [c]Complex reaction mixture.

Thus, starting from allylic alcohol **2a**, $RuH_2CO(PPh_3)_3$ (**1b**) and $RuH_2(PPh_3)_4$ (**1c**) both yielded the product (a mixture of the 1:1 adduct **3a** and 1:2 adduct **4a**) (Table 1, entries 1-2) in very high yield after only 2 h. We were very pleased to find that Ru-Cl complexes $[Ru(p\text{-cymene})Cl_2]_2$ (**1a**) and $RuCl_2(PPh_3)_3$ (**1d**) in the presence of sodium formate, HCO_2Na, were even more active catalysts in the tandem transformation (Table 1, entries 3-4).[8] In the absence of a hydride source, complex **1d** gave only isomerization of the allylic alcohol to produce the propiophenone intermediate **5a** (entry 5). Since HCO_2Na can act not only as a hydride donor, but also as a base, we studied the tandem transformation using other bases. With Na_2CO_3, the product could be obtained, albeit in low yield, after 12 h (Table 1, entry 6). ^{t}BuOK afforded complex mixtures (Entry 7). For **1a**, however, formate was not a requirement (Table 1, entry 8). We then combined Na_2CO_3 as a base with ^{i}PrOH as a hydride

(8) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522.

donor source. For both complexes, **1a** and **1d**, the reaction gave excellent results. However, the use of Na_2CO_3/^{i}PrOH resulted in slightly longer reaction times than when formate was used (compare entries 9-10 with entries 3-4).

We continued our studies with catalyst **1d** since it could be easily prepared from cheap starting materials, $RuCl_3(H_2O)_n$ and PPh_3.[9] Despite the excellent results obtained with **1a** and **1d** (Table 1, entries 3-4), we observed that the reactions sometimes lacked reproducibility (>99% yield could always be obtained, but slightly longer reaction times, *e.g.*, from 2 to 4 h). We thought that decomposition of the catalyst may occur, and that addition of an extra phosphine could prevent unwanted decomposition pathways. On the other hand, the phosphine can hinder the catalytic cycle by blocking the metal center. Furthermore, the electronic and steric properties of the added ligand may change the outcome of the reaction. Thus, we evaluated the effect of added phosphines (Table 1, entries 11-12 and Supporting Information), and it was observed that the addition of electron rich-phosphines, such as P^tBu_3 (entry 12) or P(*p*-$MeOC_6H_4)_3$ (entry 11) did not dramatically decrease the reaction time of the tandem transformation,[10] but more importantly for us, the reactions became reproducible. On the other hand, electron-poor phosphines slowed the reaction down, and bidentate phosphines completely suppressed the transformation.

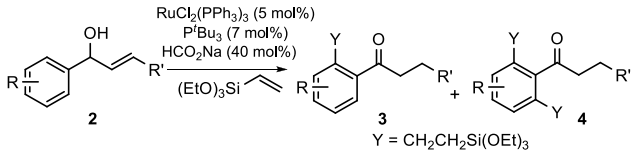
With the optimal conditions established (Table 1, entry 12), we examined the substrate scope (Table 2). The tandem process works very well for a variety of aromatic allylic alcohols (entries 1-15). The 1:1/1:2 adduct ratio (*i.e.*, **3**/**4**) can easily be improved in favor of the former by lowering the amount of triethoxyvinylsilane (entries 3, 6, 8). The temperature can be lowered to 100 °C, although longer reaction times are needed (entry 2). More substituted substrates give good results (entries 14 and 15). The allylic alcohol moiety is not a requirement for the tandem transformation to occur: the double bond can be placed more than one bond away from the carbinol (entry 16). We believe the double bond can migrate to the allylic position and then rearrange to the corresponding ketone. Lower catalyst loading can be used, although longer reaction times are required (When 2.5 mol % of Ru complex **1d** was used, the reaction time to achieved 100% conversion increased from 2 h to 12 h for **2a**).

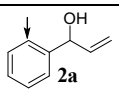
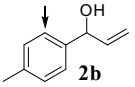
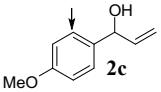
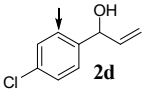
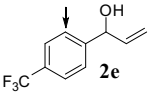
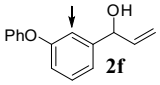
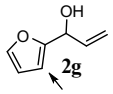
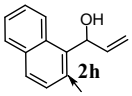
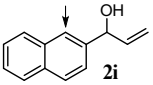
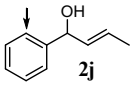
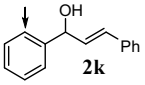
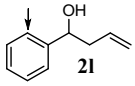
The feasibility of the reaction was also tested using styrene (Scheme 2).[5b] In this case, the added phosphine had a strong influence on the outcome of the reaction, and good yields of a mixture of linear (**6**) and branched (**7**) products are obtained only upon the addition of P^tBu_3. Disubstituted product (1:2 adducts) were not detected.

(9) Jardine, F. H. *Prog. Inorg. Chem.* **1984**, *31*, 265–370.

(10) Although the reaction times for the isomerization / C-H activation did not change much in the presence of electron rich-phosphines, when only C-H activation from propiophenone was studied, the reaction time was decreased by a factor of 2. See Supporting Information.

Table 2. Scope of the Tandem Ru-Catalyzed Isomerization / C-H Activation / C-C Bond Formation.[a]

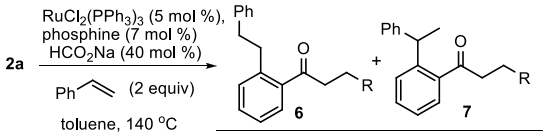


entry	substrate	time (h)	yield (**3** + **4**)[b]	**3**/**4** (%)[c]
1	 **2a**	2	>99 (86)	40/60
2[d]	**2a**	7	>99	80/20
3[e]	**2a**	4	94	92/8
4	 **2b**	5	>99 (83)	84/16
5	 **2c**	1	>99 (90)	70/30
6[e]	**2c**	4	>99	84/16
7	 **2d**	3	>99 (85)	60/40
8[e]	**2d**	6	80	95/5
9	 **2e**	7	96 (76)	84/16
10	 **2f**	3	>99 (92)	79(57:43)/ 21
11	 **2g**	3	95 (80)	-
12	 **2h**	3	91 (85)	-
13	 **2i**	2	>99 (90)	100/0
14	 **2j**	18	91	92/8
15	 **2k**	24	64 (45)	100/0
16[f]	 **2l**	14	90 (74)	94/6

[a]Alcohol **2** and triethoxyvinylsilane (2 equiv) were added to a suspension of HCO_2Na (30 mol %), **1d** (5 mol %), and P^tBu_3 (7 mol %) in toluene (0.5 mL) under a N_2 atmosphere. The flask was quickly introduced into an oil bath at 140 °C, and stirred for the time indicated. [b] The arrows indicate the position where substitution takes place. Measured by ^{1}H NMR, in parenthesis isolated yields (**3**+**4**). [c] Measured by ^{1}H NMR. [d] In an oil bath at 100 °C. [e]1.4 equiv of triethoxyvinylsilane was employed. [f] Product **3l** is identical to **3j**.

The isomerization of **2a-d_1** under similar conditions was performed (Scheme 3). Careful analysis by mass spectroscopy indicated that a mixture of non-deuterated, monodeuterated and dideuterated ketones **5a** had been produced in >95% yield.[11] Traces (~ 2%) of unsaturated ketones were also detected by ^{1}H NMR spectroscopy. Further analysis by quantitative ^{13}C NMR spectroscopy helped us to estimate the ratio and the structure of the monodeuterated and dideuterated ketones (Scheme 3).

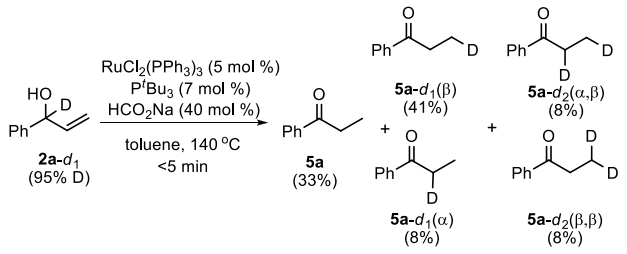
Scheme 2. Use of styrene as the olefin.



phosphine	yield (%) / **6**:**7** (%)
P^{t}Bu$_3$	72 / 80:20
P(*p*-MeOC$_6$H$_4$)$_3$	18 / nd
PPh$_3$	15 / nd

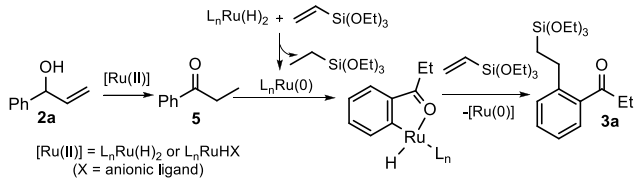
(nd = not determined)

Scheme 3. Isomerization of deuterium labeled allylic alcohol.



The deuterium distribution obtained in the isomerization of **2a-d_1** may be explained by more than one mechanism. During the tandem process, the isomerization of **2a** to ketone **5a** takes place within a very short reaction time (<5 min). We believe that this isomerization is catalyzed by Ru(II) complexes (Ru monohydrides, dihydrides or alkoxides) (Scheme 4 and Supporting Information). In a Ru dihydride mechanism, both the O–H and α-C–H(D) hydrogen atoms of the allylic alcohol can be transferred to the metal yielding a Ru dihydride and an α,β-unsaturated ketone.[12] As a result, the hydrogens are scrambled and lose their identity. Ru monohydrides or dihydrides can also be formed by reaction of Ru dichloride **1d** with HCO_2Na.[8] This latter pathway could account for some of the deuterium loss during the isomerization of deuterated **2a-d_1**. Non-regioselective and reversible insertion of the olefins into the Ru-H bonds can explain the ratio of non-deuterated, monodeuterated and dideuterated ketones that was obtained in the labeling studies shown in Scheme 3.[13] The intermediacy of Ru dihydrides has been further supported when $RuH_2(PPh_3)_4$ was used as the catalyst (Table 1, entry 3). A Ru(0)/Ru(II) mechanism is probably involved in the C–H activation.[3c] Ru(0) complexes can be produced by reaction of Ru(II) dihydrides with a hydride acceptor. We did not detect formation of alcohol by-products in the ^{1}H NMR spectra of the crude reaction mixtures.[14] Therefore, we propose that triethoxyvinyl silane, which is used in excess, can also act as hydride acceptor and mediate the reduction of Ru(II) to Ru(0) (Scheme 4).[15,16]

Scheme 4. Proposed mechanism.



In conclusion, we have described a general tandem isomerization of allylic alcohols/C-H activation catalyzed by the stable $RuCl_2(PPh_3)_3$ complex. The tandem process affords the products in excellent yields in very short reaction times. Moreover, allylic alcohol can be produced *in situ* by migration of a double bond placed more than one bond away from the carbinol. The catalytically active Ru hydride intermediates are generated under the reaction conditions allowing the use of stable ruthenium precursors.

Acknowledgment: Financial support from the Swedish Research Council (Vetenskapsrådet) and the Berzelius Center Exselent is gratefully acknowledged.

Supporting Information Available: Details of experimental procedures, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

(11) The height of the m/z peaks were corrected for the natural ^{13}C content (See Supporting Information).

(12) $RuCl_2(PPh_3)_3$ reacts with isopropanol to produce the corresponding dihydride, see: Aranyos, A.; Gsjernyik, G.; Szabó, K. J.; Bäckvall, J.-E. *J. Chem. Soc. Chem. Commun.* **1999**, 351–352.

(13) For a similar mechanistic study using Ni complexes, see: Cuperly, D.; Petrignet, J.; Crévisy, C.; Grée, R. *Chem. Eur. J.* **2006**, *12*, 3261–3274. See also scheme in Supporting Information.

(14) See crude NMR spectra in Supporting Information.

(15) Theoretical study of the mechanism, see: Matsubara, T.; Koga, N.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **1998**, *120*, 12692–12693.

(16) For direct arylations without involving Ru(0) species, see: (a) Özdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156–1157. (b) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2009**, *102*, 2299–2302.