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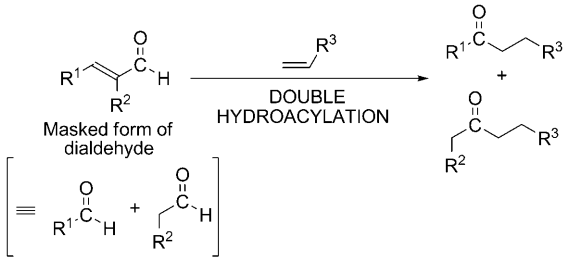
# Double Hydroacylation Reactions of Acyclic and Cyclic α,β-Unsaturated Aldehydes

**Kyung-Mi Cha, Hyejeong Lee, Jung-Woo Park, Yura Lee, Eun-Ae Jo, and Chul-Ho Jun*[a]**

*Dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday*

C–H bond activation has attracted great attention in the field of catalytic organic synthesis because it can be employed in atom economical C–C bond-forming reactions.[1] In particular, hydroacylation has emerged as a prominent example of novel C–H bond-activation reactions.[2] Among these processes, the chelation-assisted hydroacylation of alkenes with aldehydes has received great interest because decarbonylation can be avoided by using chelation-assistance by 2-aminopyridine.[3]

α,β-Unsaturated aldehydes, which have not been explored fully in the context of hydroacylation, are an interesting substrate family, because their hydroacylation reactions with alkenes could lead to the formation of two different ketones via a pathway involving retro-Mannich type C=C double-bond cleavage of initially generated β-aminoketimine intermediates.[4] It should be noted that some examples of C≡C triple-bond cleavage of alkynes and double-bond cleavage of α,β-unsaturated ketones, using retro-Mannich type cleavage procedures, have been reported.[5] In this manner, α,β-unsaturated aldehydes act as masked forms of two different aldehydes in the hydroacylation process (Scheme 1). Our recent studies leading to the development of a double hydroacylation reaction of acyclic and cyclic α,β-unsaturated aldehydes are described below. Herein, we report that these processes take place through a mechanistic pathway that involves 1,4-addition of a primary amine to the α,β-enone substrates and retro-Mannich-type fragmentation of resulting β-aminoketimine intermediates. In the case of chiral α,β-unsaturated cyclic aldehydes, enantiomers are generated in an enantiospecific manner by controlling the order of addition of two different alkenes.




Scheme 1. Double hydroacylation reactions of α,β-unsaturated aldehydes.

Reactions of α,β-unsaturated aldehydes with 1-alkenes are promoted by a mixture of catalysts that bring about chelation-assisted hydroacylation and retro-Mannich-type fragmentation. These processes yield two ketone products arising by the hydrolysis of the intermediate ketimines. For example, treatment of (*E*)-2-methyl-3-phenylacrylaldehyde (**1a**, 0.2 mmol) with 3,3-dimethylbut-1-ene (**2a**, 1.0 mmol) in the presence of chlorotris(triphenylphosphine)rhodium(I) (**3**, 5 mol% based on **1a**), 2-amino-3-picoline (**4**, 50 mol%), 4-trifluoromethylbenzoic acid (**5**, 10 mol%), and cyclohexylamine (**6a**, 100 mol%) at 130°C for 12 hours, followed by hydrolysis, leads to the generation of ketones **7a** and **8a** that were isolated in 99% and 78% yields, respectively (Table 1, entry 1). Reactions of other acyclic α,β-unsaturated aldehydes **1b** and **1c** with 1-alkenes **2b** and **2c** also take place in good yields to form the corresponding ketones, **7** and **8** (Table 1, entries 2–7).

Two possible reaction mechanisms, shown in Scheme 2, can be used to explain this process. In the first (Scheme 2a), initial chelation-assisted hydroacylation between **1a** and **2b** affords the corresponding α,β-unsaturated ketone **9a**, which undergoes conjugate addition and condensation with cyclo-

[a] K.-M. Cha, H. Lee, J.-W. Park, Y. Lee, E.-A. Jo, Prof. Dr. C.-H. Jun
Department of Chemistry and Centre
for Bioactive Molecular Hybrid (CBMH)
Yonsei University, 50 Yonsei-ro, Seodaemun-gu
Seoul 120-749 (Korea)
Fax: (+82) 2-3147-2644
E-mail: junch@yonsei.ac.kr

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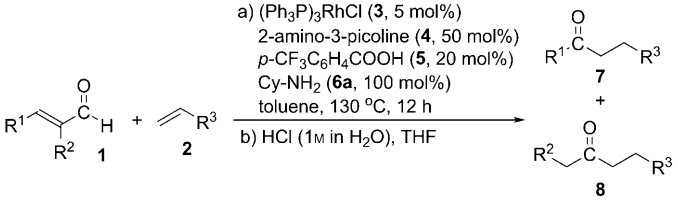
Table 1. Double hydroacylation reactions of α,β-unsaturated aldehyde (**1**) with olefins (**2**) in the presence of **3**, **4**, **5**, and **6a**.




| Entry | Aldehyde $R_1$,$R_2$ (**1**) | Olefin[a] $R_3$ (**2**) | Conversion (**7**/**8**) [%] | Yield [%] **7** | Yield [%] **8** |
|---|---|---|---|---|---|
| 1 | Ph, Me (**1a**) | $tC_4H_9$ (**2a**) | 100 (50:50) | 99 (**7a**) | 78 (**8a**) |
| 2 | | $nC_4H_9$ (**2b**) | 100 (61:39) | 82 (**7b**) | 53 (**8b**) |
| 3 | | $nC_{10}H_{21}$ (**2c**) | 100 (51:49) | 60 (**7c**) | 60 (**8c**) |
| 4 | Ph, H (**1b**) | **2a** | 100 (60:40) | 55 (**7a**) | 58 (**8d**) |
| 5 | | **2b** | 100 (69:31) | 84 (**7b**) | 78 (**8e**) |
| 6 | | **2c** | 100 (52:48) | 91 (**7c**) | 92 (**8f**) |
| 7 | Me, H (**1c**) | **2c** | n.d. | 53 (**7d**) | |

[a] 5 equivalents of **2** based on **1** (0.2 mmol) were used. THF = tetrahydrofuran. [b] Yield of isolated product. n.d. = not determined.

hexylamine (**6a**) to form β-aminoketimine **10a**. Retro-Mannich-type C=C double-bond cleavage gives aldimine **11** and enamine **12**. Aldimine **11** reacts further with **2a** through transimination and hydroiminoacylation to give ketimine **13**,[6] the precursor to ketone **7a** whereas hydrolysis of **12** affords **8a**. An alternate mechanism (Scheme 2b) begins with **6a** promoted C=C bond cleavage of aldehyde **1a** via the intermediate β-aminoaldimine **14** to generate aldimine **11** and enamine **15**. Subsequent hydroiminoacylation reactions of **11** and **15** lead to formation of ketimines, **13** and **12**, which upon hydrolysis give **7a** and **8a**.[7]

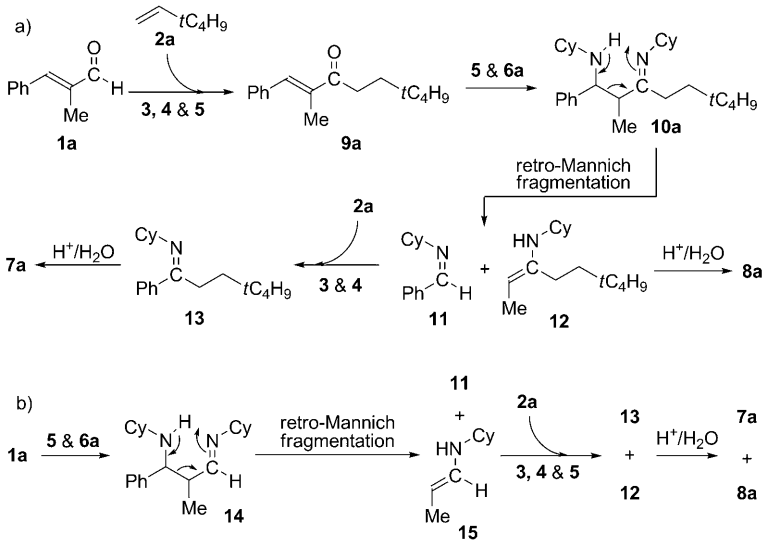
In order to gain information about which of these two mechanistic routes is operating, the progress of the reaction of **1a** with **2a**, performed at 120 °C using the catalyst mixture described above, was monitored following hydrolysis by GC (Figure 1). The results show that during a 1 hour period, about 50 % of the starting aldehyde **1a** is transformed into the hydroacylation product **9a** exclusively and, after approximately 2 hours, the final products **7a** and **8a** begin to form in nearly equal amounts, coinciding with the disappearance of **9a**. These observations demonstrate that the mechanism shown in Scheme 2a is responsible for this process.

1-Cycloalkenecarboxaldehydes are another interesting substrate family for the sequential hydroacylation/C–C bond-fragmentation process, because they can be regarded as synthetic equivalents of α,ω-dialdehydes. This observation is exemplified by the reaction of 1-cyclododecenecarboxaldehyde (**1d**) with alkene **2a**, carried out at 130 °C for 12 hours in the presence of **3**, **4**, **5**, and *n*-hexylamine (**6b**). Following hydrolytic work up, this process produces 2,2,20,20-tetramethylhenicosane-5,17-dione (**16a**) which was isolated in 68 % yield (Scheme 3).[8] Similar reactions of **1d** with other alkenes afford the respective diketones **16** in comparable yields.

In a manner that is different from the one-pot hydroacylation of **1d** described above, stepwise hydroacylation reactions of this aldehyde employing two different olefins can be used to generate unsymmetric diketones **16d** and **16e**. For example, exposure of **1d** to alkene **2a** in the presence of **3**, **4**, and **5** leads to the formation of 1-cyclododecenyl 3,3-dimethylbutyl ketone (**9b**) which was isolated in a 74 % yield (Scheme 4). Subsequently, sequential ring cleavage and hydroacylation reactions of **9b** with 1-hexene (**2b**) and trimethylvinylsilane (**2d**) form the respective unsymmetrical 1,12-diones **16d** and **16e** in moderate yields.

Another interesting substrate for this process is (−)-myrtenal (**1e**, [α] = −15°), a chiral bicyclic α,β-unsaturated aldehyde comprised of a six-membered cycloalkenyl group and four-membered cyclobutyl group. Reaction of **1e** with alkene **2a** employing the one-pot catalyst system described above at 130 °C for 48 hours results in formation of the symmetric homopinic acid analogue[9] **17a** in a 47 % isolated yield (Scheme 5).

An interesting feature of this process is that the cyclohexenyl group of **1e** is cleaved, leaving the strained cyclobutyl group. Moreover, stepwise hydroacylation reactions of myr-




Scheme 2. Two possible mechanisms for reaction of **1a** with **2a.**

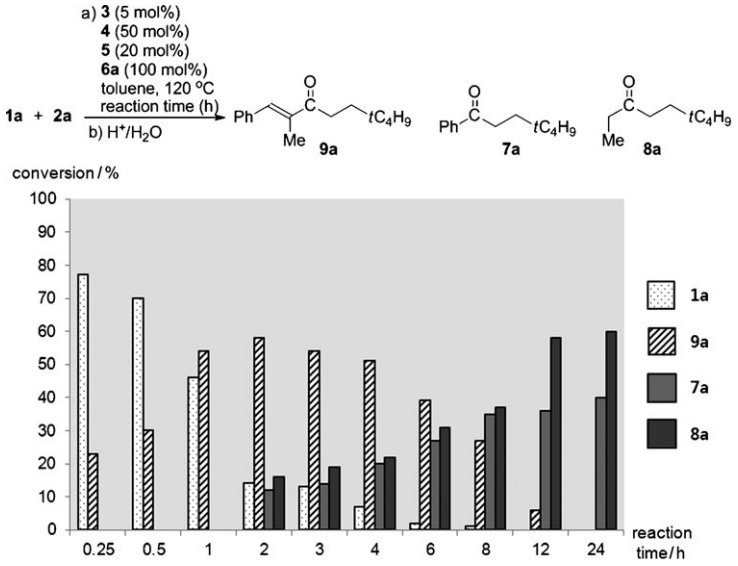
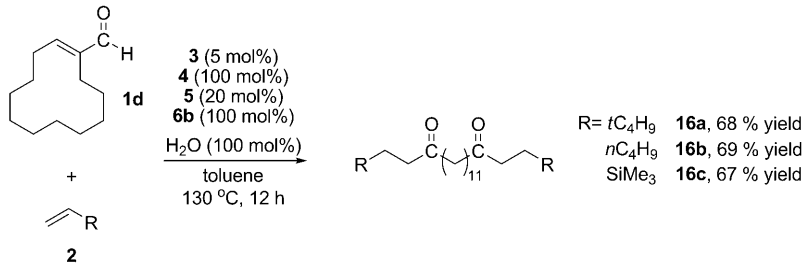


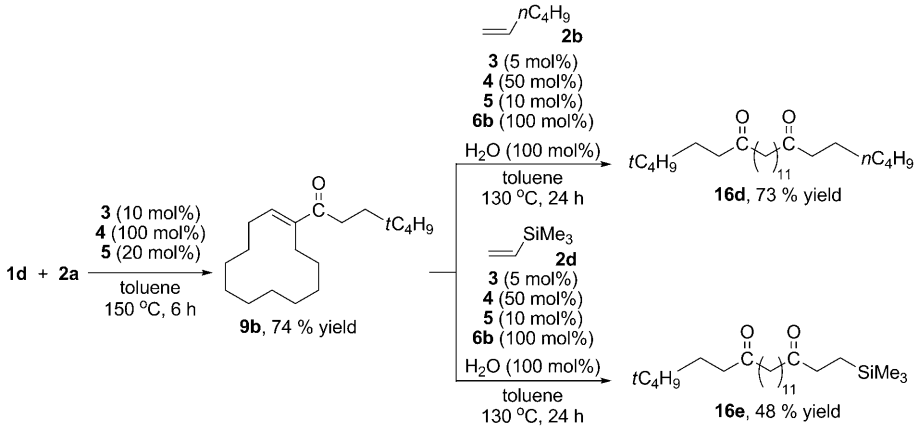

Figure 1. A plot of the ratios of the starting aldehyde **1a** and products **9a**, **7a**, and **8a** (determined by GC analysis) versus time in the reaction of **1a** with **2a** (ratio of **1a**/**2a** = 1:5) in the presence of **3**, **4**, **5**, and **6a**.




Scheme 3. Double hydroacylation of **1d** with 1-alkene **2** through C<=>C double bond cleavage. Yield is of isolated product.

tenal (**1e**) with two different olefins can be used to produce enantiomerically related chiral homopinic acid analogues (Scheme 6). For example, chelation-assisted hydroacylation of enantiopure myrtenal (**1e**) with alkene **2a** results in the generation of α,β-unsaturated ketone **9c** ([α] = −20.6°). Treatment of **9c** with alkene **2e** in the presence of the catalyst mixture results in sequential C–C bond cleavage and chelation-assisted hydroacylation to afford the (+)-rotating enantiomer of the chiral homopinic acid analogue **17b** ([α] = +2.7°). In contrast, sequential reaction of **1e** employing the reverse order of olefin addition (i.e., **2e** and then **2a**) under otherwise identical conditions leads to formation of the (−)-rotating enantiomer **17c** ([α] = −2.7°). The same results are observed for the reactions of myrtenal (**1e**) with olefins **2a** and **2f**, which produce the respective enantiomers **17d** ([α] = −3.5°) and **17e** ([α] = +3.5°. These observations show that the sequential hydroacylation protocol can be employed to generate enantiomers whose absolute configurations are governed by controlling the order of addition of two different alkenes.

In conclusion, the results of the studies described above demonstrate that double hydroacylation reactions of acyclic α,β-unsaturated aldehydes with alkenes can be employed to prepare two ketone products. Moreover, cycloalkenyl aldehydes undergo this process to afford diketones. Finally, double sequential hydroacylation reactions of the chiral cyclic α,β-unsaturated aldehyde myrtenal with two different alkenes produce chiral homopinic acid analogues, whose enantiomeric integrity can be regulated by controlling the order of alkene addition.




Scheme 4. Stepwise double hydroacylation reactions of **1d** with two different 1-alkenes (**2**). Yield is of isolated product.

## Experimental Section

*Representative Procedure for the Double Hydroacylation Reaction (Table 1, entry 1)*

A screw-capped pressure vial (1.0 mL) was charged with (*E*)-2-methyl-3-phenylacrylaldehyde (**1a**, 29.2 mg, 0.2 mmol), 3,3-dimethyl-1-butene (**2a**, 84 mg, 1.0 mmol), $(Ph_3P)_3RhCl$ (**3**, 9.25 mg, 0.01 mmol), 2-amino-3-picoline (**4**, 10.8 mg, 0.1 mmol), *para*-trifluoromethyl benzoic acid (**5**, 7.6 mg, 0.04 mmol), cy-

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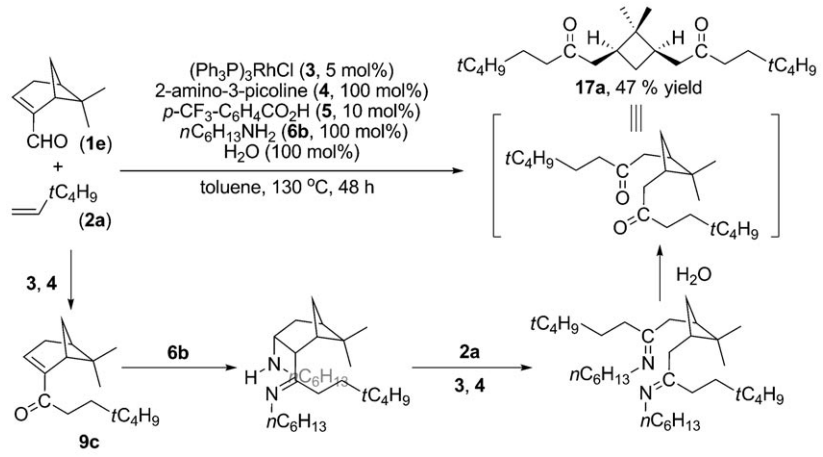
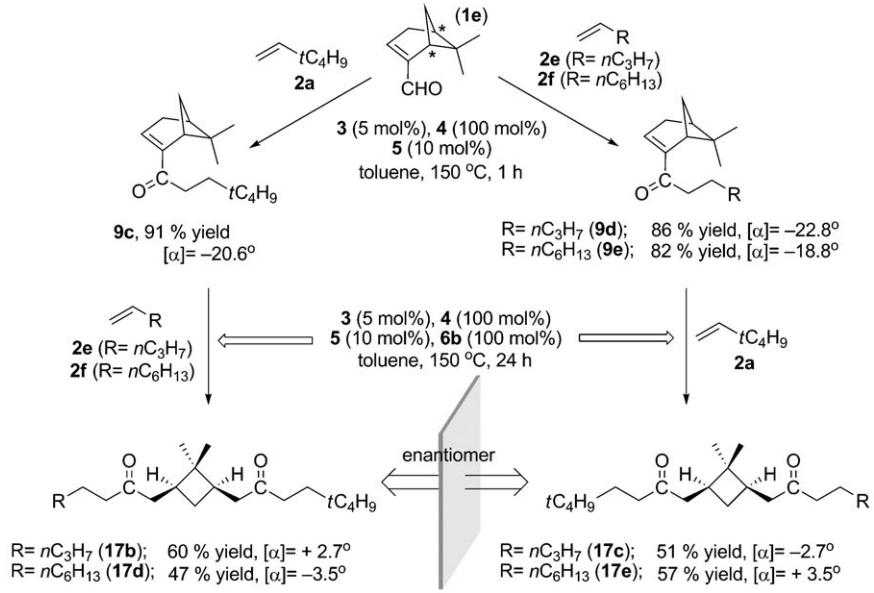



Scheme 5. Formation of *sym*-homopinic acid analogue **17a** by double hydroacylations of myrtenal (**1e**) with **2a** (ratio of **1e**/**2a** = 1:3) through ring cleavage of the C=C double bond. Yield is of isolated product.




Scheme 6. The formation of enantiomeric unsymmetric homopinic acid analogues, **17b**/**17c** and **17d**/**17e**, by the stepwise sequential hydroacylation reaction of myrtenal (**1e**) with two different 1-alkenes. Yield is of isolated product.

clohexylamine (**6a**, 19.8 mg, 0.2 mmol), and toluene (100 mg). The resulting solution was stirred at 130 °C for 12 h and filtered through a silica gel pad. The mixture was then treated with 1 M HCl and extracted with diethyl ether. The organic layer was dried over $MgSO_4$ and filtered through celite pad. Concentration in vacuo gave a residue that was subjected to column chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1) to give **7a** (99 %) and **8a** (78 %).

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**Keywords:** acylation · C–H activation · cleavage reactions · homogeneous catalysis · transition metals

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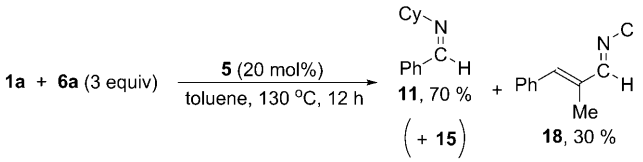
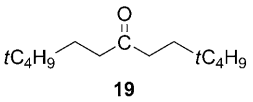
[6] C.-H. Jun, J.-B. Hong, *Org. Lett.* **1999**, *1*, 887–889.
[7] When the reaction of **1a** with **6b** is carried out at 130 °C for 12 h in the presence of **5**, the ratio of aldimine **11** and **18** is 70:30 (GC analysis).




[8] Among various primary amines tested, *n*-hexylamine (**6b**) is the most reactive. In this case, a small amount of 2,2,8,8-tetramethylnonan-5-one (**19**) is generated as a side-product, likely from reaction between **6b** and **2a**. For a related reference, see: C.-H. Jun, K.-Y. Chung, J.-B. Hong, *Org. Lett.* **2001**, *3*, 785–787.




**19**

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