ORGANIC LETTERS

2010
Vol. 12, No. 1
1−3

Synthesis of 2-Hydroxymethyl Ketones by Ruthenium Hydride-Catalyzed Cross-Coupling Reaction of α,β-Unsaturated Aldehydes with Primary Alcohols

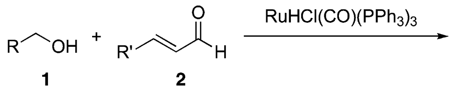
Aurélien Denichoux, Takahide Fukuyama, Takashi Doi, Jiro Horiguchi, and Ilhyong Ryu*

Department of Chemistry, Graduate School of Science, Osaka Prefecture University,
Sakai, Osaka 599-8531, Japan

ryu@c.s.osakafu-u.ac.jp

Received October 3, 2009

ABSTRACT



The cross-coupling reaction of α,β-unsaturated aldehydes with primary alcohols to give 2-hydroxymethyl ketones was achieved using RuHCl(CO)(PPh$_3$)$_3$ as a catalyst. This atom-economical reaction is likely to proceed via the hydroruthenation of α,β-unsaturated aldehydes followed by an aldol reaction of the resultant enolates with aldehydes to give α-formylated ketones, which undergo transfer hydrogenation with primary alcohols leading to α-hydroxymethyl ketones. The reduction step can generate aldehydes, participating in the next catalytic cycle.

Development of new catalytic coupling processes accompanied with atom economy is highly desirable in organic synthesis.[1,2] In this regard, we are interested in the potentials of ruthenium hydride-catalyzed bond forming reactions in conjunction with the use of readily available oxygenated substrates, such as alcohols, ketones, and aldehydes.[3−5] Recently, we have reported that dimerization of primary unsaturated alcohols[4a] and reductive dimerization of α,β-unsaturated aldehydes[5] were effectively catalyzed by RuHCl(CO)(PPh$_3$)$_3$. In the latter homocoupling reaction of enals, secondary alcohols such as isopropanol act as a hydrogen source, which is converted to acetone, an inert compound in the system (Scheme 1, eq 1). Since the pioneering work of Gregorio and co-workers on catalytic dimerization of primary alcohols,[6] many researchers have pursued the potential of cross-coupling reactions of primary alcohols via transfer hydrogenation.[7] In this regard, recent work by

---

(1) Beller, M.; Bolm, C., Eds. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, 1998; Vols. *1 and 2*. (b) Cornils, B.; Herrmann, A. W., Eds. *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996; Vol. 1 and 2.

(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (c) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630.

(3) For selected reviews of ruthenium-catalyzed C−C coupling, see: (a) Bruneau, C.; Dixneuf, H. P., Eds. *Ruthenium Catalysts and Fine Chemisty*; Springer-Verlag: Berlin, Heidelberg, 2004. (b) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (c) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (d) Kondo, T; Mitsudo, T.-a. *Curr. Org. Chem.* **2002**, *6*, 1163. (e) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630. (f) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102.

(4) For our previous work on the use of the ruthenium hydride catalyst, see: (a) Doi, T.; Fukuyama, T.; Minamino, S.; Husson, G.; Ryu, I. *Chem. Commun.* **2006**, 1875. (b) Doi, T.; Fukuyama, T.; Horiguchi, J.; Okamura, T.; Ryu, I. *Synlett* **2006**, 721. (c) Fukuyama, T.; Doi, T.; Minamino, S.; Omura, S.; Ryu, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 5559. (d) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, 14094. (e) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741.

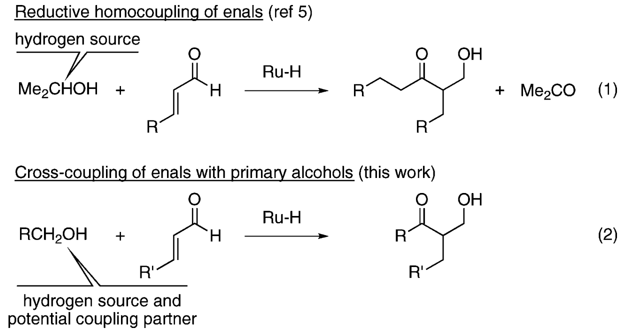
(5) Doi, T.; Fukuyama, T.; Minamino, S.; Ryu, I. *Synlett* **2006**, 3013.

(6) Gregorio, G.; Pregaglia, G. F.; Ugo, R. *J. Orgnomet. Chem.* **1972**, *37*, 385.

10.1021/ol902289r

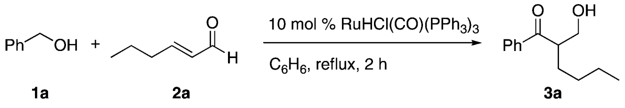
Krische and co-workers that demonstrates Ru- and Ir-catalyzed cross-coupling of alcohols with unsaturated C−C double and triple bonds is noteworthy.[8] We thought that if primary alcohols, such as benzyl alcohol, are employed as a hydrogen source, the resulting aldehydes would act as a coupling partner to give cross-coupling products (Scheme 1, eq 2). We report herein the Ru−H-catalyzed atom-economical cross-coupling reaction of α,β-unsaturated aldehydes with primary alcohols leading to α-hydroxymethyl ketones.

Scheme 1. Ru−H Catalyzed Coupling Reactions of Enals



When a benzene solution of benzyl alcohol (**1a**, 1.2 equiv) and 2-hexenal (**2a**) in the presence of $RuHCl(CO)(PPh_3)_3$ (10 mol %) was heated under reflux for 2 h (Procedure A, Scheme 2), 2-hydroxymethyl-1-phenyl-1-hexanone (**3a**) was obtained in 40% yield. In this case, a significant amount of dimer derived by reductive coupling of **2a** was formed as byproduct (**3a**/dimer = 5/1). To suppress the undesired dimerization course, **2a** was added slowly using a syringe pump over the period of 1 h, then the resulting mixture was stirred for another 1 h (Procedure B). In this case, the desired **3a** was obtained in 61% yield. Since in the initial stage of the reaction **2a** was consumed by transfer hydrogenation to produce benzaldehyde, we decided to add a small amount of aldehyde beforehand (Procedure C). This caused further improvement of the yield of **3a** up to 72%.

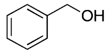
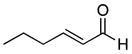
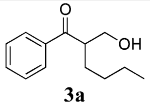
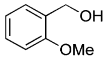
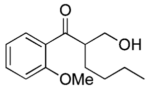
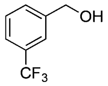
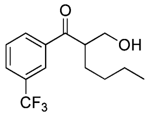
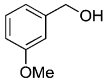
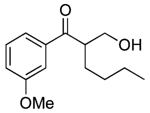
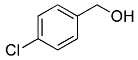
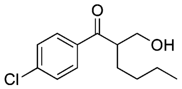
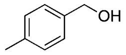
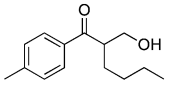
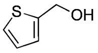
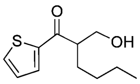
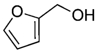
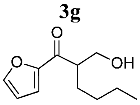
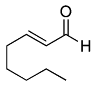
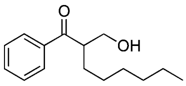
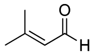
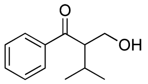
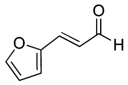
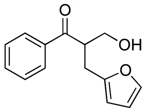
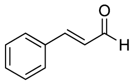
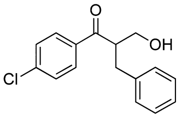
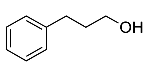
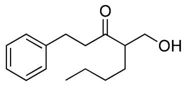
Scheme 2. Optimization of the Reaction Conditions



Procedure A : stirred	40%
Procedure B : syringe pump addition of **2a**	61%
Procedure C : syringe pump addition of **2a** benzaldehyde (11 mol%)	72%

Having an optimized procedure C in hand, we then examined the generality of the present cross-coupling reaction with various alcohols and enals (Table 1). The reactions of 2-hexenal (**2a**) with several benzylic alcohols, having an

Table 1. Cross-Coupling Reaction of α,β-Unsaturated Aldehydes with Benzylic Alcohols[a]

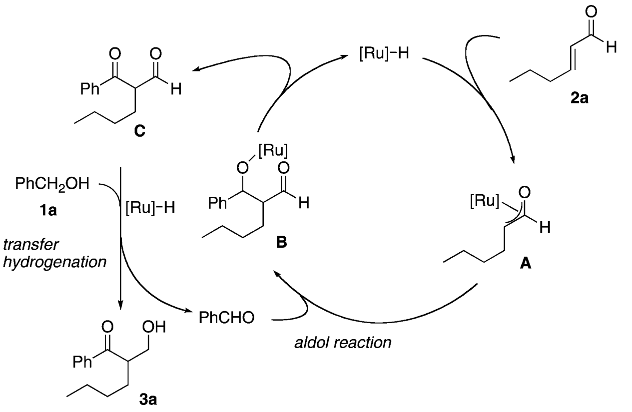
entry	benzyl alcohol **1**	enal **2**	β-hydroxymethyl ketone **3**	yield[b]
1	 **1a**	 **2a**	 **3a**	72%
2	 **1b**	**2a**	 **3b**	53%
3	 **1c**	**2a**	 **3c**	66%
4	 **1d**	**2a**	 **3d**	59%
5	 **1e**	**2a**	 **3e**	74%
6	 **1f**	**2a**	 **3f**	67%
7[c]	 **1g**	**2a**	 **3g**	64%
8	 **1h**	**2a**	 **3h**	66%
9	**1a**	 **2b**	 **3i**	66%
10	**1a**	 **2c**	 **3j**	45%
11	**1a**	 **2d**	 **3k**	60%
12[c]	**1e**	 **2e**	 **3l**	69%
13	 **1i**	**2a**	 **3m**	30%

[a] Conditions: **1** (1.2 equiv), **2** (0.8 mmol), corresponding aldehyde (10 mol %), $RuHCl(CO)(PPh_3)_3$ (0.08 mmol), benzene (4 mL). A benzene solution of **1** (5 mL) was added using a syringe pump over the period of 1 h, then the mixture was heated at reflux for 1 h. [b] Isolated yield after flash chromatography on SiO_2. [c] A benzene solution of **1g** and **2a** was added over the period of 1 h.

electron-donating substituent or an electron-withdrawing substituent, gave the 2-hydroxymethyl ketone **3** in good yields (entries 1−6). The reaction also worked well with alcohols having heteroaromatic rings such as 2-thiophenemethanol (**1g**) and 2-furanmethanol (**1h**) (entries 7 and 8). In the case of the alcohol **1g**, transfer hydrogenation of **1g** and **2a** leading to 2-thiophenecarboxyaldehyde and 1-hexanol was fast with the procedure C. Thus, syringe pump addition of a mixture solution of **1g** and **2a** was examined, giving the desired coupling product **3g** in good yield. Disubstituted enal **2c** also reacted with **1a**, whereas the yield of **3j** was rather modest (entry 10). Enals having an aromatic substituent at the β-position, such as **2d** and **2e**, gave the corresponding 2-hydroxymethyl ketones in good yields (entries 11 and 12). The reaction of nonbenzylic type alcohol **1i** also gave the coupling **3m** in 30%, which requires further efforts for yield optimization.

A possible mechanism for this enal/alcohol coupling reaction is shown in Scheme 3 with an example of the reaction of **1a** and **2a**. The hydroruthenation of **2a** would give ruthenium enolate **A**,[9,10] which then undergoes aldol reaction with benzaldehyde.[11,12] β-Elimination from the resulting aldol adduct **B** would lead to the keto aldehyde **C**. Finally, transfer hydrogenation[13] between the aldehyde moiety of **C** and benzyl alcohol (**1a**) gives 2-hydroxymethyl ketone **3a** and benzaldehyde which then reacts with another molecule of ruthenium enolate **A**, creating a catalytic cycle.

Scheme 3. Possible Mechanism for the Coupling of **1a** and **2a**



In summary, we have shown that a novel cross-coupling reaction of enals with primary alcohols is effectively catalyzed by $RuHCl(CO)(PPh_3)_3$, which leads to good yields of 2-hydroxymethyl ketones. The reaction is likely to proceed via an aldol reaction of a ruthenium enolate followed by a transfer hydrogenation, where primary alcohols act as both a hydrogen source and a latent aldehyde. The simplicity, atom efficiency, mild reaction conditions, and short reaction times make this an appealing methodology for accessing 2-hydroxymethyl ketones. Synthetic applications of the present reaction are currently underway in this laboratory.

Acknowledgment. A.D. thanks a Grant-in-Aid for JSPS Fellows. T.F. and I.R. thank JSPS and MEXT Japan for funding.

Supporting Information Available: Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902289R

---

(7) For reviews, see: (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H S. A.; Slatford, P. A.; Williams, J. M. *Adv. Synth. Catal.* **2007**, *349*, 1555 For recent examples. (c) Cho, S. K.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020. (d) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72. (e) Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, *7*, 4017. (f) Cho, C. S. *J. Mol. Catal. A: Chem.* **2005**, *240*, 55. (g) Martínez, R.; Ramón, D. J.; Yus, M. *Tetrahedron* **2006**, *62*, 8988. (h) Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71*, 8023. (i) Hall, M. I.; Pridmore, S. J.; Williams, J. M. J. *Adv. Synth. Catal* **2008**, *350*, 1975. (j) Pridmore, S. J; Williams, J. M. J. *Tetrahedron Lett.* **2008**, *49*, 7413. (k) Jensen, T.; Madsen, R. *J. Org. Chem.* **2009**, *74*, 3990. (l) Grigg, R.; Lofberg, C.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 849. (m) Shimizu, K.; Sato, R.; Satsuma, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 3982.

(8) (a) Bower, J. F.; Skucas, E.; Patma, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134. (b) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. Also see recent reviews: (c) Bower, J. F.; Kim, I. S.; Patman, R. L; Krische, M. J. *Angew. Chem., Int. Ed* **2009**, *48*, 34, and ref 3f and references therein.

(9) For studies on ruthenium enolate complexes, see: (a) Hartwig, J. F.; Andersen, R. A.; Bergman, G. B. *J. Am. Chem. Soc.* **1990**, *112*, 5670. (b) Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. *Organometallics* **1991**, *10*, 3326. (c) Tasley, B. T.; Rapta, M.; Kulawiec, R. J. *Organometallics* **1996**, *15*, 2852.

(10) For examples of catalytic transformations based on ruthenium enolates, see: (a) Matsuda, I.; Shibata, M.; Sato, S. *J. Organomet. Chem.* **1988**, *340*, C5. (b) Sato, S.; Matsuda, I.; Shibata, M. *J. Organomet. Chem.* **1989**, *377*, 347. (c) Murahashi, S.-I.; Naota, T.; Taki, H.; Mizuno, M.; Takaya, H.; Komiya, S.; Mizuho, Y.; Oyasato, N.; Hiraoka, M.; Hirano, M.; Fukuoka, A. *J. Am. Chem. Soc.* **1995**, *117*, 12436. (d) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 8081. (e) Uma, R.; Davies, M.; Crévisy, C.; Grée, R. *Tetrahedron Lett.* **2001**, *42*, 3069.

(11) For Ru-catalyzed aldol type reactions, see: (a) Naota, T.; Taki, T.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954. (b) Mizuho, Y.; Kasuga, N.; Komiya, S. *Chem. Lett.* **1991**, 2127. (c) Wang, M.; Yang, X.-F.; Li, C.-J. *Eur. J. Org. Chem.* **2003**, 998. (d) Yang, X.-F.; Wang, M.; Varma, R. S.; Li, C.-J. *Org. Lett.* **2003**, *5*, 657. (e) Yang, X.-F.; Wang, M.; Varma, R. S.; Li, C.-J. *J. Mol. Catal. A: Chem.* **2004**, *214*, 147. (f) Martín-Matute, B.; Bogár, K.; Edin, M.; Kaynak, F. B.; Bäckvall, J.-E. *Chem.—Eur. J.* **2005**, *11*, 5832. (g) Bartoszewicz, A.; Livendahl, M.; Martín-Matute, B. *Chem.—Eur. J.* **2008**, *14*, 10547.

(12) For reviews on catalytic reductive aldol coupling, see: (a) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135. (b) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12. (c) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653. (e) Chiu, P. *Synthesis* **2004**, 2210.

(13) For reviews on transfer hydrogenation, see: (a) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567. (b) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (d) Bäckvall, J.-E. *J. Organomet. Chem.* **2002**, *652*, 105. (e) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67. Transfer hydrogenation reactions catalyzed by $RuHCl(CO)(PPh_3)_3$: (f) Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2441. (g) Gordon, E. M.; Gaba, D. C.; Jebber, K. A.; Zacharias, D. M. *Organometallics* **1993**, *12*, 5020. (h) Hiraki, K.; Nonaka, A.; Matsugana, T.; Kawano, H. *J. Organomet. Chem.* **1999**, *574*, 121. Also see ref 8.