ORGANIC LETTERS

2006
Vol. 8, No. 6
1125−1128

An Improved Asymmetric Reformatsky Reaction Mediated by (−)-*N*,*N*-Dimethylaminoisoborneol

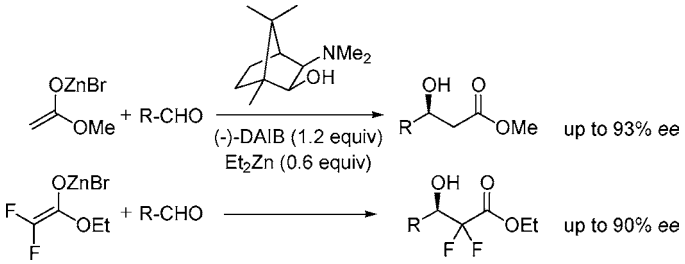
Ralf J. Kloetzing, Tobias Thaler, and Paul Knochel*

Department of Chemistry and Biochemistry, Ludwig-Maximilians-University, Butenandtstrasse 5-13, 81377 Munich, Germany

paul.knochel@cup.uni-muenchen.de

Received December 27, 2005

ABSTRACT



(−)-*N*,*N*-Dimethylaminoisoborneol ((−)-DAIB) was found to be an excellent ligand for the enantioselective addition of Reformatsky reagents to aromatic and aliphatic aldehydes. Enantioselectivities up to 93% ee were obtained with sulfur-containing aldehydes.

Organozinc reagents are useful synthetic intermediates as a result of their convenient synthesis and high tolerance toward functional groups.[1,2] The Reformatsky reaction allows the synthesis of β-hydroxy esters by the direct insertion of zinc in α-halogenated esters and subsequent addition of the resulting organozinc enolate to aldehydes or ketones.[3] An enantioselective reaction allows an easy and direct access to synthetically useful chiral β-hydroxy esters,[4] which are valuable precursors for the synthesis of natural products and pharmaceutically active compounds. So far, several methods have been reported using chiral auxiliaries[5] or ligands.[6] Recently, a highly efficient imino-Reformatsky reaction, affording β-amino esters, has been disclosed.[7] The methods for the direct Reformatsky reaction using the insertion of activated zinc into α-bromo acetates lack generality, and high enantioselectivities could not be achieved.

To improve this reaction, we have tested various amino alcohols that proved to give high asymmetric inductions as chiral ligands for the addition of diethylzinc to aldehydes.[2] Benzaldehyde was chosen as a test substrate for the enantioselective addition of the Reformatsky reagent (**1a,b**), which was prepared from bromoacetic esters via the direct insertion of zinc (Scheme 1 and Table 1). All reactions were

(1) (a) Knochel, P. *Sci. Synth.* **2004**, *3*, 5−90. (b) Nakamura, E. In *Organometallics in Synthesis, a Manual*; Schlosser, M., Ed; Wiley: New York, 2002; p 579. (c) Fürstner, A. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: New York, 1999; p 287.

(2) For an overview on the enantioselective addition of organozinc reagents to aldehydes, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; p 255. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.

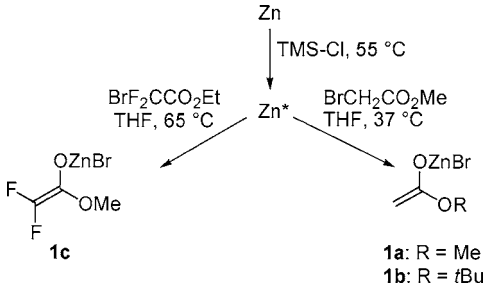
(3) (a) Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210−1211. For a review, see: (b) Ocampo, R.; Dolbier, W. R., Jr. *Tetrahedron* **2004**, *60*, 9325−9374. (c) Orsini, F.; Sello, G. *Curr. Org. Chem.* **2004**, *1*, 111−135. (d) Fürstner, A. *Synthesis* **1989**, 571−590. (e) Suh, Y.; Rieke, R. D. *Tetrahedron Lett.* **2004**, *45*, 1807−1809.

(4) For other recent asymmetric syntheses of β-hydroxy carbonyl compounds, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (b) List, B. *Tetrahedron* **2002**, *58*, 5573−5590 and references therein. (c) Jeon, S.-J.; Chen, Y. K.; Walsh, P. J. *Org. Lett.* **2005**, *7*, 1729−1732. (d) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602−8603. (e) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774−3789. (f) Kesanli, B.; Lin, W. *Chem. Commun.* **2004**, 2284−2285. (g) Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2501−2504. (h) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882−2883.

(5) (a) Marcotte, S.; Pannecoucke, X.; Feasson, C.; Quirion, J.-C. *J. Org. Chem.* **1999**, *64*, 8461−8464. For an imino variant with sulfinylimines, see: (b) Sorochinsky, A.; Voloshin, N.; Markovsky, A.; Belik, M.; Yasuda, N.; Uekusa, H.; Ono, T.; Berbasov, D. O.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 7448−7454.

10.1021/ol0531381 CCC: $33.50
Published on Web 02/21/2006

Scheme 1. Preparation of Reformatsky Reagents **1a**−**c**

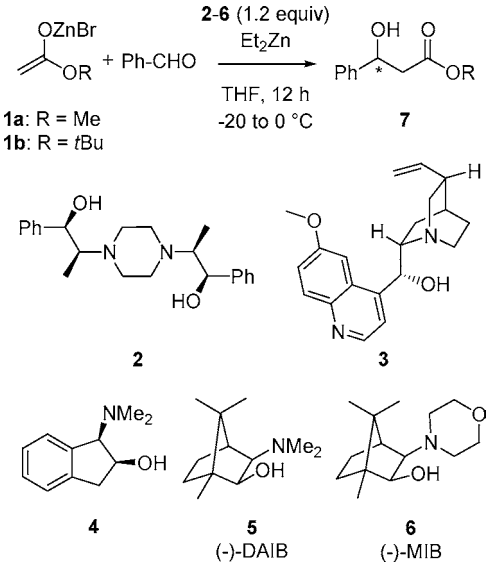


performed using 1.2 equiv of the chiral amino alcohol. 1,4-Pyridazine derivative **2**[8] (entry 1) gave high conversion but only moderate enantiomeric excess. When quinine (**3**)[6e,9] or the indanol derivative **4**[10] were used, the enantioselectivity remained low (entries 2 and 3), whereas with (−)-*N*,*N*-dimethylaminoisoborneol (**5**, (−)-DAIB)[11] an enantioselectivity of 86% ee and an isolated yield of 75% were achieved (entry 4). The use of sterically hindered *tert*-butyl bromoacetate (entry 5, R = *t*-Bu) for the preparation of the Reformatsky reagent led to a decreased enantioselectivity of 78% ee. Nugent's morpholine derivative **6**[12] ((−)-MIB), which is more readily available than (−)-DAIB (**5**), yielded here a slightly lower enantioselectivity of 72% ee (entry 6).

Diethylzinc was used for the deprotonation of the amino alcohol in order to avoid using an excess of the Reformatsky reagent **1**. With BuLi as base, product **7a** was obtained in racemic form, and with MeMgCl as deprotonating agent only a low enantioselectivity of 20% ee was found.

The scope of the reaction using (−)-DAIB (**5**) as chiral inductor was examined (Table 2). For *o*- and *p*-bromobenzaldehyde (entries 1 and 3) the resulting enantioselectivities were lower than those for the reaction with benzaldehyde. The lowest enantioselectivity (78% ee) was found with the *ortho*-isomer (entry 2). For 4-chlorobenzaldehyde (entry 3) the enantioselectivity is comparable with those of the bromo-benzaldehydes (80% ee). The electron-withdrawing nitrile group (entry 4) led to an even lower enantioselectivity (72% ee), but better results were obtained with electron-rich aldehydes (entries 5 and 6). Although the conversion is lower, better enantioselectivities are achieved (88% and 93% ee). When thiophene aldehydes were used (entries 7−9), the enantioselectivity was also high. The sterically most hindered β-benzothiophene aldehyde reacted slowly (62% conversion) but gave 90% ee. The 2- and 3-thiophene aldehydes yielded the best enantioselectivities (92% and 93% ee). Product **7g** is a key intermediate in a synthesis of duloxetine, a potent inhibitor of the serotonine and norepinephedrine uptake carriers.[13] The best reported enantioselective synthesis to date gave product **7g** with 90% ee.[13] Furfural (entry 10) produces the β-hydroxy ester **7k** with a enantioselectivity (84% ee) similar to that of benzaldehyde (86% ee). These experiments show that a sulfur-

Table 1. Reformatsky Reaction with Various Chiral Amino Alcohols



entry	amino alcohol	R	yield (%)	ee[d] (%)
1	**2**	Me	99[b]	61
2	**3**	Me	99[b]	9
3	**4**	Me	99[b]	26
4	**5**	Me	75[c]	86
5	**5**	*t*Bu	84[b]	78
6	**6**	Me	93[b]	72

[a] All reactions were performed on a 0.5 mmol scale using amino alcohol (1.2 equiv, 0.6 equiv in case of **2**), Et_2Zn (0.7 equiv), and Reformatsky reagent (1.1 equiv). [b] Conversion determined by GC analysis with tetradecane as internal standard. [c] Isolated yield. [d] Determined by GC analysis (Chiraldex CB).

(6) For the use of sparteine, see: (a) Sorger, K.; Petersen, H.; Stohrer, J. Eur. Pat. Appl. EP 1394140, 2004. High enantioselectivity (91% ee) could also be achieved with thiophene-2-carbaldehyde. (b) Guetté, M.; Guetté, J. P.; Capillon, J. *Tetrahedron Lett.* **1971**, *12*, 2863−2863. (c) Guetté, M.; Capillon, J.; Guetté, J. P. *Tetrahedron* **1973**, *29*, 3659−3667. For the use of amino alcohols, see: (d) Fujiwara, Y.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003,** *44*, 6161−6163. (e) Ojida, A.; Yamano, T.; Taya, N.; Tasaka, A. *Org. Lett.* **2002**, *4*, 3051−3054. (f) Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* **2000**, *56*, 1217−1223. (g) Mi, A.; Wang, Z.; Chen, Z.; Jiang, Y.; Chan, A. S. C.; Yang, T. *Tetrahedron: Asymmetry* **1995**, *6*, 2641−2642. (h) Pini, D.; Mastantuono, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1875−1876. (i) Soai, K.; Oshio, A.; Saito, T. *J. Chem. Soc., Chem. Commun.* **1993**, 811−812. (j) Soai, K.; Kawase, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 781−784.

(7) (a) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600−3603. (b) Ukaji, Y.; Takenaka, S.; Horita, Y.; Inomata, K. *Chem. Lett.* **2001**, *3*, 254−255. For a large scale Reformatsky reaction with imines, see: (c) Awasthi, A. K.; Boys, M. L.; Cain-Janicki, K. J.; Colson, P.-J.; Doubleday: W. W.; Duran, J. E.; Farid, P. N. *J. Org. Chem.* **2005**, *70*, 5387−5397. (d) Clark, J. D.; Weisenburger, G. A.; Anderson, D. K.; Colson, P.-J.; Edney, A. D.; Gallagher, D. J.; Kleine, H. P.; Knable, C. M.; Lantz, M. K.; Moore, C. M. V.; Murphy, J. B.; Rogers, T. E.; Ruminski, P. G.; Shah, A. S.; Storer, N.; Wise, B. E. *Org. Proc. Res. Dev.* **2004**, *8*, 51−61.

(8) Ortiz, A.; Farfán, N.; Höpfl, H.; Santillan, R.; Ochoa, M. E.; Gutiérrez, A. *Tetrahedron: Asymmetry* **1999**, *10*, 799−811.

(9) (a) Park, D. H.; Choi, H. J.; Lee, S.-G. *J. Korean Chem. Soc.* **2003**, *47*, 597−600. (b) Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135−137. (c) Muchow, G.; Vannoorenberghe, Y.; Buono, G. *Tetrahedron Lett.* **1987**, *28*, 6163−6166.

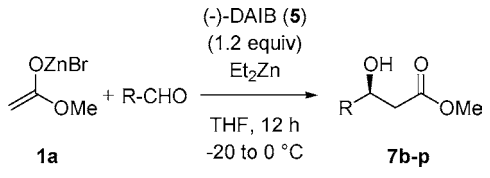
(10) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881−3884.

(11) (a) White, J. D.; Wardrop, D. J.; Sundermann, K. F. *Org. Synth.* **2003**, *79*, 125−138. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842. (c) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6072−6074.

(12) Nugent, W. A. *Chem. Commun.* **1999**, 1369−1370.

(13) Ratovelomanana-Vidal, V.; Girard, C.; Touati, R.; Tranchier, J. P.; Hassine, B. B.; Genêt, J. P. *Adv. Synth. Catal.* **2003**, *345*, 261−274.

Table 2. Reformatsky Reaction with (−)-DAIB and Various Aldehydes[a]



1a **7b-p**

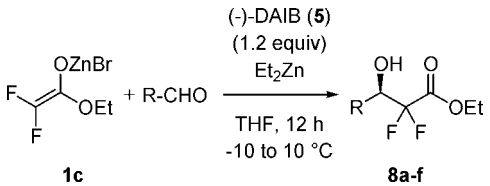
entry	R	product	conv (%)	yield[b] (%)	ee[c,d] (%)
1	4-bromophenyl	**7b**	79	87	81
2	2-bromophenyl	**7c**	71	91	78
3	4-chlorophenyl	**7d**	85	65	80
4	4-cyanophenyl	**7e**	89	88	72
5	4-isopropylphenyl	**7f**	63	90	88
6	4-methylthiophenyl[e]	**7g**	57	93	93
7	3-benzothienyl	**7h**	62	94	90
8	2-thienyl	**7i**	86	85	92
9	3-thienyl	**7j**	88	87	93
10	2-furyl	**7k**	99	86	84
11	neopentyl	**7l**	77	83	92
12	*n*-pentyl	**7m**	64	88	78
13	2,2-dimethyl-2-methoxyethyl	**7n**	61	85	74
14	benzyloxymethyl	**7o**	79	87	66
15	2-phenylvinyl	**7p**	48	92	71

[a] See Table 1. [b] Isolated yield based on conversion. [c] Determined by chiral GC (Chiraldex CB) or chiral HPLC (Chiralcel OD-H). [d] The absolute stereochemistry (*S*) was assigned by comparison of the optical rotation with literature data.[4e,13] [e] For a procedure, see ref 17.

containing heterocycle enhances the enantiomeric excesses regardless of the sulfur's position. For aliphatic aldehydes (entries 11 and 12), a sterically hindered aldehyde must be used in order to achieve high enantioselectivity. As an example, 3,3-dimethylbutanal (entry 11) gave 92% ee, whereas with hexanal (entry 12) only 78% ee was achieved. The same phenomenon was observed when aliphatic aldehydes containing an ether moiety were used (entries 13 and 14). The sterically hindered 3-methoxy-3-methylbutanal (entry 13) provided a higher enantioselectivity (74% ee), whereas benzyloxy acetaldehyde gave only 66% ee. Cinnamyl aldehyde (entry 15) led to 71% ee along with a low conversion.

We have extended the scope of the reaction to the difluoro-Reformatsky reagent **1c**, which was prepared by direct insertion of zinc into ethyl bromodifluoroacetate (Scheme 1 and Table 3).[14] The 2,2-difluoro-3-hydroxycarboxylates are versatile intermediates for the synthesis of fluorinated peptides.[15] As a result of its high electronegativity, the CF_2 group is an isosteric and isopolar replacement site for oxygen.[16] With benzaldehyde (Table 3, entry 1), an enantioselectivity of 88% ee was observed. The decrease of enantioselectivity, when electron-poor aldehydes were used,

Table 3. Reformatsky Reaction with the Difluoro Reagent **1c**, (−)-DAIB and Various Aldehydes



1c **8a-f**

entry	R	product	conv (%)	yield[b] (%)	ee[c,d] (%)
1	phenyl	**8a**	92	82	88
2	4-bromophenyl	**8b**	96	83	87
3	4-cyanophenyl	**8c**	91	88	84
4	2-thienyl	**8d**	66	90	90
5	3-thienyl	**8e**	69	84	87
6	neopentyl	**8f**	91	81	80

[a−c] See Table 2. [d] The absolute stereochemistry (*R*) was assigned by comparison of the optical rotation with literature data.[14a]

was lower than for the Reformatsky reagent **1a**, so that 87% ee was obtained in the case of *p*-bromobenzaldehyde (entry 2) and 84% ee with *p*-cyanobenzaldehyde (entry 3). With 2- or 3-thiophene aldehyde (entries 4 and 5) high enantioselectivity could be accomplished (90% and 87% ee). The advantageous influence of the sulfur heterocycle is less marked than for the Reformatsky reagent **1a**. With the sterically hindered aliphatic aldehyde 3,3-dimethylbutanal (entry 6) 80% ee was obtained.

To gain an insight into the nature of the beneficial effect of sulfur-containing heterocyclic substrates on the enantio-

(14) (a) Andrés, J. M.; Martínez, M. M.; Pedrosa, R.; Pérez-Encabo, A. *Synthesis* **1996**, 1070−1072. (b) Braun, M.; Vonderhagen, A.; Waldmüller, D. *Liebigs Ann.* **1995**, 1447−1450. (c) Sato, K.; Tarui, A.; Kita, T.; Ishida, Y.; Tamura, H.; Omote, M.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **2004**, *45*, 5735−5737.

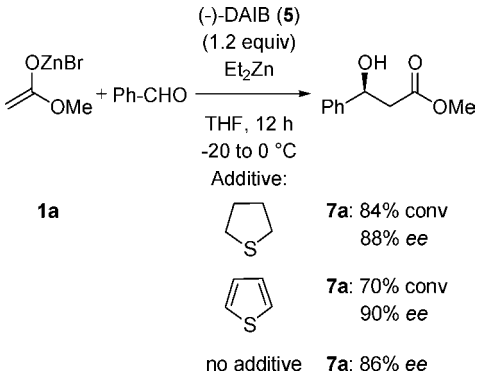
(15) Kirk, K. L. In *Fluorine-Containing Amino-Acids*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: New York, 1995; p 343.

(16) For other asymmetric syntheses of 2,2-difluoro-3-hydroxycarboxylates, see: (a) Kuroki, Y.; Asada, D.; Iseki, K. *Tetrahedron Lett.* **2000**, *41*, 9853−9858. (b) Iseki, K.; Kuroki, Y.; Asada, D.; Kobayashi, Y. *Tetrahedron Lett.* **1997**, *38*, 1447−1448. For diastereoselective syntheses, see: (c) Evans, G. B.; Furneaux, R. H.; Lewandowicz, A.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2003,** *46*, 3412−3423. (d) Ding, Y.; Wang, J.; Abboud, K. A.; Xu, Y.; Dolbier, W. R., Jr.; Richards, N. G. J. *J. Org. Chem.* **2001**, *66*, 6381−6388.

(17) **Procedure for the Synthesis of Alcohol 7g.** (Table 2, entry 6) In a 25 mL three-necked flask equipped with an efficient reflux condenser, a dropping funnel, a magnetic stirring bar and a thermometer, zinc (dust, 1.26 g, 19.3 mmol) was suspended in THF (8 mL) and stirred vigorously. The temperature was raised to 40 °C, and trimethylsilyl chloride (0.30 mL, 0.26 g, 2.4 mmol) was added. The temperature was then raised to 55 °C and kept for 15 min. The pressure in the flask was reduced to 330 mbar, which ensures that the temperature is kept at 37 °C (refluxing THF). Methyl bromoacetate (1.68 mL, 2.70 g, 17.7 mmol) was added during 10 min (CAUTION: exothermic reaction) and stirred for 5 min. The flask was then refilled with argon, and the remaining solid material was allowed to settle. The supernatant liquid was decanted with a cannula. The concentration was determined by titration with iodine in THF (2 mL) at 0 °C to be 1.7 M. (−)-DAIB (**5**, 140 mg, 0.728 mmol) was dissolved in THF (0.5 mL) and diethylzinc (1.9 m in THF, 0.23 mL, 0.44 mmol) was added at 0 °C. After the mixture had been stirred for 10 min, the temperature was lowered to −20 °C, and the above prepared Reformatsky reagent (0.41 mL, 0.70 mmol) was added. Then the mixture was stirred for 20 min. The aldehyde (94.2 mg, 0.619 mmol) was added as a solution in THF (0.5 mL) together with tetradecane as internal standard. After 2 h, the temperature was allowed to rise to 0 °C. Concentrated aqueous ammonia (3 mL) and a saturated solution of NH_4Cl (30 mL) were added after 12 h, and the mixture was extracted with ethyl acetate. The organic phase was washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the product was purified by column chromatography (SiO_2, pentane/diethyl ether 3:1 to 1:1). Alcohol **7g** was obtained as white solid (74 mg, 0.33 mmol, 93% based on 57% conv).

selectivity of the addition, the reaction of the Reformatsky reagent **1a** with benzaldehyde (Table 1) was performed, using thiophene or tetrahydrothiophene as additives (Scheme 2).

Scheme 2. Reformatsky Reaction Using Sulfur Additives



With thiophene as additive (1.2 equiv) 70% conversion and 90% ee were obtained. With tetrahydrothiophene (1.2 equiv) 84% conversion and 88% ee were observed. Without additive, the reaction led to 86% ee (Table 1, entry 4). This shows that tetrahydrothiophene and especially thiophene are suitable additives that increase the enantioselectivity of the Reformatsky reaction. An attempt to use (−)-DAIB in catalytic amounts (10 mol %) along with stoichiometric amounts of thiophene (1.2 equiv) gave the product **7a** only with 19% ee.

In conclusion, we have shown that (−)-DAIB is an excellent ligand for the enantioselective addition of the Reformatsky reagent **1a** to various aldehydes. High enantioselectivities were obtained for thiophene aldehydes (up to 93% ee) or sterically hindered aliphatic aldehydes (92% ee). The addition of the difluoro zinc reagent **1c** also proceeded with high enantioselectivity (up to 90% ee). Extensions of this enantioselective Reformatsky reaction are currently underway in our laboratories.

Acknowledgment. R.J.K. thanks the Stiftung Stipendien-Fonds des VCI (Frankfurt) and the Bundesministerium für Bildung und Forschung for a scholarship. We thank WACKER Chemie GmbH (München) for the gift of chemicals.

Supporting Information Available: Experimental details, chromatograms, and spectra for all compounds and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0531381