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High Chelation Control of Three Contiguous Stereogenic Centers in the Reformatsky Reactions of Indium Enolates with α-Hydroxy Ketones: Unexpected Stereochemistry of Lactone Formation

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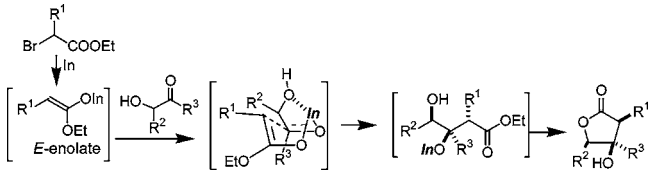
ABSTRACT



A boat-type of chelated bicyclic transition state involving highly diastereoselective construction of three contiguous stereogenic centers in the Reformatsky reaction of indium enolates with α-alkoxy/hydroxy ketones is proposed. α-Hydroxy ketones with indium enolates furnished highly diastereoselective lactones, while α-alkoxy ketones gave acyclic esters in moderate selectivities. X-ray structure analyses of key products unequivocally revealed the unexpected stereochemistry of products and the reaction pathway.

A major challenge in synthetic organic chemistry is stereochemical control during the C−C bond construction. Stereoselective additions of organometallic reagents to carbonyl compounds are the backbone of organic synthesis. The control of stereogenic centers in the additions to carbonyl compounds leading to diastereomers demands one of the following: (a) bulky substituents in the starting reagents, (b) a cyclic/rigid transition state, and (c) a chelation-controlled addition. Among the organometallic reactions, Reformatsky reactions are well-established processes for the C−C bond formation.[1,2] However, the protocols for highly stereoselective construction of stereogenic centers under the Reformatsky conditions are not well explored with respect to ketones in comparison with aldehydes.[3] Despite the rapid developments, to the best of our knowledge, there exists no report on the Reformatsky reaction of α-hydroxy ketone with zinc

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(2) For some reviews on Reformatsky reactions, 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) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325. (d) Orsini, F.; Sello, G. *Curr. Org. Synth.* **2004**, *1*, 111.

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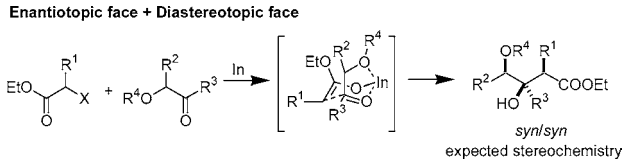
enolate except our own example using a tin-based reagent.[2,4] This is because the chelation-controlled nucleophilic addition to carbonyl compounds with free hydroxyl moieties without protection is a tough task. Perhaps the organometals for chelates are readily quenched by the protic sites.

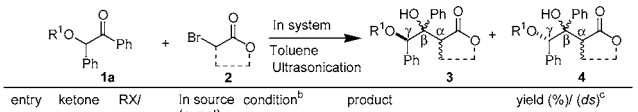
Recently, we reported the efficient construction of two stereogenic centers in the Reformatsky-type addition of indium enolates to ketones.[5] The cyclic chelation transition state is essential for the excellent stereoselectivity (over 98%) from the combination of α-alkoxy ketones/β-keto esters and indium enolates. In addition, the reaction conditions have been optimized for the strict chelation, employing In(I) enolate in toluene solvent under ultrasonication at room temperature. Taking an impetus from this observation, we easily envisaged that if α-substituted α-alkoxy ketone and α-substituted α-halo ester were treated, the stereoselective construction of three contiguous stereogenic centers would be completed as illustrated in Scheme 1, in which a chair-like transition state would furnish a syn/syn adduct. Herein, we report the excitingly unexpected efficient stereochemical outcome and mechanism of the Reformatsky reactions of indium enolates[6−8] with α-hydroxy ketones to complete the streocontrol of three contiguous streogenic centers.

Scheme 1



At first, under the established reaction conditions for the two stereogenic centers, the reaction of **1a** and **2a** in toluene in the presence of In(I)X system was carried out. However, no addition took place (entry 1, Table 1) because of very low reactivity of the linear α-bromo ester **2a** in toluene. Although the reaction was effectively promoted in THF solvent, a mixture of four stereoisomers was observed in ^{1}H NMR. The column chromatographic purification afforded only the major isomer **3a** of 80% yield in pure form (entry 2). Next, the cyclic bromo ester **2b** which was very active toward indium species was employed instead of **2a** to afford only two isomers **3b**/**4b** under ultrasonication in toluene, in which the maximum diastereoselectivity was 80:20 (**3b**/**4b**, entry 4). In contrast, no selectivity was achieved in THF (entry 3). In a further investigation, a bulky alkoxy moiety perhaps disturbed the chlelation to lose the sterocontrol (entry 5).

Table 1



entry	ketone (mmol)[a]	RX/ (mmol)[a]	In source (mmol)	condition[b] (h)	product	yield (%)/ (*ds*)[c]
1	**1a** (0.5)	**2a**(1.0)	InCl (1.0)	US (3)		NR
2	**1a** (1.0)	**2a** (1.6)	In (1.1)	67 °C (1)	**3a**	**3a**; 80[d]
3	**1a** (1.0)	**2b** (2.0)	In (1.2)	rt (4)	**3b**[f] **4b**[f]	95 (**3b**:**4b** = 50:50)[e]
4	**1a** (0.5)	**2b**(1.0)	InCl (1.0)	US (2)	**3b**[f] **4b**[f]	95 (**3b**:**4b** = 80:20)
5	**1b** (0.5)	**2b** (1.0)	InI (1.0)	US (2)	**3c** **4c**	82 (**3c**:**4c** = 50:50)

[a] **1a**: R^1 = Me; **1b**: R^1 = Pr^i; **2a**: ethyl 2-bromopropionate; **2b**: 2-bromo-γ-butyrolactone. [b] US = ultrasonication (38 kHz, 120 W) at 25 °C in dry toluene (2 mL). [c] Diastereoselectivities were determined from the crude ^{1}H NMR spectra. [d] THF was used, isolated yield for major isomer **3a**. For the X-ray structure see the Supporting Information; minor isomers were isolated as a mixture. [e] THF was used. [f] X-ray structure analysis revealed the stereochemistry.

Although we screened the reactions using indium, In(I)X, and In−InCl$_3$ systems[5] under various conditions to obtain a single isomer, at this stage a complete stereocontrol over three stereogenic centers could not be established using α-alkoxy ketones.

Stereochemistry. The stereochemistries of adducts **3a**, **3b**, and **4b** were unambiguously established from the single-crystal X-ray structure analyses. The stereochemistry between OH (C$^\beta$) and OMe (C$^\gamma$) moieties in all the products (**3** and **4**) is syn. This undoubtedly indicates that the syn stereochemistry has been constructed by the perfect chelation-controlled reaction mechanism. Notably, the expected stereochemistry between (C$^\alpha$) and (C$^\beta$) is syn; however, the obtained stereochemistry of major isomers **3a** and **3b** is anti.

Although a fair stereocontrol was established in the above reactions, the stereochemistry obtained was unexpected one.

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(6) For some reviews on indium reagents, see: (a) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (b) Cintas, P. *Synlett* **1995**, 1087. (c) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959. (d) Araki, S.; Hirashita, T. *Main Group Met. Org. Synth.* **2004**, *1*, 323. (e) Chan, T. H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (f) Loh, T.-P. *Sci. Synth.* **2004**, *7*, 413. (g) Babu, S. A. *Synlett* **2002**, 531. (h) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (i) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 1149. (j) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16. (k) Kumar, S.; Kaur, P.; Kumar, V. *Curr. Org. Chem.* **2005**, *9*, 1205.

(7) For the early works on indium-based nondiastereoselective Reformatsky reactions, see: (a) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron* **2001**, *57*, 9453. (b) Chao, L.-C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253. (c) Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453. (d) Schick, H.; Ludwig, R.; Schwarz, K.-H.; Kleiner, K.; Kunath, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1191. (e) Araki, S.; Katsumura, N.; Kawasaki, K.-I.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 499. (f) Yi, X.-H.; Meng, Y.; Li, C.-J. *Tetrahedron Lett.* **1997**, *38*, 4731.

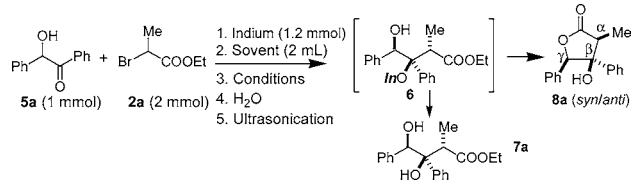
(8) For some recent papers on indium reagents, see: (a) Min, J.-H.; Jung, S.-Y.; Wu, B.; Oh, J. T.; Lah, M. S.; Koo, S. *Org. Lett.* **2006**, *8*, 1459. (b) Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2005**, *7*, 2767. (c) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464. (d) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793. (e) Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 7186. (f) Loh, T.-P.; Yin, Z.; Song, H.-S.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 911. (g) Yi, X.-H.; Meng, Y.; Li, C.-J. *J. Chem. Soc, Chem. Commun.***1998**, 449. (h) Hirashita, T.; Kamei, T.; Satake, M.; Horie, T.; Shimizu, H.; Araki, S. *Org. Biomol. Chem.* **2003**, *1*, 3799. (i) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *Synlett* **2004**, 1223. (j) Paquette, L. A. *Synthesis* **2003**, 765. (k) Khan, F. A.; Dash, J. *E. J. Org. Chem.* **2004**, 2692.

So, to examine the details and achieve an absolute stereocontrol we had to aim to obtain only a single isomer by treating α-hydroxy ketones instead of α-alkoxy ketones.[9] We effectively believed that a very strong chelation control by the hydroxyl moiety would lead to the perfect diastereoselection through a most rigid transition state.

Though no reports exist on the zinc-mediated Reformatsky conditions for the chelation-controlled reaction using free hydroxyl moieties, we envisioned the indium-mediated reactions will lead to the products because of its moisture tolerance.[4,8]

Surprisingly, the trial addition of **2a** to α-hydroxy ketone **5a** afforded the highly diastereoselective lactone **8a** (87% yield, ds 92%) as an exclusive product constructed with three contiguous stereogenic centers (entry 1, Table 2), in which

Table 2

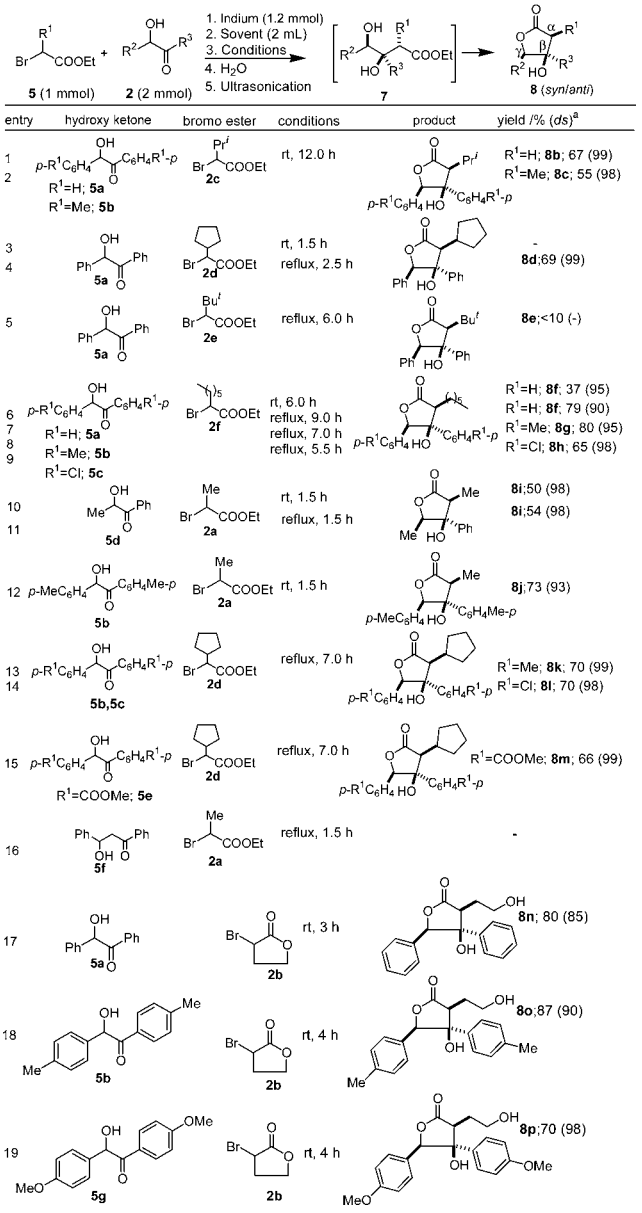


entry	metal	solvent	conditions (h)	yield of **7a**/%	yield of **8a**/% (ds)[a]
1	In	THF	0 °C, 1.5	7	87 (92)
2	In	THF	rt, 1.5	7	89 (92)
3	InCl	THF	rt, 1.5	0	61 (96)
4	In	THF	reflux, 1.5	9	69 (94)
5	In	DMF	rt, 1.5	3	89 (69)
6	In	CH_2Cl_2	rt. 1.5	15	40 (57)
7	In	MeCN	rt, 1.5	3	82 (56)
8	In	1,4-dioxane	rt, 1.5	4	88 (96)
9	In	MeOH	rt, 1.5	0	5 (−)
10	Zn	THF	rt, 1.5	0	<15 (81)
11	Sn	THF	rt, 1.5	0	0

[a] Diastereoselectivities were determined from the crude ^{1}H NMR spectra; in all runs, because the stereochemistry between C^β and C^γ has been completely controlled, the values of ds are related C^α/C^β.

the transesterification effectively promoted the cyclization under the reaction conditions.[10a] In fact, noncyclic product **7a** was detected in some runs. Various conditions/solvents/metals were employed to optimize the reaction conditions. THF and 1,4-dioxane were found to be the most suitable solvents. Solvents such as DMF and MeCN gave comparable yields, but with low selectivity. Poor results were found in methanol. Other metals such as zinc[10b] or tin gave very low yields. The scope and generality of this interesting stereoselective reaction were tested with various α-hydroxy ketones **5a**−**g** and a variety of branched α-halo esters **2a**−**f** (Table 3). In all runs using α-hydroxy ketones, an excellent

Table 3



[a] Diastereoselectivities were determined from the crude ^{1}H NMR spectra; in all runs, because the stereochemistry between C^β and C^γ has been completely controlled, the values of ds are related C^α/C^β.

stereocontrol was achieved. Ethyl 2-bromoisovalerate (**2c**) with **5a**/**5b** afforded the lactones **8b** (67%, ds 99) and **8c** (55%, ds 98), respectively. Ethyl 2-bromo-2-cyclopentyl

(9) For some reports on the chelation-controlled reactions of α-hydroxy ketones, see: (a) Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *Org. Lett.* **2003**, *5*, 1365. (b) Yasuda, M.; Fujibayashi, T.; Baba, A. *J. Org. Chem.* **1998**, *63*, 6401. (c) Paquette, L. A.; Lobben, P. C. *J. Org. Chem.* **1998**, *63*, 5604. (d) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; Dimare, M. *J. Org. Chem.* **1996**, *61*, 868. (e) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, *124*, 6357. (f) Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massaccesi, M. *E. J. Org. Chem.* **2005**, 2867. (g) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *Chem. Lett.* **1991**, 879. (h) Lawson, E. C.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron Lett.* **1999**, *40*, 593. (i) Evans, P. A.; Lawler, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 8642. (j) Simpura, I.; Nevalainen, V. *Tetrahedron* **2003**, *59*, 7535. (k) Evans, D. A.; Hoveyda, A. *J. Org. Chem.* **1990**, *55*, 5190.

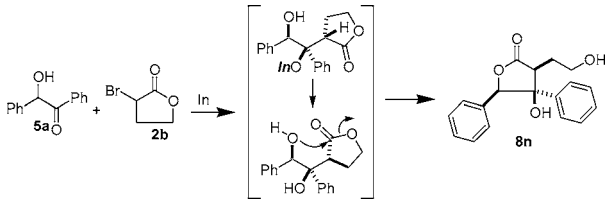
(10) (a) After the addition of water to quench the reaction, ultrasonication for 2 min was essential to obtain the lactonization product **8** exclusively (see the Supporting Information for the experimental procedure). (b) As noted in ref 4, the reaction of **5a** either under Reformatsky condition or with lithium enolate could not proceed effectively, and a significant amount of **5a** was recovered.

acetate (**2d**) with benzoin afforded the lactone **8d** (69%, ds 99) exclusively.

Ethyl 2-bromo-3,3-dimethylbutyrate (**2e**) with benzoin could not afford the lactone effectively even under the refluxing conditions because of the bulky *tert*-butyl substituent. Next, ethyl 2-bromooctanoate (**2f**) and α-hydroxy ketones **5a**−**c** afforded the lactones **8f**−**h**, with very high diastereoselectivities respectively (entries 6−9).

In line with exploring the scope, the α-hydroxy ketone **5d** having a methyl substituent instead of phenyl group was also reacted with **2a** to give the diastereoselective lactone **8i** (54%, ds 98). Next, anisoin (**5b**) and 4,4′-dichlorobenzoin (**5c**) were treated with **2a** and **2d** to furnish the lactones **8j** (73%, ds 93), **8k** (70%, ds 99), and **8l** (70%, ds 98). Further, the α-hydroxy ketone **5e** with **2d** also furnished the stereoselective lactone **8m** (66%, ds 99). However, its a limitation that the *β*-hydroxy ketone **5f** with **2a** failed to afford the diastereoselective product (entry 16). Finally the α-hydroxy ketones **5a**, **5b**, and **5g** were treated with 2-bromo *γ*-butyrolactone (**2b**) in the presence of indium powder. These reactions also afforded the stereoselective products **8n**−**p** with very high diastereoselectivities over three stereogenic centers (entries 17−19). Surprisingly, in these cases also, diastereselective lactone rings were newly constructed via the cleavage of the lactone moiety of **2b** (Scheme 2).

Scheme 2

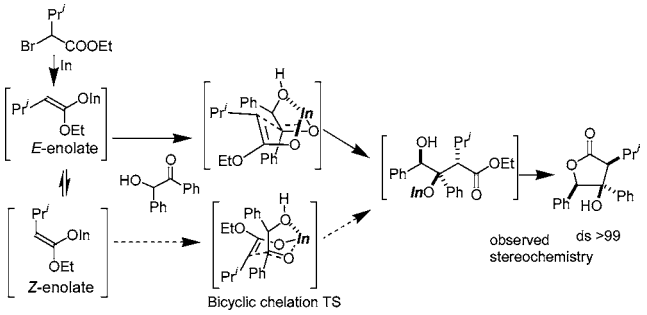


The X-ray structure analyses revealed the stereochemisry of lactones **8a**,**8n**; hence, the sterochemistry of lactones **8b**−**p** was also assigned. Apparently, all lactones were obtained from the cyclilzation (lactonization) of adducts **7** having unexpected syn/anti configuration. The unexpected stereochemical outcome in the Reformatsky reactions of α-hydroxy ketones with indium enolates can be accounted in the following mechanism.

Mechanism. Acyclic branched α-halo esters with indium could be transformed into *E* or *Z* enolates to react with ketones unlike the 2-bromo *γ*-butyrolactone (**2b**) where only a rigid *E*-enolate is possible. Both the acyclic and cyclic esters gave similar stereochemical lactones in which their anti configuration for C^{α} and C^{β} strongly indicates the involvement of a cyclic transition state rather than an acyclic path; hence, the participation of *E*-enolates is plausible conclusively.

In addition, we have already established the formation of *E*-enolates from the acyclic α-halo esters.[5] On the basis of these results, the observed excellent diastereoselectivities and stereochemistries of lactones **8a**−**p** could be explained through a boat-type bicyclic transition state from the *E*-enolates (Scheme 3). The popular chair-like bicyclic transition state[11] needs the *Z*-enolate to give the observed unexpected diasteroselectivity; however, the *E*-enolate would lead to the minor isomer.

Scheme 3



In conclusion, we have established an efficient protocol for the stereocontrol over three contiguous stereogenic centers during the C−C bond formation. A boat-type of chelated bicyclic transition state is involved in the Reformatsky reaction of indium enolates with α-hydroxy ketones to furnish the unexpected stereochemical lactones successfully.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. Thanks are due to Mr. H. Moriguchi, Faculty of Engineering, for assistance in obtaining MS spectra.

Supporting Information Available: Experimental procedures, spectral data of products, ^{1}H and ^{13}C NMR charts of pure products, and details of X-ray structure analyses (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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