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A One-Pot Reformatsky/Cyclopropanation Sequence Induced by Diethylzinc

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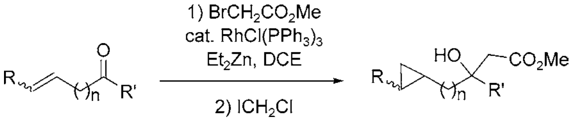
ABSTRACT



A one-pot Reformatsky/cyclopropanation sequence induced by diethylzinc allows the transformation of *ω*-unsaturated ketones and aldehydes to *ω*-cyclopropyl alcohols.

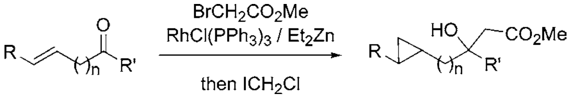
Synthetic organic chemistry has developed several highly efficient procedures that allow the preparation of complex molecules with excellent regio-, chemo-, diastereo-, and enantioselectivity. In general, in a traditional step-by-step approach, each intermediate needs to be purified. Today, it is not a question of what we can synthesize but how we can do it, and the increase in efficiency has to be taken into consideration as well as the amount of labor and purification.

"Domino" or "cascade" reactions are attractive in organic synthesis, as several bonds are formed in one sequence and structural complexity increases during the process. The example of biomimetic ring closure of steroids from squalene epoxide, which was transformed selectively into lanosterol,[1a] has been used as a method for the synthesis of progesterone.[1b] Anionic, cationic, radical, or pericyclic reactions or transition metal-catalyzed reactions can be implied in "domino" reactions.[2]

The development of two or more sequential reactions, mediated by the same catalyst precursor, is a particularly attractive process. For example, the ability of Grubbs' catalysts to function as a catalyst for olefin metatheses, atom transfer reactions, olefin hydrogenations, and isomerizations has led to several examples where combinations of these transformations provide efficient entries into useful products.[3]

Sequential reactions can also be achieved by using compatible catalysts when they are able to perform reactions with different rates.[4] Recently, we have demonstrated that a one-pot cross-metathesis/hydrogenation/lactonization reaction could take place between an olefin and an α,*β*-unsaturated carbonyl compound in the presence of ruthenium alkylidene complexes and PtO_2 under 1 atm of hydrogen.[5] Another attractive process is a one-pot procedure induced by one reagent. Here, we report that a one-pot Reformatsky/cyclopropanation sequence can be performed on *ω*-unsaturated ketones to produce *ω*-cyclopropyl alcohols by using the same reagent, diethylzinc (Et_2Zn) (Scheme 1).

Scheme 1



The Reformatsky reaction is a well-recognized carbon−carbon bond-forming reaction of α-haloesters with aldehydes or ketones in the presence of zinc metal to give *β*-hydroxyesters.[6] Since the reaction is initiated by insertion

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(1) (a) Corey, E. J.; Ortiz de Montellano, P. R.; Yamamoto, H. *J. Am. Chem. Soc.* **1968**, *90*, 6254. Corey, E. J.; Virgil, S. C.; Liu, D. R.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 1524. (b) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9.

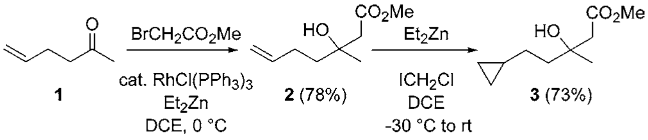
(2) (a) Catellani, M. *Synlett* **2003**, 298. (b) McCaroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215. (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

10.1021/ol048142b CCC: $30.25

of zinc into the halogen−carbon bond, efforts have been focused on the activation of zinc. Recently, it has been shown that aromatic and aliphatic aldehydes reacted smoothly with methyl bromoacetate in the presence of the Wilkinson's catalyst and diethylzinc to give β-hydroxyesters in good yields.[7] Diethylzinc can also react with chloroiodomethane in dichloroethane to produce (chloromethyl)ethylzinc, which is the precursor of the carbene intermediate for cyclopropanation.[8] The use of diethylzinc as a common reagent to achieve a tandem Reformatsky/cyclopropanation reaction of ω-unsaturated aldehydes and ketones was envisaged.

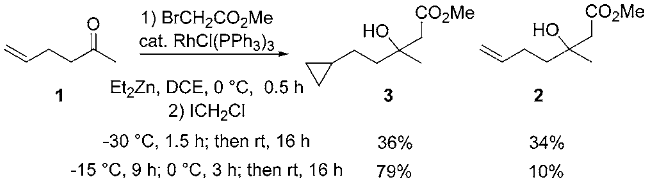
Before achieving the tandem Reformatsky/cyclopropanation one-pot sequence, we had to verify that the Reformatsky reaction could take place in dichloroethane, which is the solvent used for the cyclopropanation. After treatment of a solution of enone **1** in dichloroethane (DCE) at 0 °C with methyl bromoacetate (1 equiv) and Et_2Zn (2 equiv) in the presence of the Wilkinson's catalyst [$RhCl(PPh_3)_3$], the tertiary alcohol **2** was isolated in 78% yield. This yield was identical to that obtained when the reaction was performed in THF. Compound **2** was then treated with chloroiodomethane (6 equiv) in the presence of Et_2Zn (3 equiv) at −15 °C in DCE, and cyclopropane **3** was isolated in 73% yield. The overall yield of **3** was 57% (Scheme 2).

Scheme 2



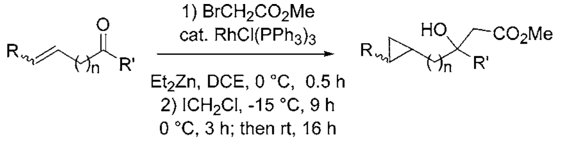
As the Reformatsky and cyclopropanation reactions can be performed in DCE, the one-pot Reformatsky/cyclopropanation sequence was performed on enone **1**. Enone **1** was treated with methyl bromoacetate (1 equiv) in the presence of $RhCl(PPh_3)_3$ (5 mol %) and Et_2Zn (5 equiv) in DCE at 0 °C. After 30 min, the reaction mixture was cooled to −30 °C and ICH_2Cl (6 equiv) was added. After 1.5 h at −30 °C, the temperature was raised to room temperature, and after 16 h, the reaction mixture was quenched with a saturated NH_4Cl aqueous solution. The desired cyclopropyl alcohol **3** and the Reformatsky compound **2** were isolated in 36 and 34% yield, respectively. To increase the conversion of **2** to **3**, the cyclopropanation was carried out at −15 °C for 9 h; then, the temperature was raised to 0 °C, and after 3 h, the reaction was left at room temperature for 16 h. Under these conditions, compound **2** was isolated in only 10% yield and the desired cyclopropyl alcohol **3** was obtained in 79% yield (Scheme 3). By applying a one-pot Reformatsky/cyclopropanation sequence to enone **1**, we obtained a much better yield of **3** than when the two reactions were performed separately (79 vs 57%). It is worth noting that the cyclopropanation can be performed in a reverse mode, as usually the substrate is added to the carbene.[8]

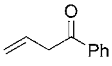
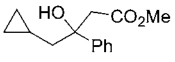
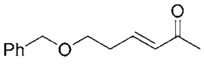
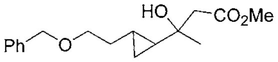
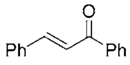
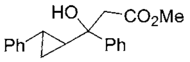
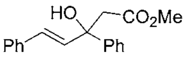
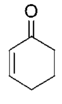
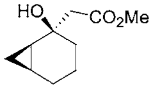
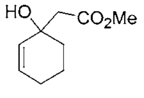
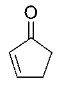
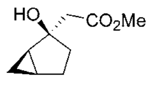
Scheme 3



The one-pot Reformatsky/cyclopropanation was then generalized to acyclic and cyclic ω-unsaturated ketones by using the optimized conditions, and the results are reported in Table 1. Under the one-pot Reformatsky/cyclopropanation sequence, allyl phenyl ketone **4** was transformed to the cyclopropyl alcohol **9** (71%). Cyclopropyl carbinols **10** and **11** were isolated as one diastereomer in 43 and 52% yield from the conjugated ketones **5** and **6**, respectively.

Table 1. Cyclopropyl Alcohols from Unsaturated Ketones



Entry	Starting Material	Products (Yields)
1	 **4**	 **9** (71%)
2	 **5**	 **10** (43%)
3	 **6**	 **11** (52%)  **11'** (10%)
4	 **7**	 **12** (68%)  **12'** (5%)
5	 **8**	 **13** (31%)

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[3] (a) Arjona, O.; Csáky, A. G.; Medel, R.; Plumet, J. *J. Org. Chem.* **2002**, *67*, 1380. (b) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390. (c) Schmidt, B. *Eur. J. Org. Chem.* **2003**, 816.

[4] Review: (a) Lee, J. M.; Na, Y.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (b) Siebeneicher, H.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3042. (c) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (d) Ko, S.; Lee, C.; Choi, M. G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607.

[5] Cossy, J.; Bargiggia, F.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 459.

[6] Reformatsky, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1210.

[7] Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549.

[8] (a) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53. (b) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.

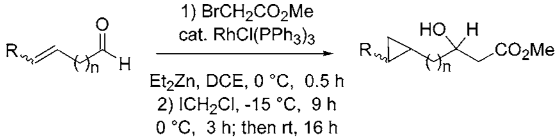
It is worth noting that for compound **6**, 10% of the Reformatsky compound **11′** was also isolated. The bicyclic cyclopropyl carbinol **12** (68%) was synthesized from cyclohexenone **7**, and bicyclic cyclopropyl carbinol **13** was formed from cyclopentenone **8** with a moderate yield of 31% due to the fact that cyclopentenone polymerizes easily. Furthermore, for enones **7** and **8**, only traces of the Reformatsky compounds were detected.

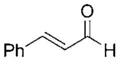
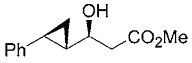
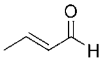
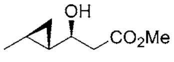
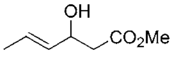
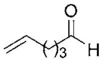
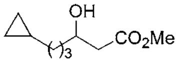
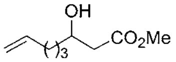
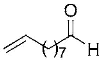
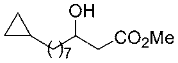
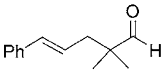
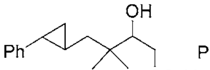
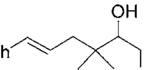
The one-pot Reformatsky/cyclopropanation sequence was also applied to aldehydes **14**−**18** by using the same experimental conditions as for ω-unsaturated ketones. The results are reported in Table 2.

When α,β-unsaturated aldehydes **14** and **15** were treated under the one-pot Reformatsky/cyclopropanation conditions, compounds **19** (21%) and **20** (48%) were obtained in moderate yields as the expected single *trans*,*syn* diastereomers.[9] In the case of ω-unsaturated aldehydes **16**−**18**, the Reformatsky/cyclopropanation compounds were isolated as **21**, **22**, and **23** in good yields of 74, 88, and 71%, respectively. It is worth noting that **23** was isolated as a mixture of two diastereomers in a ratio of 1.5/1.[10] Furthermore, compounds **21** and **23** were accompanied by the respective Reformatsky compounds **21′** and **23′** in aproximatively 10% yield.

We have demonstrated that a one-pot Reformatsky/cyclopropanation sequence can be utilized to transform ω-unsaturated ketones and aldehydes to the corresponding cyclopropyl alcohols by using a common reagent, Et_2Zn, to generate the Reformatsky reagent and a carbene intermediate. This procedure, which avoids numerous purifications and the handling of the hazardous Et_2Zn several times, led to the formation of ω-cyclopropyl alcohols from ω-unsaturated ketones and aldehydes more efficiently than when the Reformatsky and cyclopropanation reactions were performed stepwise.

Table 2. Cyclopropyl Alcohols from Unsaturated Aldehydes



Entry	Starting Material	Products (Yields)	
1	 **14**	 **19** (21%)	
2	 **15**	 **20** (48%)	 **20'** (3%)
3	 **16**	 **21** (74%)	 **21'** (7%)
4	 **17**	 **22** (88%)	
5	 **18**	 **23** (71%)	 **23'** (13%)

Supporting Information Available: Experimental procedures and characterization data and/or a reference for compounds **2**, **3**, **9**−**13**, **19**−**23**, **11′**, **12′**, **20′**, **21′**, and **23′**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL048142B

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[9] Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966. Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257.

[10] Ratio of diastereomers was determined by analysis of the ^{1}H NMR spectra.