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Rhodium-Catalyzed Synthesis of γ-Pyrones by Three Consecutive Redox–Aldol Reactions of Allylic Alcohols with α,β-Unsaturated Aldehydes

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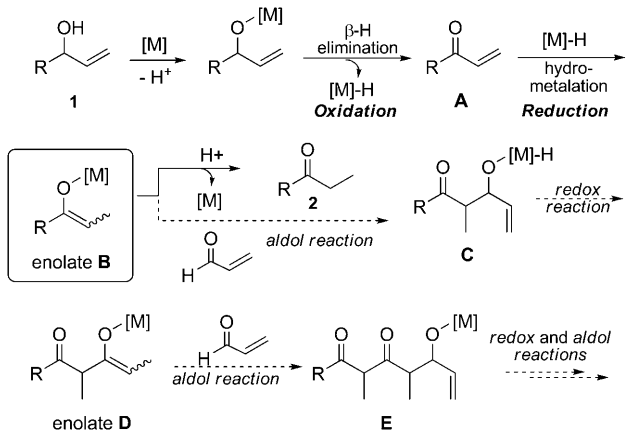
Consecutive 1,3-dicarbonyl units are an important feature of compounds[1] as a precursor for a variety of polyketides with diverse biological activities. Various methods for the synthesis of 1,3-diketones have been reported, such as the Claisen-type reaction between ketone enolates and acylating agents,[2] oxidation of aldol compounds,[3] N–O bond cleavage of isoxazoles[4] and others.[5] On the contrary, there are few reports of a concise method for the preparation of 1,3,5-triketones or their equivalents.[6]

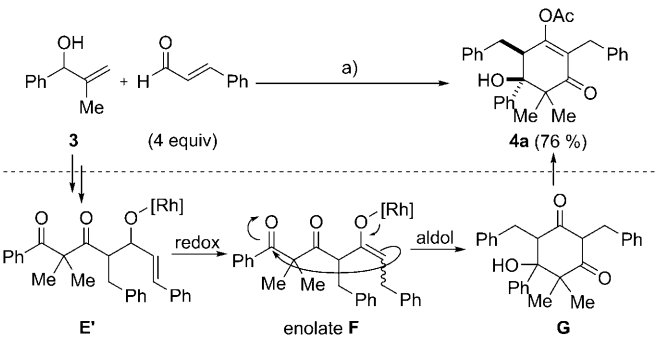
Secondary allylic alcohols **1** are known to undergo isomerization to saturated ketones **2** with several transition-metal catalysts, such as Rh and Ru, through β-hydride elimination to give α,β-unsaturated ketones **A** followed by hydrometalation of the enones by the generated metal hydride (Scheme 1).[7] Although metal enolates **B** are generated in this process,[8] protonation by the allylic alcohols to give ketones usually occurs and only a few reports deal with application to carbon–carbon bond-forming processes, such as aldol reactions.[9] Herein, we report a Rh^{I}-catalyzed reaction for the unique formation of γ-pyrones, a 1,3,5-triketone equivalent, through three consecutive redox–aldol reactions.[10]



Scheme 1. Concept of consecutive redox–aldol reactions.

Our basic idea is as follows: By using α,β-unsaturated aldehydes as acceptors for the enolates generated from allylic alcohols by the oxidation–reduction process, the aldol products formed (**C**) are again allylic alcohols. Then, a further redox–aldol reaction with another molecule of the aldehyde would give allylic alcohols **E**. Repetition of these processes would give consecutive 1,3-diketones in a single operation (Scheme 1).

With these considerations, we first examined the reaction of allylic alcohol **3** and cinnamaldehyde using various Rh catalysts. It was found that when allylic alcohol **3** was treated with cinnamaldehyde (4 equiv) in the presence of [{RhOH(cod)}$_2$] (0.5 equiv; equimolar based on Rh metal, cod = 1,5-cyclooctadiene) and PPh_3 (2 equiv) in THF at room temperature, cyclohexenone **4a** was obtained in 76% yield after treatment with acetyl chloride (Scheme 2). The proposed mechanism for the formation of this product is as



Scheme 2. Consecutive redox–aldol reaction. a) 1) [{Rh(OH)(cod)}$_2$] (0.5 equiv), PPh_3 (2 equiv), THF, RT, 24 h; 2) AcCl, cat. 4-dimethylaminopyridine (DMAP), pyridine, 0 °C to RT.

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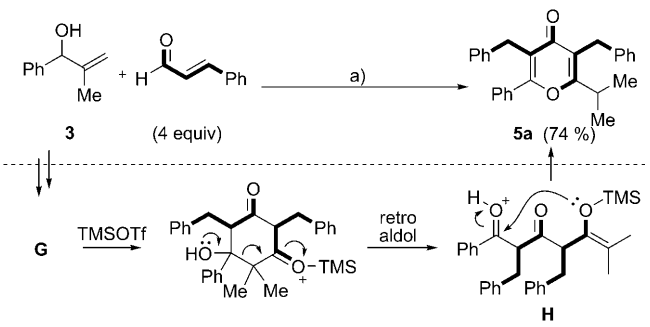
follows: Twofold consecutive redox–aldol reactions proceeded between **3** and cinnamaldehyde to afford **E′**. This compound once again underwent a redox reaction to give the Rh–enolate of triketone **F**, which finally underwent an intramolecular aldol reaction to give the 1,3-cyclohexanedione **G**. Since this product was found to be unstable, it was isolated as acetylated cyclohexenone **4a** by treatment with acetyl chloride.

As three consecutive redox–aldol reactions were found to proceed as expected, we then examined various reaction conditions to realize catalytic reactions. The amount of Rh catalyst could be reduced to 20 mol% based on Rh metal by using $[\{RhCl(coe)_2\}_2]$ (coe = cyclooctene) in combination with a stoichiometric amount of BuLi as a base for Li alkoxide formation. 1,4-Dioxane also gave a better result than THF. Furthermore, it was found that treatment of the crude product with trimethylsilyl trifluoromethanesulfonate (TMSOTf) instead of an acetylating agent gave γ-pyrone **5a** in high yield, which is thought to be produced through an intramolecular *O*-cyclization of triketone enolate **H** generated from cyclic diketone **G** by a retro-aldol reaction (Scheme 3).



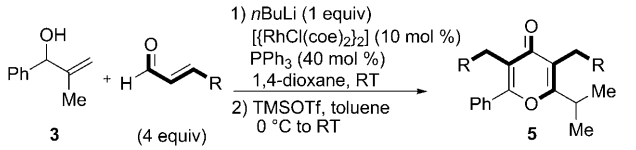
Scheme 3. Rhodium(I)-catalyzed consecutive redox–aldol reaction. a) 1) *n*BuLi (1 equiv), $[\{RhCl(coe)_2\}_2]$ (10 mol%), PPh_3 (40 mol%), 1,4-dioxane, RT; 2) TMSOTf, toluene, 0°C to RT.

Thus, under the optimized conditions, γ-pyrone **5a** was obtained in 74% yield by the reaction of the lithium salt of allylic alcohol **3** and cinnamaldehyde with $[\{RhCl(coe)_2\}_2]$ (10 mol%) and PPh_3 (40 mol%) in 1,4-dioxane at room temperature followed by treatment of the crude product with TMSOTf in toluene at 0°C to room temperature.

The reaction of several aldehydes with allylic alcohol **3** was carried out according to the optimized conditions (Table 1). Unsaturated aldehydes, which possess *p*-anisyl, 2-furyl,[11] methyl, ethyl, and isopropyl groups at the β position, gave the corresponding γ-pyrones in good yields (Table 1, entries 2 and 4–7). In the case of *p*-CF_3-substituted cinnamaldehyde, the yield of the product was somewhat lowered (Table 1, entry 3). Acrolein and β,β-disubstituted unsaturated aldehyde did not give γ-pyrones at all.

Next, we carried out the reaction using several allylic alcohols with cinnamaldehyde (Table 2). Allylic alcohols **6a** and **6b**, which possess an electron-donating and -withdrawing substituent on the phenyl ring, gave the corresponding

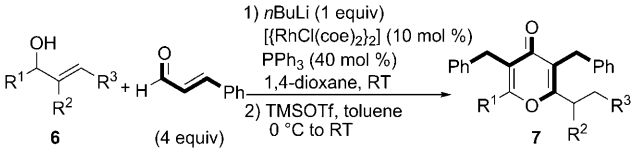
Table 1. Reactions of several α,β-unsaturated aldehydes with **3**.



Entry	R	Product	Yield [%]
1	Ph	**5a**	74
2[a,b]	4-$MeOC_6H_4$	**5b**	64
3	4-$CF_3C_6H_4$	**5c**	44
4	2-furyl	**4d**[c]	68
5[a]	Me	**5e**	59
6	Et	**5f**	71
7	*i*Pr	**5g**[d]	69

[a] $[\{RhCl(coe)_2\}_2]$ (15 mol%) and PPh_3 (60 mol%) were used. [b] 23% of the starting material was recovered. [c] The yield of the acetylated product. [d] The reaction for step 2 was carried out at 60°C for 1 h.

Table 2. Reactions of several allylic alcohols with cinnamaldehyde.



Entry	Alcohol	R^1	R^2	R^3	Product	Yield [%]
1	**6a**	4-$MeOC_6H_4$	Me	H	**7a**	62
2	**6b**	4-$CF_3C_6H_4$	Me	H	**7b**	76
3	**6c**	2-furyl	Me	H	**8c**[b]	80
4	**6d**	2-thienyl	Me	H	**7d**	74
5[a,c]	**6e**	Ph	Me	Me	**7e**	52
6[a,d]	**6f**	Ph	Me	Ph	**7f**	55
7[a]	**6g**	Ph	H	Ph	**7g**	53

[a] $[\{RhCl(coe)_2\}_2]$ (15 mol%) and PPh_3 (60 mol%) were used. [b] The yield of the acetylated product. [c] 28% of the starting material was recovered. [d] 26% of the starting material was recovered.

γ-pyrones in good yields (Table 2, entries 1–2). Heteroaromatics, such as furan[11] and thiophene, as R^1 were applicable for this Rh^I-catalyzed consecutive reaction (Table 2, entries 3 and 4). In the case of allylic alcohols **6e** and **6f**, which possess methyl or phenyl groups as substituent R^3, corresponding γ-pyrones were obtained in reasonable yields and 20–30% of the starting materials were recovered (Table 2, entries 5 and 6). Even allylic alcohol **6g**, which has no α substituent (R^2 = H), gave the corresponding γ-pyrone **7g** in an acceptable yield (Table 2, entry 7).[12,13]

In summary, we have developed a new and simple synthetic approach for the production of γ-pyrones[6a,b,13] as a triketide equivalent by the novel rhodium-catalyzed tandem redox–aldol reaction of allylic alcohols with α,β-unsaturated aldehydes. Further studies are currently in progress to expand the scope and utility of this reaction.

Experimental Section

General procedure: *n*BuLi (0.13 mL of a 1.57 M solution in hexanes, 0.20 mmol) was added to a solution of allylic alcohol **3** (30.2 mg,

0.204 mmol) in 1,4-dioxane (4.0 mL) at 0 °C and the mixture was warmed to room temperature, and then [{RhCl(coe)$_2$}$_2$] (14.3 mg, 0.020 mmol, 0.040 mmol based on Rh atom) and PPh_3 (21.0 mg, 0.080 mmol) were added. After the catalyst almost dissolved (ca. 1 min), cinnamaldehyde (100 μL, 0.79 mmol) was added to the reaction mixture and then the reaction mixture was kept in a closed system and was stirred for 24 h at room temperature. The reaction was quenched by addition of pH 7 phosphate buffer. The organic layer was extracted with Et_2O twice, and the combined organic layer was washed with brine. After the organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure. The residue was dissolved in toluene (5.0 mL), and TMSOTf (0.15 mL, 0.96 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 2 h and at room temperature for 2 h. The reaction was quenched by addition of pH 7 phosphate buffer. The organic layer was extracted with AcOEt twice, and the combined organic layer was washed with H_2O and brine. After the organic layer was dried over $MgSO_4$, the solvent was removed under reduced pressure. The residue was purified by preparative TLC (20% ethyl acetate in hexanes) to afford γ-pyrone **5a** as a colorless oil (58.0 mg, 0.147 mmol, 74%).

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Keywords: aldehydes · aldol reaction · allylic compounds · homogeneous catalysis

[1] a) A. V. Kel'in, A. Maioli, *Curr. Org. Chem.* **2003**, *7*, 1855–1866; b) A. V. Kel'in, *Curr. Org. Chem.* **2003**, *7*, 1691–1711.

[2] For representative recent examples, see: a) K. Sato, S. Yamazoe, R. Yamamoto, S. Ohata, A. Tarui, M. Omote, I. Kumadaki, A. Ando, *Org. Lett.* **2008**, *10*, 2405–2408; b) D. Lim, F. Fang, G. Zhou, D. M. Coltart, *Org. Lett.* **2007**, *9*, 4139–4142; c) Y. Nishimura, Y. Miyake, R. Amemiya, M. Yamaguchi, *Org. Lett.* **2006**, *8*, 5077–5080; d) A. R. Katritzky, N. K. Meher, S. K. Singh, *J. Org. Chem.* **2005**, *70*, 7792–7794, and references therein.

[3] For representative examples, see: a) K. Jeyakumar, D. K. Chand, *Synthesis* **2009**, 306–310; b) V. Fargeas, M. Baalouch, E. Metay, J. Baffreau, D. Ménard, P. Gosselin, J.-P. Bergé, C. Barthomeuf, J. Lebreton, *Tetrahedron* **2004**, *60*, 10359–10364; c) S. Katayama, K. Fukuda, T. Wantanabe, M. Yamauchi, *Synthesis* **1988**, 178–183; d) A. B. Smith III, P. A. Levenberg, *Synthesis* **1981**, 567–570, and references therein.

[4] For a recent review, see: A. I. Kotyatkina, V. N. Zhabinsky, V. A. Khripach, *Russ. Chem. Rev.* **2001**, *70*, 641–653.

[5] For other recent examples of 1,3-diketone syntheses, see: a) M. Sada, S. Matsubara, *J. Am. Chem. Soc.* **2010**, *132*, 432–434; b) A. A. Ibrahim, S. M. Smith, S. Henson, N. J. Kerrigan, *Tetrahedron Lett.* **2009**, *50*, 6919–6922; c) Z. Ikeda, T. Hirayama, S. Matsubara, *Angew. Chem.* **2006**, *118*, 8380–8383; *Angew. Chem. Int. Ed.* **2006**, *45*, 8200–8203; d) S. Kamijo, G. B. Dudley, *Org. Lett.* **2006**, *8*, 175–177.

[6] For examples of Claisen-type reactions, such as a coupling of dianions of 1,3-diketones with acylating agents, see: a) A. Sakakura, H. Watanabe, K. Ishihara, *Org. Lett.* **2008**, *10*, 2569–2572; b) H. Arimoto, S. Nishiyama, S. Yamamura, *Tetrahedron Lett.* **1990**, *31*, 5619–5620; c) P. J. Wittek, K. B. Hindley, T. M. Harris, *J. Org. Chem.* **1973**, *38*, 896–901. For examples of oxidation of the corresponding β-hydroxyketone derivatives, see: d) I. Paterson, A. S. Franklin, *Tetrahedron Lett.* **1994**, *35*, 6925–6928; e) N. E. Pratt, Y. Zhao, S. Hitchcock, K. F. Albizati, *Synlett* **1991**, 361–362, and references therein.

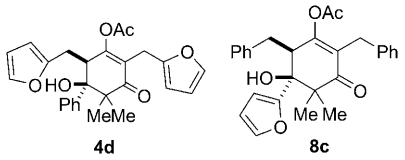
[7] For reviews on catalytic isomerization of allylic alcohols, see: a) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27–51; b) R. C. van der Drift, E. Bouwman, E. Drent, *J. Organomet. Chem.* **2002**, *650*, 1–24, and references therein.

[8] For recent reviews of transition metal-catalyzed reductive aldol reaction, see: a) S. Garner, S. B. Han, M. J. Krische in *Modern Reductions* (Eds.: P. Andersson, I. Munslow), Wiley-VCH, Weinheim, **2008**, 387–408; b) H. Nishiyama, T. Shiomi, *Top. Curr. Chem.* **2007**, *279*, 105–137; for other representative examples, see: c) A. E. Russell, N. O. Fuller, S. J. Taylor, P. Aurriset, J. P. Morken, *Org. Lett.* **2004**, *6*, 2309–2312, and references therein.

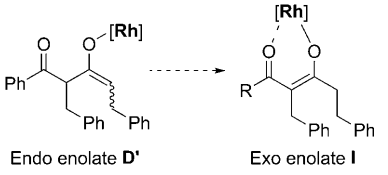
[9] For representative recent examples, see: a) N. Ahlsten, B. Martín-Matute, *Adv. Synth. Catal.* **2009**, *351*, 2657–2666; b) A. Bartoszewicz, M. Livendahl, B. Martín-Matute, *Chem. Eur. J.* **2008**, *14*, 10547–10550; c) D. Cuperly, J. Petrignet, C. Crévisy, R. Grée, *Chem. Eur. J.* **2006**, *12*, 3261–3274; d) X.-F. Yang, M. Wang, R. S. Varma, C.-J. Li, *J. Mol. Catal. A* **2004**, *214*, 147–154; e) L. J. Gazzard, W. B. Motherwell, D. A. Sandham, *J. Chem. Soc. Perkin Trans. 1* **1999**, 979–993, and references therein; see also: f) J. Petrignet, I. Prathap, S. Chandrasekhar, J. S. Yadav, R. Grée, *Angew. Chem.* **2007**, *119*, 6413–6416; *Angew. Chem. Int. Ed.* **2007**, *46*, 6297–6300; g) D. Cuperly, C. Crévisy, R. Grée, *J. Org. Chem.* **2003**, *68*, 6392–6399.

[10] The 1,3-diketone synthesis by a similar concept, consecutive reduction–aldol–oxidation reactions by Ru^{II} complex, has been reported, see: T. Fukuyama, T. Doi, S. Minamino, S. Omura, I. Ryu, *Angew. Chem.* **2007**, *119*, 5655–5657; *Angew. Chem. Int. Ed.* **2007**, *46*, 5559–5561, and references of related works therein.

[11] In these cases, treatment with TMSOTf gave a complex mixture of unidentified products. Thus, the crude product of Rh^{I}-catalyzed reaction was treated with Ac_2O instead of TMSOTf to afford **4d** and **8c**, respectively.



[12] It should be noted that in case of an allylic alcohol with no substituent on the α position, the *exo*-enolate **D′** generated might undergo isomerization to the more stable *endo*-enolate **I**, however, this isomerization did not take place as a major reaction pathway.



[13] 1-Alkyl-substituted allylic alcohols gave isomerized ketones only. It is likely the reactivity of the enolates is lower.

[14] For representative examples of γ-pyrone synthesis, see: a) Y. R. Lee, J. Y. Suk, B. S. Kim, *Org. Lett.* **2000**, *2*, 1387–1389; b) V. I. Tyvorskii, D. N. Bobrov, O. G. Kulinkovich, W. Aelterman. N. De Kimpeb, *Tetrahedron* **2000**, *56*, 7313–7318; c) S. Yamamura, S. Nishiyama, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2025–2037; d) Josemin, K. N. Nirmala, C. V. Asokan, *Tetrahedron Lett.* **1997**, *38*, 8391–8394; e) S. W. McCombie, W. A. Metz, D. Nazareno, B. B. Shankar, J. Tagat, *J. Org. Chem.* **1991**, *56*, 4963–4967, and references therein.

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