ORGANIC LETTERS

2003
Vol. 5, No. 5
629−632

Reformatsky-Type Reaction of Chiral Nonracemic α-Bromo-α′-sulfinyl Ketones with Aldehydes. Synthesis of Enantiomerically Pure 2-Methyl-1,3-diol Moieties

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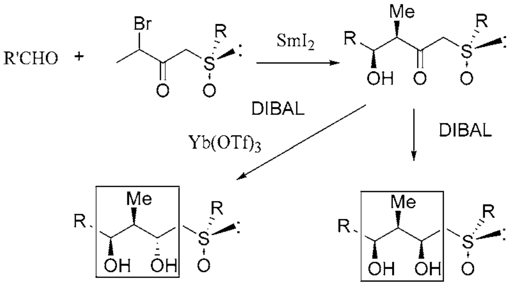
Received November 4, 2002 *(Revised Manuscript Received January 27, 2003)*

ABSTRACT



Chiral nonracemic α-bromo-α′-sulfinyl ketones were shown to react with aldehydes in the presence of SmI_2 in a Reformatsky-type reaction to give the corresponding adduct with excellent syn diastereoselectivity. Further reduction of the Reformatsky adducts furnished *anti*- and *syn*-2-methyl-1,3-diol moieties in excellent yields and diastereoselectivities.

The Reformatsky reaction employing zinc metal is a convenient and useful protocol for carbon−carbon bond formation using α-halo carbonyl compounds.[1] However, the yield and diastereoselectivity of this type of reaction are not always satisfactory.

To overcome these problems, most efforts have been focused on the activation of zinc such as Rieke-Zn, Zn−Cu couple, Zn/Hg amalgam, or the use of a variety of other metals and low-valent metal reagents.[2]

Highly stereocontrolled asymmetric Reformatsky reactions are of current interest, and an efficient asymmetric version of the Reformatsky reaction would be very useful for the synthetic chemist. To date, very few asymmetric Reformatsky reactions are known.[3]

In this field, samarium(II)iodide is known to be a polyvalent reducing agent that has been applied to a multitude of important synthetic reactions with generally high chemoselectivity and high levels of stereochemical control.[4]

Its use in an intramolecular sense in an asymmetric Reformatsky reaction has already been reported.[5] In addition, Fukuzawa recently described the SmI_2-mediated Reformatsky-type reaction of chiral 3-bromoacetyl-2-oxazolidinones with various aldehydes.[3b]

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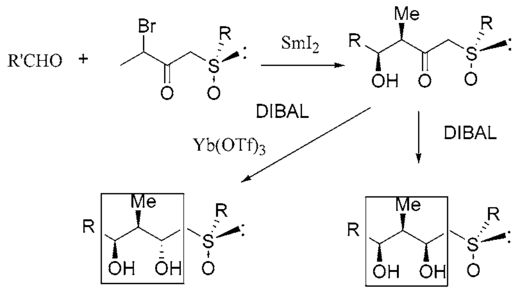
(1) For recent reviews of the Reformatsky reaction, see: (a) Fürstner, A. *Synthesis* **1989**, *571*. (b) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; New York, **1991**; Vol. 2, p 277. (c) Fürstner, A. In *Organozinc Reagents*; Knochel, P., Jones,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

(2) (a) Shibata, I.; Suwa, T.; Sakakibara, H.; Baba, A. *Org. Lett.* **2002**, *4*, 301. (b) Kagoshima, H.; Hashimoto, Y.; Saigo, K. *Tetrahedron Lett.* **1998**, *39*, 8465. (c) Shimizu, M.; Kobayashi, F.; Hayakawa, R. *Tetrahedron* **2001** *57*, 9591. (d) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Kutsuna, T.; Saigo, K. *Tetrahedron Lett.* **1998**, *39*, 1203. (e) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549. (f) Wessjohann, L.; Gabriel, T. *J. Org. Chem.* **1997**, *62*, 3772.

10.1021/ol027223+ CCC: $25.00

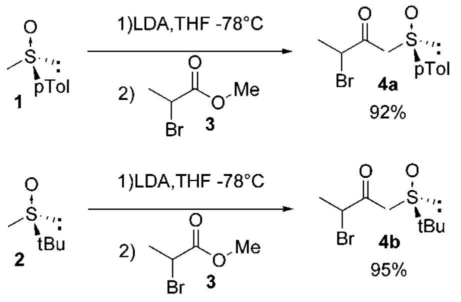
In this communication, we report a highly stereoselective Reformatsky addition of chiral nonracemic α-bromo-α′-sulfinyl ketones with various aldehydes promoted by samarium(II)diiodide. Further stereoselective reduction of the Reformatsky adduct led to *anti*- and *syn*-2-methyl-1,3-diols, very useful moieties in total synthesis of biologically active compounds (Scheme 1).

Scheme 1



The chiral nonracemic α-halo-α′-sulfinyl ketones were prepared according to the Bravo procedure (Scheme 2).[6]

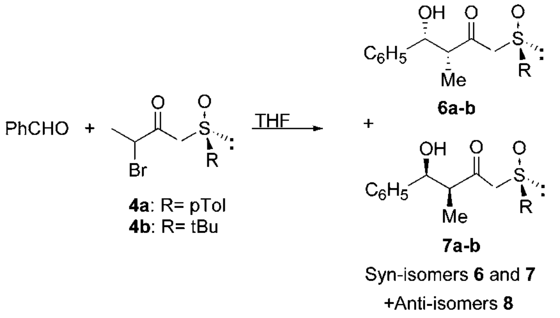
Scheme 2



Condensation of the lithiated anion of (+)-(*R*)-methyl-*p*-tolylsulfoxide[7] **1** or (−)-(*R*)-methyl-tert-butylsulfoxide[8] **2** on the methyl-2-bromopropionate **3** afforded the α-bromo-α′-sulfinyl ketones **4a** and **4b** in 92 and 95% yields, respectively.

Initially, we performed the reaction of α-halo-α′-*p*-tolylsulfinyl ketones **4a** with benzaldehyde using various sources of metals (GeI_2/K[3a]; $ZnEt_2$/$RhCl(PPh_3)_3$[2e]; $CrCl_2$/LiI[2f]; $CrCl_2$; SmI_2[3b]), and the results are summarized in Table 1.

Table 1. Diastereoselective Reformatsky Reaction of **4a−b** with Benzaldehyde



entry	4	metal	T (°C)	syn/anti[a]	6/7[a]	% yield[b]
1	**4a**	GeI_2/K	25	65/35	45/55	15
2	**4a**	$ZnEt_2$/ $RhCl(PPh_3)_3$	0	60/40	55/45	57
3	**4a**	$CrCl_2$/LiI	25	40/60	40/60	60
4	**4a**	$CrCl_2$	−78 → −10	45/55	70/30	55
5	**4a**	$CrCl_2$/LiI	−78 → −20	70/30	45/55	45
6	**4a**	SmI_2	−78	70/30	80/20	47
7	**4a**	SmI_2	−100	70/30	85/15	47
8	**4b**	SmI_2	−78	75/25	90/10	45
9	**4b**	SmI_2	−100	75/25	96/4	51

[a] Determined by ^{1}H NMR analysis of the product. [b] Isolated yield of the mixture of diastereomers. Reaction conditions: **4a** (1 equiv), PhCHO (1.1 equiv), SmI_2 (2 equiv), THF, 30 min.

The best syn diastereoselectivity was obtained using SmI_2 in THF at −100 °C. The diastereofacial selectivity is higher at −100 °C than at −78 °C (entries 6 and 7).

Using activated germanium, diethylzinc with rhodium catalyst, and chromiumdichloride did not improve the diastereoselectivity (entries 1−5).

Then we thought that the selectivity could be improved by using a more hindered substituent on the sulfur. We choose the optimum conditions established before to perform the Reformatsky reaction between the α-bromo-α′-*tert*-butylsulfinyl ketone **4b** (with *tert*-butyl instead of *p*-tolyl on the sulfoxide) and benzaldehyde (entries 8 and 9). We observed a higher diastereofacial selectivity leading to a syn ratio of 96/4 instead of 85/15 with *p*-tolyl sulfinyl derivatives (entries 7 and 9).

Then the SmI_2-promoted asymmetric Reformatsky reaction with **4b** was applied to various aldehydes at −100 °C (Table 2).

As shown in Table 2, excellent diastereoselectivities and moderate to good yields were obtained with linear aliphatic aldehydes (entries 4−7). The yields were slightly improved when an excess amount of **4b** (2 equiv instead of 1equiv) was employed.

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(3) (a) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691. (b) Fukuzawa, S.-I.; Matsuzawa, H.; Yoshimitsu, S.-I. *J. Org. Chem*. **2000**, *65*, 1702. (c) Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *32*, 3417. (d) Ito, Y.; Terashima, S. *Tetrahedron* 1991, *47*, 2821. (e) Soai, K.; Kawase, Y. *Tetrahedron Asymmetry* **1991**, *2*, 781. (f) Soai, K.; Oshio, A.; Saito, T. *Chem. Commun.*. 1993, 811.

(4) For recent reviews of samarium(II)iodide in organic synthesis, see: (a) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (b) Molandar, G. A.; Harris, C. H. *Chem. Rev.* **1996**, *96*, 307.

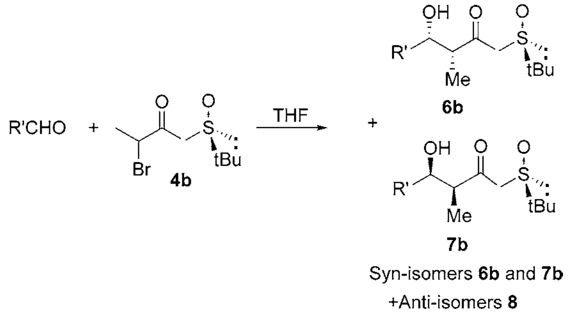
(5) (a) Molandar, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.

(6) Bravo, P.; Resnati, G. *Tetrahedron Lett.* **1985**, *26*, 5601.

(7) (+)-(*R*)-Methyl-*p*-tolylsulfoxide was prepared from the (−)-(*S*)-menthyl-*p*-tolylsulfinate: Solladié G.; Hutt, J.; Girardin, A. *Synthesis* **1987**, 173.

(8) (−)-(*R*)-Methyl-*tert*-butylsulfoxide was prepared by addition of *tert*-butylmagnesiumchloride followed by methylmagnesiumbromide on chiral sulfites: Rebiere, F.; Samuel, O.; Ricard, L.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 5991.

Table 2. Diastereoselective Reformatsky Reaction of **4b** with Various Aldehydes



entry	R′CHO	syn/anti[a]	**6b**/**7b**[a]	% yield[b]
1	PhCHO	75/25	96/4	61%
2	*t*BuCHO	55/45		55%
3	isovaleraldehyde	90/10	90/10	55%
4	*n*-C_2H_5CHO	98/2	95/5	85%
5	*n*-C_3H_7CHO	98/2	95/5	85%
6	*n*-C_5H_{11}CHO	98/2	92/8	75%
7	*n*-C_7H_{15}CHO	98/2	95/5	77%
8	acroleine	75/25	92/8	65%
9	n-*trans*-2-hexenal	45/55	80/20	87%

[a] Determined by ^{1}H NMR analysis of the product. [b] Isolated yield of the mixture of diastereomers. Reaction conditions: **4b** (2 equiv), R′CHO (1 equiv), SmI_2 (2 equiv), THF, −100 °C, 30 min.

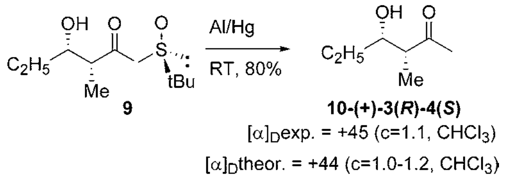
Isovaleraldehyde, which is more hindered, gave good diastereoselectivity but a lower yield (entry 3). With pivalaldehyde, no selectivity was observed (entry 2).

Surprisingly, condensation with acroleine and *n*-*trans*-2-hexenal did not give a high diastereoselectivity (entries 8 and 9).

To confirm the strong effect of the *tert*-butyl group on sulfur on the diastereofacial selectivity, we carried out the condensation of α-halo-α′-*p*-tolyl-sulfinyl ketone **4a** with *n*-hexanal and we found as expected a lower diastereoselectivity (syn/anti = 85/15; **6a**/**7a** = 85/15).

The absolute configuration of **9** (R = C_2H_5) was determined after sulfoxide reductive cleavage with aluminum amalgam, giving the known methyl ketone **10** (Scheme 3).

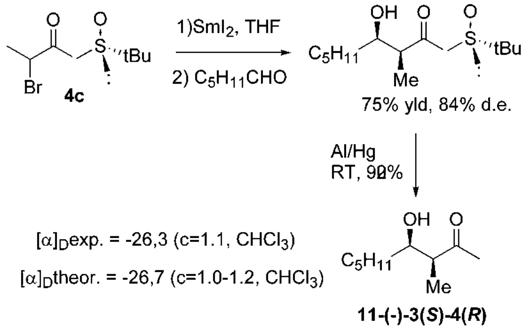
Scheme 3



By comparison with the literature,[9] the configuration 3(*R*)-4-(*S*) was assigned to **10**.

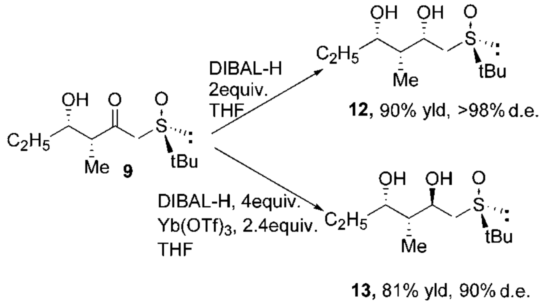
On the other hand, we performed the Reformatsky reaction starting from α-bromo-α′-tert-butylsulfinyl ketone **4c** with the opposite configuration on the sulfoxide (S(*S*)). Condensation of **4c** with *n*-hexanal followed by sulfoxide reductive elimination afforded the known methyl ketone **11**, whose absolute configuration (by comparison with literature[9]) was confirmed to be 3(*S*)-4-(*R*) (Scheme 4).

Scheme 4



With these Reformatsky adducts **6b** in hand, we performed the well-known diastereoselective reduction of *β*-ketosulfoxides[10] either with DIBAL-H only or with DIBAL-H in the presence of Yb(OTf)$_3$. Starting from adduct **9** (obtained by Reformatsky condensation with *n*-propanal) the 2-methyl-1,3 syn or anti diols **12** and **13**, respectively, were obtained in good yields and diastereoselectivities[11] (Scheme 5).

Scheme 5



In this paper, the sulfoxide auxiliary was shown to be efficient for the asymmetric samarium Reformatsky reaction by providing high stereoselectivities and chemical yields with linear aliphatic aldehydes. The particular advantage of this reaction stems from the fact that the site of reaction is strictly determined by the halogen moiety. Regioselective enolate formation can occur in contrast with base-induced proton abstraction.

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(10) (a) Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435. (b) Solladié, G.; Demailly, Greck, C. *J. Org. Chem.* **1985**, *50*, 1552. (c) Solladié, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912. (d) Solladié-Cavallo, A.; Suffert, J.; Adib, A.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6649. (e) Solladié, G.; Rubio, A.; Carreño, M. C.; Garcia-Ruano, J. L. *Tetrahedron: Asymmetry* **1990**, *1*, 187. (f) Carreño, M. C.; Garcia Ruano, J. L.; Martin, A.; Pedregal, C.; Rodriguez, J. H.; Rubio, A.; Sanchez, J.; Solladié, G. *J. Org. Chem.* **1990**, *55*, 2120.

Further diastereoselective reduction of the β-ketosulfoxide was performed as expected with high diastereoselectivities leading to *anti*- and *syn*-2-methyl-1,3-diol moieties. These asymmetric syntheses are promising because methods to remove or transform the chiral sulfoxide are well-known.[12] Extension of this methodology is now under investigation in our laboratory.

Acknowledgment. This work was supported by the CNRS and Ministère de la Recherche. M.O. thanks the Ministère de la Recherche for a fellowship.

Supporting Information Available: Experimental procedures for **4b**, **9**, **12**, and **13**, spectral and analytical data, reductive elimination of **9** and **4c** with ^{1}H and ^{13}C NMR data, and correlation of configuration. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (*S*)-Configuration of the new hydroxylic carbon in compound **12** and the (*R*)-configuration in compound **13** were expected from the reaction mechanism already proposed[10d] and also from our ^{1}H NMR characterization of the product. From the numerous examples of reduction of β-ketosulfoxides already reported,[11a−d] we noticed that the nonequivalence of the methylene hydrogens α to the sulfoxide group is quite different in the two diastereomers: in the [(*R*),S(*R*)]-configuration the $\Delta\nu$ value between these two hydrogens is around 40 Hz (in **13**, $\Delta\nu = 50$ Hz) and around 80 Hz in the [(*S*),S(*R*)]-epimers (in **12** $\Delta\nu = 79$ Hz). (a) Colobert, F.; Des Mazery, R.; Solladié, G.; Carreno, M. C. *Org. Lett*. **2002**, *4*, 1723. (b) Solladié, G.; Gressot, L.; Colobert, F. *Eur. J. Org. Chem*. **2000**, 357. (c) Solladié, G.; Adamy, M.; Colobert, F. *J. Org. Chem*. **1996**, *61*, 4369. (d) Solladié, G.; Colobert, F.; Denni, D. *Tetrahedron: Asymmetry* **1998**, *9*, 3081.

(12) (a) De Lucchi, O.; Mioti, U.; Modena, G. *Org. React.* **1991**, *40*, 157 (b) Zasshi, Y. *J. Pharm. Soc. Jpn.* **1997**, *117*, 282.