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Rhodium-Catalyzed Reformatsky-Type Reaction

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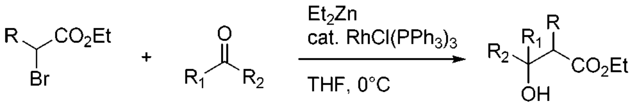
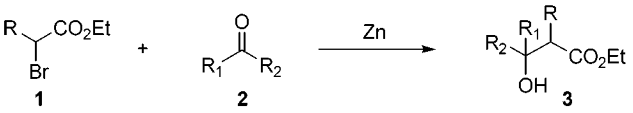
ABSTRACT



A novel Reformatsky-type reaction was developed using $RhCl(PPh_3)_3$ and diethylzinc. Inter- and intramolecular Reformatsky-type reactions were achieved efficiently under mild reaction conditions to give β-hydroxy esters.

The Reformatsky reaction is a well-recognized carbon−carbon bond-forming reaction of an α-halo ester with an aldehyde or a ketone in the presence of zinc metal to give a β-hydroxy ester (Scheme 1).[1]

Scheme 1 The Reformatsky Reaction



A particular advantage of this reaction stems from the fact that the site of reaction is strictly determined by the halogen moiety. This may be advantageously used for regioselective enolate formation in polycarbonyl compounds which are difficult to achieve by base-induced proton abstraction.[2] To extend the scope of the Reformatsky reaction, variable parameters have been extensively investigated. Since the reaction is initiated by insertion of zinc into the halogen−carbon bond, most efforts have been focused on the activation of zinc or the utilization of other metals, such as magnesium,[3] cadmium,[4] nickel,[5] indium,[6] cerium,[7] and lithium,[8] to facilitate the insertion. With activated zincs, such as Rieke-Zn,[9] Zn−Cu couple,[10] Zn/Ag-graphite,[11] and so on, the Reformatsky reaction can be conducted under milder reaction conditions. However, these reagents usually must be freshly prepared because of their instability to air and moisture. Although little attention has been focused on the catalytic version of this type of reaction, there is an interesting variant which utilized zinc and a catalytic amount of titanocene dichloride.[12] This prompted us to investigate an efficient and mild transition metal-catalyzed Reformatsky-type reaction. We would like to disclose herein a new Reformatsky-type reaction promoted by rhodium catalysis and conducted under mild reaction conditions.

We first studied the intermolecular reaction as shown in Table 1.[13]

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(1) For recent reviews of the Reformatsky reaction, see: (a) Fürstner, A. *Synthesis* **1989**, 571. (b) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; New York, 1991; Vol. 2, p 277. (c) Fürstner, A. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds; Oxford University Press: New York, 1999; p 287.

(2) For examples, see: (a) Vedejs, E.; Ahmad, S. *Tetrahedron Lett.* **1988**, *29*, 2291. (b) Dener, J. M.; Zhang, L. H.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 1159. (c) Binch, H. M.; Griffin, A. M.; Schwidetzky, S.; Ramsay, M. V. J.; Gallagher, T.; Lichtenthaler, F. W. *J. Chem. Soc., Chem. Commun.* **1995**, 967.

(3) (a) Moriwake, T. *J. Org. Chem.* **1996**, *31*, 983. (b) Borno, A.; Bigley, D. B. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1311.

(4) Burkhardt, E.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 416.

(5) Inaba, S.-I.; Rieke, R. D. *Tetrahedron Lett.* **1985**, *26*, 155.

(6) For recent review, see: Cintas, P. *Synlett* **1995**, 1087.

(7) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

(8) Villieras, J.; Perriot, P.; Bourgain, M.; Normant, J. F. *J. Organomet. Chem.* **1975**, *102*, 129.

(9) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452.

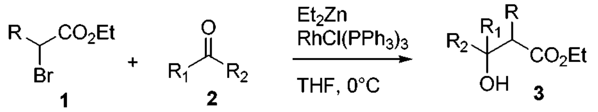
(10) Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698.

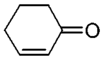
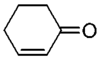
(11) Csuk, R.; Fürstner, A.; Weidmann, H. *J. Chem. Soc., Chem. Commun.* **1986**, 775.

(12) Ding, Y.; Zhao G. *J. Chem. Soc., Chem. Commun.* **1992**, 941.

10.1021/ol006268c CCC: $19.00

Table 1. Intermolecular Reaction

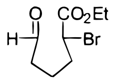
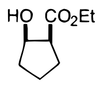
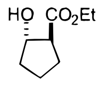
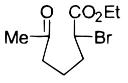
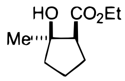
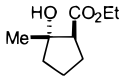
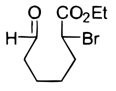
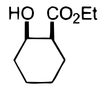
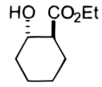
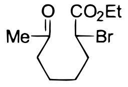
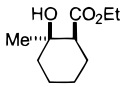
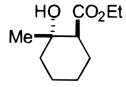


entry	R	R_1	R_2	**3** (isolated yield)
1	H	H	Ph	**3a** (82)
2	Me	H	Ph	**3b** (74) (syn/anti = 1/1)
3	H	H	$Ph(CH_2)_2$	**3c** (85)
4	Me	H	$Ph(CH_2)_2$	**3d** (76) (syn/anti = 1/1)
5	H	Me	Ph	**3e** (77)
6	Me	Me	Ph	**3f** (84) (syn/anti = 1/1)
7	H	Me	$Ph(CH_2)_2$	**3g** (77)
8	H	$-(CH_2)_5-$		**3h** (79)
9	Me	$-(CH_2)_5-$		**3i** (65)
10	H			**3j** (62)
11	Me			**3k** (49) 2 / 1 = (1R*,1'S*) / (1R*,1'R*)

Aromatic and aliphatic aldehydes or ketones reacted smoothly with ethyl bromoacetate or ethyl 2-bromopropionate in the presence of Wilkinson's catalyst and diethylzinc[14] to give β-hydroxy esters[15] in moderate to good yields. It is noteworthy that *no ethyl adduct was produced* and *the reactions were usually completed within 5 min* under the conditions described above. When ethyl 2-bromopropionate was used as the α-halo ester, essentially no diastereoselectivity[16] was observed under the conditions employed (entries 2, 4, 6, and 11). With 2-cyclohexenone as a Reformatsky acceptor, only 1,2-adducts were obtained (entries 10 and 11), as is the case for conventional Reformatsky conditions. In the absence of either RhCl(PPh$_3$)$_3$ or diethylzinc, recovery of the starting material was observed after 1 h at 0 °C. This suggests that Rh(I) efficiently catalyzes the reaction.

Encouraged by the results obtained above, we next focused our attention on the intramolecular reaction. As shown in Table 2, the reaction developed above also effected intramolecular carbon−carbon bond formation, as expected, providing secondary and tertiary cycloalkanols in good to excellent yields under similar reaction conditions. For the reactions forming five-membered rings (entries 1 and 2), high diastereoselectivities were observed, giving *cis*-hydroxy ester **5a** as the major product. This result should be attributed to the sterically and electronically more favored rigid conformation of the transition state including zinc as depicted in Figure 1.[17]

Table 2. Intermolecular Reaction

entry	substrate	products (isolated yield; %)	
1	 **4a**	 **5a** (63)	 **6a** (5)
2	 **4b**	 **5b** (59)	 **6b** (5)
3	 **4c**	 **5c** (41)	 **6c** (33)
4	 **4d**	 **5d** (65)	 **6d** (26)

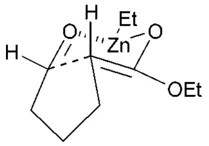


Figure 1. Transition state for zinc enolate providing *cis*-hydroxy ester **5a**.

On the other hand, in entries 3 and 4, reactions forming six-membered rings, the stereoselections were diminished remarkably. From the results obtained above, it is also apparent that zinc also plays an important role in the stereocontrol of the reaction as previously reported.[17]

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(13) **Representative procedure for the intermolecular Reformatsky-type reaction:** To a stirred solution of RhCl(PPh$_3$)$_3$ (5 mol %) in THF at 0 °C were added α-halo ester **1**, carbonyl compound **2**, and a ca. 1.0 M hexane solution of Et$_2$Zn (2.2 molar equiv). After stirring for 5 min at 0 °C, saturated aqueous NaHCO$_3$ was added. The reaction was filtered, and the filtrate was partitioned between Et$_2$O and brine. The organic extract was dried (Na$_2$SO$_4$), and the residue was purified by column chromatography on silica gel.

(14) In entry 1, Table 1, the reaction gave **3a** in a 32% yield, and unreacted benzaldehyde was recovered (66%) with 1.1 molar equiv of diethylzinc.

(15) **3a:** Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796. **3b:** Hart, J. D.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457. **3c:** Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. **3d:** Kiyooka, S.; Shahid, K. A.; Hena, M. A. *Tetrahedron Lett.* **1999**, *40*, 6447. **3e:** Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453. **3f:** See ref 7. **3g:** Martin, J.; Pinhey, J. T. *Molecules* **1998**, *3*, M59. **3h:** Couffignal, R.; Gaudemar, M. *J. Organomet. Chem.* **1973**, *60*, 209. **3i:** Enholm, E. J.; Jiang, S.; Abboud, K. *J. Org. Chem.* **1993**, *58*, 4061. **3j:** Conan, A.; Sibille, S.; Perichon, J. *J. Org. Chem.* **1991**, *56*, 2018. **3k:** Ruano, J. L. G.; Barros, D.; Maestro, M. C.; Araya-Maturana, R.; Fischer, J. *J. Org. Chem.* **1996**, *61*, 9462.

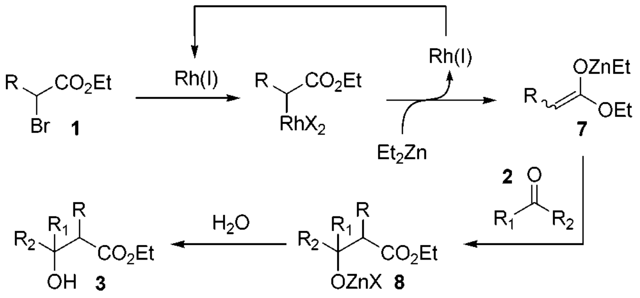
(16) Under the conventional Reformatsky reaction conditions, the *syn*:*anti* product ratios are 37:63 for **3b** and 67:33 for **3f** (refs 1 and 17).

(17) Heathcock, C. H.; In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 144.

On the basis of the detailed mechanistic investigation of the ethylzinc enolate formation from 2-bromo-4,4-dimethyl-3-pentanone and diethylzinc by Heathcock,[18] a plausible mechanism was proposed as depicted in Scheme 2, where oxidative addition of α-halo ester **1** into Rh(I) initiates the reaction. After formation of a rhodium(III) complex, transmetalation with diethylzinc produces ethylzinc enolate **7** and Rh(I), by which the reaction could be catalyzed again. Nucleophilic addition of **7** to carbonyl compound **2** would then afford zinc alkoxide **8**, which upon hydrolysis should give *β*-hydroxy ester **3**.

Thus, we have developed a mild and efficient Reformatsky-type reaction catalyzed by $RhCl(PPh_3)_3$ and diethylzinc which can be conducted under mild reaction conditions. Extension of this methodology is now under investigation in this laboratory.

Scheme 2. Proposed Mechanism for the Rhodium-Catalyzed Reformatsky-Type Reaction



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

OL006268C

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[18] Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069. Palmer and Reid reported the generation of *n*-propylzinc ester enolate from (−)-menthyl bromoacetate and di-*n*-propylzinc. *However, their condition for preparing zinc enolate was relatively vigorous compared to ours developed above*, see: Palmer, M. H.; Reid, J. A. *J. Chem. Soc*. **1962**, 1762.