Ruthenium-catalyzed tandem allylic substitution/isomerization: a direct route to propiophenones from cinnamyl chloride derivatives

Marion Helou, Jean-Luc Renaud,* Bernard Demerseman, François Carreaux and Christian Bruneau*

Received (in Montpellier, France) 22nd January 2008, Accepted 28th March 2008
First published as an Advance Article on the web 15th April 2008
DOI: 10.1039/b801159a

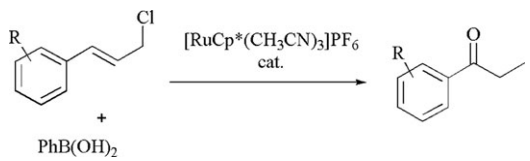
A tandem nucleophilic substitution/redox isomerization catalyzed by a single ruthenium catalyst leads to the direct transformation of allylic chlorides into propiophenones.

Rapid and economical catalytic syntheses of target compounds promoted by a single catalyst precursor are of utmost interest with respect to green chemistry and sustainable development. Efforts are therefore being made to generate well-defined catalysts with multifunctional activities, with the objective of performing successive transformations in a single pot *via* tandem, cascade or sequential catalytic reactions.[1] Among the variety of ruthenium complexes that have been used for the redox isomerization of allylic alcohols into ketones,[2] ruthenium(II) complexes with a cyclopentadienyl type ligand and ruthenium(IV) complexes featuring an allylic ligand have emerged as very efficient catalytic systems. The mononuclear $RuCpCl(PPh_3)_2$, $Ru(indenyl)Cl(PPh_3)_2$, $[RuCp(MeCN)_3]PF_6$, $[RuCp(MeCN)_2(PR_3)]PF_6$ and $RuCpCl(diphosphine)$[3] complexes have shown good catalytic activities for the isomerization of aliphatic and aromatic allylic alcohols into ketones or aldehydes at 65–100 °C. The binuclear ruthenium catalyst $[(Ru(CO)_2)_2(H)(C_5Ph_4OHOC_5Ph_4)]$ is also very efficient for this type of isomerization and has led to faster reactions than with the previous examples.[4] More recently, $RuCp^*Cl(Ph_2PCH_2CH_2NH_2)$[5] and $Ru(C_5MePh_4)X(CO)_2$ (X = Br, Cl)[6] complexes have been shown to be very active Cp-containing ruthenium isomerization catalysts, which operate close to ambient temperature with a large scope of substrates.

Ruthenium(IV) complexes bearing the bis(allyl) dodeca-2,6,10-triene-1,12-diyl (**L1**)[7a] or 2,7-dimethylocta-2,6-dien-1,8-diyl (**L2**)[7b] ligand in $RuCl_2$(**L1**), $[RuCl_2$(**L2**)$]_2$, $RuCl_2(L)$(**L2**) and $RuCl$(**L2**)$(MeCN)_2]SbF_6$ (L = CO, phosphine, *t*BuNC, MeCN or $PhNH_2$) have also shown very high turnover frequencies in the redox isomerization of allylic alcohols into carbonyl compounds, both in organic solvents and in water at 75 °C.

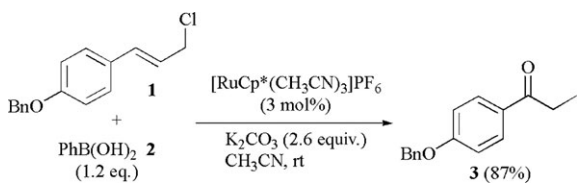
On the other hand, ourselves and others have shown that Cp*Ru(II) complexes are able to activate allylic halides and carbonates, and generate Ru(IV) species bearing an allylic ligand, which are efficient catalysts for the regioselective nucleophilic substitution of allylic substrates by *C*-, *N*- and *O*-nucleophiles to form branched products.[8] With these ideas in mind, we were interested in performing a sequence of catalytic reactions to directly transform allylic substrates into ketones.

We report here the direct transformation of cinnamyl derivatives into propiophenones, useful precursor substrates leading towards biologically-active substances, *via* a regioselective substitution by hydroxide ion, followed by isomerization catalyzed by $[RuCp^*(MeCN)_3]PF_6$, as shown in eqn (1).



(1)

The reaction of phenylboronic acid (**2**), which has already been used in ruthenium-catalyzed C–C bond formation in Heck- and Suzuki–Miyaura-type reactions,[9] and aromatic arylation,[10] did not lead to phenyl group transfer but to regioselective hydroxy group transfer onto the allylic moiety. In addition, this transfer was followed by the Cp*Ru-catalyzed isomerization of the initial allylic alcohol into the corresponding ketone. Thus, when 0.5 mmol of *para*-benzyloxycinnamyl chloride (**1**) and 0.6 mmol of **2** (1.2 equiv.) were reacted in 1 ml of acetonitrile at room temperature for 16 h in the presence of 2.6 equiv. of K_2CO_3 and 0.015 mmol of $[RuCp^*(MeCN)_3]PF_6$ (3 mol%), *para*-benzyloxypropiophenone (**3**) was isolated in 87% yield as the sole reaction product (eqn (2)).

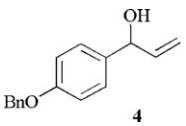


(2)

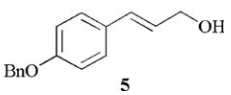
We showed that no reaction took place in the absence of either the ruthenium catalyst or **2**, which indicates that the boronic acid was the hydroxide source and that the reaction was catalyzed by a ruthenium species. Without a boron activator, no reaction took place. Cesium carbonate and potassium fluoride had a positive effect on the reactivity, and the best results were obtained with potassium carbonate.

UMR 6226, Sciences Chimiques de Rennes, CNRS-Université de Rennes 1, Campus de Beaulieu, 35042 Rennes Cedex, France. E-mail: jean-luc.renaud@univ-rennes1.fr. E-mail: christian.bruneau@univ-rennes1.fr; Fax: +33 (0)223236939; Tel: +33 (0)223236283

When water was used as a hydroxide source under basic conditions, no reaction took place, and when the reaction was carried out with **2** in the presence of K_2CO_3, introduced as an aqueous solution (0.5 M), the yields drastically decreased. We anticipate that this transformation took place *via*, firstly, allylic activation by $[RuCp^*(CH_3CN)_3]PF_6$, resulting in the regioselective formation of the internal allylic alcohol **4**, followed by isomerization into ketone **3**, catalyzed by the metal species generated from the same ruthenium precursor. According to the definitions proposed by Fogg and dos Santos,[1a] this sequence corresponds to an auto-tandem catalytic transformation. Indeed, we showed that the reaction at room temperature was fast, and that branched alcohol **4** was present at the beginning of the reaction but disappeared completely after 3 h, whereas no linear alcohol, **5**, could be detected. After a 1.5 h reaction time, substrate **1** was completely converted into **3** and **4** in a 54 : 46 ratio, and after 3 h only **3** was observed. In a parallel experiment, we showed that the linear alcohol **5** was isomerized into the corresponding aldehyde under our catalytic conditions, but that the reaction was much slower, as only 67% conversion of **5** into the aldehyde was obtained after 16 h at room temperature. This is in line with previous results from the literature, which point out the higher reactivity of internal allylic alcohols when forming ketones than primary alcohols when forming aldehydes.[6,7]

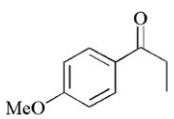


4

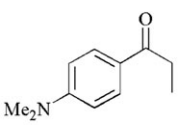


5

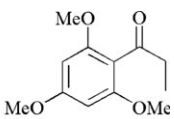
Under the catalytic conditions of eqn (2), the propiophenones **6–8** were obtained in good yields after a 16 h reaction time from *para*-methoxy-, *para*-dimethylamino- and 2,4,6-trimethoxy-phenylprop-3-en-1-yl chloride, respectively.



6 (89%)



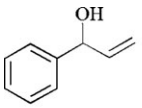
7 (69%)



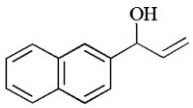
8 (75%)

It is noteworthy that though all the cinnamyl substrates tested under the catalytic conditions of eqn (2) led to allylic alcohols, only those with a phenyl ring substituted by one or several groups having an electron-donating mesomeric effect (alkoxy, dialkylamino) underwent the isomerization reaction. On the other hand, treatment with cinnamyl chloride or 3-naphthylprop-2-enyl chloride at room temperature led to the formation of the branched allylic alcohols **9** and **10** in 77 and 90% yields, respectively, with high regioselectivity (branched/linear ratio = 98 : 2 and 100 : 0, respectively).[11] Even after 16 h at 90 °C, only 18% of propiophenone was formed, alongside the 57% of branched 1-phenylprop-2-en-1-ol (**9**) and 25% of linear 3-phenylprop-2-en-1-ol, showing that the allylic alcohol intermediates with no electron-donating substituents were not easily isomerized into carbonyl compounds.

As far as the mechanisms of these tandem reactions are concerned, the ruthenium-catalyzed isomerization of allylic alcohols into carbonyl compounds is well documented.[3b,6,7b]



9



10

However, the delivery of the nucleophile *via* a boron intermediate is less common. It has been exemplified in a few cases by the palladium-catalyzed substitution of 1,3-diphenylpropenyl acetate by an alkoxy group using $B(OR)_3$ in the presence of K_2CO_3 or KF as an additive,[12] and in the intramolecular delivery of an alkoxy nucleophile from a borate formed *in situ*.[13] An interaction between the Lewis acid site of the boronic acid and a halide, leading to a borate-type intermediate, might favour the controlled delivery of the hydroxy group to the reactive allylic ligand.

In conclusion, we have described a new example of tandem catalysis initiated by Cp*-ruthenium catalysts[14] based on the allylic substitution and isomerization of allylic derivatives, which affords propiophenones directly from cinnamyl chloride derivatives at room temperature. Aromatic ketones are available by Friedel–Crafts synthesis, but even though pure synthetic relevance is not the strongest point of this new methodology, this sequence represents the first example of such a one-pot transformation of allylic substrates into propiophenones in the presence of ruthenium catalysts in organic solvents under mild conditions, with an unexpected role for **2**, which may offer an alternative to hydroxide sources and aqueous media.

Experimental

General procedure

In a Schlenk tube, 0.5 mmol of cinnamyl chloride, 0.6 mmol of boronic acid, 1.3 mmol of K_2CO_3 and 0.015 mmol of $[Cp^*Ru(CH_3CN)_3]PF_6$ (3 mol%) were added to 1 ml of acetonitrile under an argon atmosphere. The reaction mixture was then stirred for 16 h at room temperature. In the case of **3**, this reaction time was optimized to a much shorter 3 h. The product was isolated by purification over silica gel with a 9 : 1 heptane/diethyl ether mixture as the eluent. NMR analyses were performed in $CDCl_3$ on a 200 MHz Bruker spectrometer. The isolated propiophenones are known compounds and their NMR analyses are in agreement with published data.

1-(4-Benzyloxyphenyl)propan-1-one (**3**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00 (d, 2H, J = 8.8 Hz), 7.50–7.30 (m, 5 H), 7.00 (d, 2H, J = 8.8 Hz), 5.10 (s, 2H), 2.95 (q, 2H, J = 7.3 Hz) and 1.20 (t, 3H, J = 7.3 Hz).

1-(4-Methoxyphenyl)propan-1-one (**6**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00 (d, 2H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.8 Hz), 3.95 (s, 3H), 3.05 (q, 2H, J = 7.3 Hz) and 1.20 (t, 3H, J = 7.3 Hz).

1-(4-Dimethylaminophenyl)propan-1-one (**7**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00 (d, 2H, J = 8.8 Hz), 6.95 (d, 2H, J = 8.8 Hz), 3.00 (s, 6H), 2.95 (q, 2H, J = 7.3 Hz) and 1.20 (t, 3H, J = 7.3 Hz).

1-(2,4,6-Trimethoxyphenyl)propan-1-one (**8**). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.10 (s, 2H), 3.85 (s, 9H), 2.95 (q, 2H, J = 7.3 Hz) and 1.20 (t, 3H, J = 7.3 Hz).

References

1 (*a*) D. Fogg and E. N. dos Santos, *Coord. Chem. Rev*., 2004, **248**, 2365; (*b*) L. F. Tietze, *Chem. Rev*., 1996, **96**, 115; (*c*) Metal Catalyzed Cascade Reactions, *Topics in Organometallic Chemistry*, ed. T. J. J. Müller, Springer, Berlin, Heidelberg, 2006, vol. **19**; (*d*) A. Ajamian and J. L. Gleason, *Angew. Chem., Int. Ed*., 2004, **43**, 3754.

2 R. Uma, C. Crévisy and R. Grée, *Chem. Rev*., 2003, **103**, 27.

3 (*a*) B. M. Trost and R. J. Kulawiec, *Tetrahedron Lett*., 1991, **32**, 3039; (*b*) B. M. Trost and R. J. Kulawiec, *J. Am. Chem. Soc*., 1993, **115**, 2027; (*c*) C. Slugovc, E. Rüba, R. Schmid and K. Kirchner, *Organometallics*, 1999, **18**, 4230; (*d*) R. C. van der Drift, M. Vailati, E. Bouwman and E. Drent, *J. Mol. Catal. A: Chem*., 2000, **159**, 163; (*e*) R. C. van der Drift, M. Gagliardo, H. Kooijman, A. L. Spek, E. Bouwman and E. Drent, *J. Organomet. Chem*., 2005, **690**, 1044.

4 J.-E. Bäckvall and U. Andreasson, *Tetrahedron Lett*., 1993, **34**, 5459.

5 M. Ito, S. Kitahara and T. Ikariya, *J. Am. Chem. Soc*., 2005, **127**, 6172.

6 B. Martin-Matute, K. Bogar, M. Edin, F. B. Kaynak and J.-E. Bäckvall, *Chem.–Eur. J*., 2005, **11**, 5832.

7 (*a*) V. Cadierno, S. E. Garcia-Garrido and J. Gimeno, *Chem. Commun*., 2004, 232; (*b*) V. Cadierno, S. E. Garcia-Garrido, J. Gimeno, A. Varel-Alvarez and J. A. Sordo, *J. Am. Chem. Soc*., 2006, **128**, 1360.

8 (*a*) M. D. Mbaye, B. Demerseman, J.-L. Renaud, L. Toupet and C. Bruneau, *Angew. Chem., Int. Ed*., 2003, **42**, 5066; (*b*) M. D. Mbaye, B. Demerseman, J.-L. Renaud, L. Toupet and C. Bruneau, *Adv. Synth. Catal*., 2004, **346**, 835; (*c*) J.-L. Renaud, C. Bruneau, B. Demerseman and M. D. Mbaye, *Curr. Org. Chem*., 2006, **10**, 115; (*d*) C. Bruneau, J.-L. Renaud and B. Demerseman, *Chem.–Eur. J*., 2006, **12**, 5178; (*e*) B. M. Trost, P. L. Fraisse and Z. T. Ball, *Angew. Chem., Int. Ed*., 2002, **41**, 1059; (*f*) T. Kondo, H. Ono, N. Satake, T. Mitsudo and Y. Watanabe, *Organometallics*, 1995, **14**, 1945; (*g*) R. Hermatschweiler, I. Fernandez, P. S. Pregosin and F. Breher, *Organometallics*, 2006, **25**, 1440; (*h*) I. Fernandez, R. Hermatschweiler, P. S. Pregosin, A. Albinati and S. Rizzato, *Organometallics*, 2006, **25**, 323; (*i*) S. Constant, S. Tortoioli, J. Müller and J. Lacour, *Angew. Chem., Int. Ed*., 2007, **46**, 2082.

9 (*a*) E. J. Farrington, J. M. Brown, C. F. J. Barnard and E. Rowsell, *Angew. Chem., Int. Ed*., 2002, **41**, 169; (*b*) Y. Na, S. Park, S. B. Han, H. Han, S. Ko and S. Chang, *J. Am. Chem. Soc*., 2004, **126**, 250.

10 (*a*) F. Kakiuchi, Y. Matsuura, S. Kan and N. Chatani, *J. Am. Chem. Soc*., 2005, **127**, 5936; (*b*) F. Kakiuchi, S. Kan, K. Igi, N. Chatani and S. Murai, *J. Am. Chem. Soc*., 2003, **125**, 1698.

11 A. Bouziane, M. Helou, B. Carboni, F. Carreaux, B. Demerseman, C. Bruneau and J.-L. Renaud, *Chem.–Eur. J*., 2008, **14**, DOI: 10.1002/chem.200702030, in press.

12 Y. Hamada, N. Seto, Y. Takayanagi, T. Nakano and O. Hara, *Tetrahedron Lett*., 1999, **40**, 7791.

13 (*a*) B. M. Trost, E. J. McEachern and F. D. Toste, *J. Am. Chem. Soc*., 1998, **120**, 12702; (*b*) B. M. Trost, B. S. Brown, E. J. McEachern and O. Kuhn, *Chem.–Eur. J*., 2003, **9**, 4442.

14 C. Bruneau, S. Dérien and P. H. Dixneuf, in *Topics in Organometallic Chemistry*, ed. T. J. J. Müller, Springer, Berlin, Heidelberg, 2006, vol. **19**, pp. 295–326.