ORGANIC LETTERS

2003
Vol. 5, No. 3
329−331

Asymmetric Halo Aldol Reaction (AHA)

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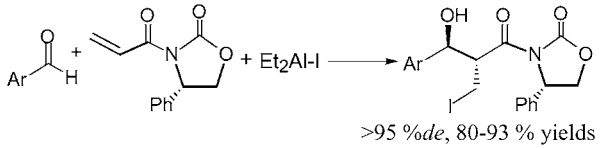
Received November 23, 2002

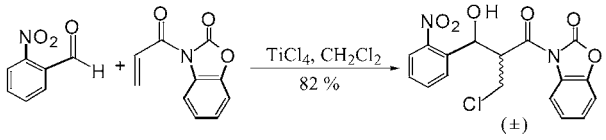
ABSTRACT



The asymmetric halo aldol reaction (AHA) using Evans oxazolidinones as chiral auxiliaries has been established for tandem I–C/C–C bond formations. The new asymmetric reaction provides a practical approach to a variety of halo aldols of a non-Evans type that cannot be easily synthesized by other methods. Excellent diastereoselectivity (>95%) and yields (80–93%) have been obtained for eight examples.

The aldol reaction is among the most important C−C bond formation reactions in organic chemistry.[1−4] Recently, halo aldol reaction[5,6] has become an active topic because the resulting halo aldols can be converted to a variety of extended aldols by using S_N2 substitutions with different nucleophiles and to the Morita−Baylis−Hillman (MBH) adducts[7,8] by treatment with tertiary amines or other organic bases. Meanwhile, halo aldol reaction serves as a key step of the mechanism of the MBH-type reaction promoted by metal halides. We recently developed the $TiCl_4$-mediated MBH reaction without the direct use of any Lewis bases. This reaction was unambiguously confirmed through halo aldol reaction in which halo aldols were isolated when α,β-unsaturated *N*-acyl benzoxalinone was employed as the Michael acceptor (Scheme 1).[5a] A similar mechanism also exists in the Et_2AlI-promoted MBH-type processes.[8d,e,9] The later reaction greatly extended the scope of the $TiCl_4$-based system (Scheme 2).

Scheme 1



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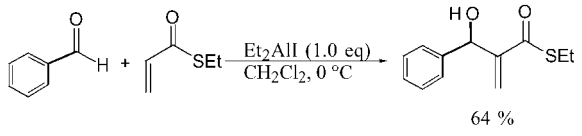
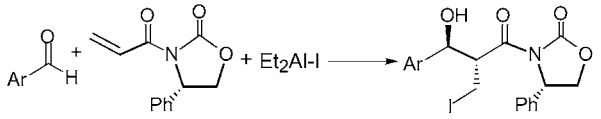
10.1021/ol027344+ CCC: $25.00
Published on Web 01/09/2003

Scheme 2



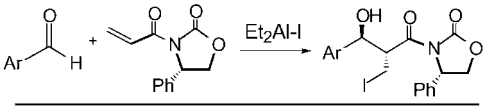
So far, an effective asymmetric halo aldol reaction for the formation of X−C(sp^3)/C(sp^3)−C(sp^3) bonds has not been well documented. In the past two years, we have attempted to render such an asymmetric halo aldol reaction, but the success has been very limited. In this report, we are pleased to report our preliminary results of this asymmetric reaction using Evans oxazolidinone auxiliaries. The reaction is represented in Scheme 3, and the results are summarized in Table 1.

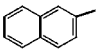
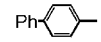
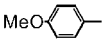
Scheme 3



The present AHA reaction was achieved by performing the slow addition of the solution of diethylaluminum iodide (1.3 equiv) into the mixture of α,β-unsaturated *N*-acyl-4-phenyl-oxazolidinone and aldehyde (2.0 equiv) in dichloromethane stirring at −20 °C under the protection of nitrogen gas. The reaction proceeded to completion within a period of 20 h at this temperature as revealed by thin-layer chromatography.[10]

Table 1. Results of Et_2AlI-Mediated AHA Reaction



entry[a]	Ar		yield[b]	*de*%[c]
1		**1**	91	>95
2		**2**	80	>95
3		**3**	85	>95
4		**4**	93	>95
5		**5**	91	>95
6		**6**	82	>95
7		**7**	89	>95
8		**8**	84	>95

[a] Preliminary results showed that 85% yield and >95% de were obtained for aliphatic phenylacetaldehyde. [b] Purified yields after column chromatography. [c] Determined by ^{1}H NMR analysis of crude products. Values >95% mean only one isomer was observed.

The absolute stereochemistry of the asymmetric induction was determined by the X-ray crystal analysis of a sample of (4*S*,2′*R*,3′*S*)-3-(2′-iodomethyl-3′-hydroxy-3′-phenyl-1′-oxopropyl)-4-phenyl-2-oxazolidinone. The crystals were obtained after recrystallization using a cosolvent consisting of di-

(8) For the MBH reaction without the direct use of any Lewis bases see: (a) ref 6a. (b) Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett.* **2000**, *2*, 617. (c) Basavaiah, D.; Screenivasulu, B.; Rao, J. S. *Tetrahedron Lett.* **2001**, *42*, 1147. (d) Pei, W.; Wei, H.-X.; Li, G. *J. Chem. Soc., Chem. Commun.* **2002**, *17*, 1856. (e) Pei, W.; Wei, H.-X.; Li, G. *J. Chem. Soc., Chem. Commun.* **2002**, 2412. For the MBH reaction using the combinations of Lewis acids and Lewis bases, see: (f) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1383. (g) Yagi, K.; Turitani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111. (h) Shi, M.; Jiang, J. K.; Cui, S. C.; Feng, Y. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390.

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(10) The representative experiment is demonstrated by the preparation of product **1** in Table 1. Into a dry vial was loaded freshly distilled dichloromethane (2.0 mL), benzaldehyde (0.03 mL, 0.30 mmol), and α,β-unsaturated *N*-acyl-4-phenyl-oxazolidinone (33 mg, 0.15 mmol). The resulting mixture was protected by nitrogen gas, cooled to −20 °C, and stirred for 10 min. A solution of diethylaluminum iodide (1 M in toluene, 0.20 mL, 0.20 mmol) was then added into the above mixture dropwise via a syringe at the rate of 0.1 mL/h. The resulting homogeneous yellow mixture was stirred for 20 h at −20 °C. The reaction was finally quenched by 1 N aqueous HCl (5.0 mL). The dichloromethane layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 5.0 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated. Purification was carried out by column chromatography (1:4 (v/v) ethyl acetate/hexane) to give product **1**, 62 mg (91% yield) as a white solid. ^{1}H ($CDCl_3$, 300 MHz): δ 7.33−7.26 (m, 8H), 7.15−7.12 (m, 2H), 5.50 (dd, *J* = 3.6, 8.7 Hz, 1H), 4.98 (m, 1H), 4.74 (m, 2H), 4.24 (dd, *J* = 3.6, 8.7 Hz, 1H), 3.28 (dd, *J* = 9.8, 9.8 Hz, 1H), 3.05 (dd, *J* = 4.3, 9.8 Hz, 1H), 2.96 (d, *J* = 7.6 Hz, 1H). **Compound 2.** ^{1}H ($CDCl_3$, 300 MHz): δ 7.87−7.65 (m, 4H), 7.50 (m, 3H), 7.18 (m, 1H), 7.05−6.92 (m, 4H), 5.46 (dd, *J* = 3.5, 8.6 Hz, 1H), 5.06 (m, 1H), 4.97 (dd *J* = 7.5, 7.5 Hz, 1H), 4.69 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.17 (dd, *J* = 3.5, 8.6 Hz, 1H), 3.37 (dd, *J* = 9.6, 9.6 Hz, 1H), 3.19 (d, *J* = 8.1 Hz, 1H), 3.14 (dd, *J* = 4.3, 9.6 Hz, 1H). **Compound 3.** ^{1}H ($CDCl_3$, 300 MHz): δ 7.33 (m, 4H), 7.19−7.10 (m, 3H), 5.51 (dd, *J* = 3.3, 8.6 Hz, 1H), 4.85 (m, 1H), 4.73 (m, 2H), 4.25 (dd, *J* = 3.3, 8.6 Hz, 1H), 3.26 (dd, *J* = 11.1, 11.1 Hz, 1H), 3.01 (dd, *J* = 4.2, 9.6 Hz, 1H), 2.86 (d, *J* = 7.5 Hz, 1H). **Compound 4.** ^{1}H ($CDCl_3$, 300 MHz): δ 7.32 (m, 3H), 7.21−7.03 (m, 5H), 5.53 (dd, *J* = 3.3, 8.7 Hz, 1H), 4.88 (m, 1H), 4.73 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.67 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.26 (dd, *J* = 3.3, 8.7 Hz, 1H), 3.25 (dd, *J* = 9.8, 9.8 Hz, 1H), 2.99 (dd, *J* = 4.2, 9.8 1H), 2.76 (d, *J* = 7.5 1H). **Compound 5.** ^{1}H ($CDCl_3$, 300 MHz): δ 7.62−7.47 (m, 7H), 7.37−7.23 (m, 7H), 5.52 (dd, *J* = 3.4, 8.2 Hz, 1H), 4.94 (m, 1H), 4.83 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.73 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.25 (dd, *J* = 3.6, 8.7 Hz, 1H), 3.34 (dd, *J* = 9.9, 9.9 Hz, 1H), 3.13 (dd, *J* = 4.5, 9.9 Hz, 1H), 3.00 (d, *J* = 7.5 Hz, 1H). **Compound 6.** ^{1}H ($CDCl_3$, 300 MHz): δ 7.36−7.17 (m, 7H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.52 (dd, *J* = 3.3, 8.5 Hz, 1H), 4.87 (m, 1H), 4.73 (m, 2H), 4.26 (dd, *J* = 3.3, 8.5 Hz, 1H), 3.82 (s, 3H), 3.25 (dd, *J* = 9.8, 9.8 Hz, 1H), 3.02 (dd, *J* = 4.2, 9.8 Hz, 1H), 3.83 (d, *J* = 7.3 Hz, 1H). **Compound 7.** ^{1}H ($CDCl_3$, 300 MHz): δ 7.33 (m, 3H), 7.26−7.15 (m, 4H), 7.06 (m, 2H), 5.46 (dd, *J* = 3.3, 8.5 Hz, 1H), 4.84 (m, 2H), 4.70 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.24 (dd, *J* = 3.3, 8.7 Hz, 1H), 3.32 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.16 (dd, *J* = 4.6, 9.5 Hz, 1H), 3.17 (d, *J* = 6.0 Hz, 1H). **Compound 8.** ^{1}H ($CDCl_3$, 300 MHz): δ 7.51 (d *J* = 8.1 Hz, 2H), 7.33 m 5H), 7.01 (dd *J* = 1.5, 7.8 Hz, 2H), 5.45 (dd *J* = 3.5, 8.6 Hz, 1H), 4.91 (m 2H), 4.70 (dd *J* = 8.6, 8.6 Hz, 1H), 4.25 dd *J* = 3.5, 8.9 Hz, 1H), 3.37 (dd *J* = 9.8, 9.8 Hz, 1H), 3.32 (d *J* = 8.6 Hz, 1H), 3.23 (d *J* = 5.1, 9.8 Hz, 1H).

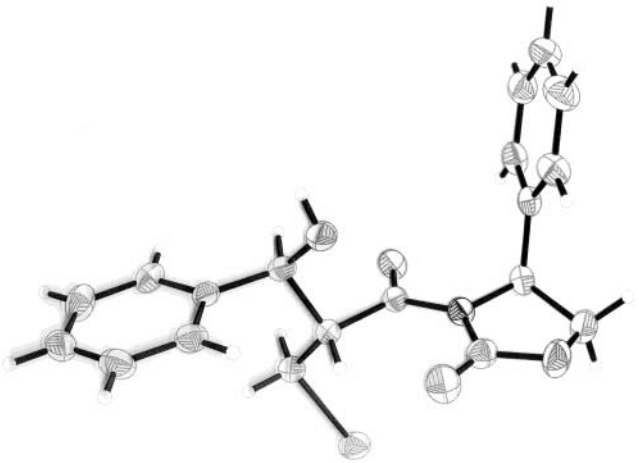


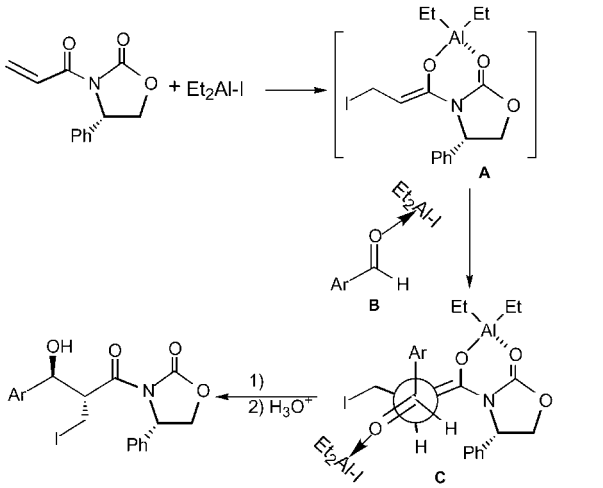
Figure 1. X-ray Structure of a Halo Aldol Product.

chloromethane and hexane (v/v, ~1:1) at 0 °C for a period of one month. The data collected in Table 1 shows that good to excellent yields (80−93%) have been obtained for all aldehydes examined. Excellent diastereoselectivity has been achieved for all of these cases. Essentially, only one isomer was observed for each example, as revealed by ^{1}H NMR analysis of crude products. Both yields and diastereoselectivity are not effected by different substitutions on aromatic rings for substituted aromatic aldehydes. Although only aromatic aldehydes were employed at this stage, aliphatic aldehydes also showed promise in terms of both yields and diastereoselectivity.

Besides 4-phenyl-oxazolidinone, Oppolzer's sultam-attached α,β-unsaturated *N*-acyl substrate was also used as the substrate but resulted in partial success. Modest diastereoselectivity (~2:1) and decreased yields (<60%) were obtained from a more complex mixture of products generated. In addition, α,β-unsaturated *N*-acyl-4-isopropyl-oxazolidinone substrate also resulted in a good yield (~80%), but the diastereoselectivity was decreased to 1.8:1. Meanwhile, when enantiomerically pure 4-benzyl-oxazolidinone was employed as the chiral auxiliary, results similar to those from its isopropyl counterpart were obtained. Obviously, the rigidity of Evans' 4-phenyl-oxazolidinone auxiliary is responsible for the excellent diastereoselectivity for the current asymmetric reaction.

The working hypothesis of this reaction is proposed as shown in Scheme 4. The initial step involves the addition of Et_2AlI to the α,β-unsaturated *N*-acyl-4-isopropyl-oxazolidinone to generate the aluminum enolate (**A**). The Michael-type addition for the formation of this enolate intermediate could be accelerated by the coordination of carbonyl oxygen of aldehyde to the aluminum center to further free the iodine anion. Before the aldol reaction occurs, aldehyde is coordinated onto Lewis acid Et_2AlI to form species **B**. Importantly,

Scheme 4



such coordination allows enolate **A** to remain chelated during the aldol reaction. According to a similar model proposed by Heathcock,[11] the reaction proceeds through an open transition state (**C**). This mechanism hypothesis can account for the observed anti diastereochemistry and chirality of halo aldol adducts.

An excess of diethylaluminum iodide proved to be necessary to achieve high yields and diastereoselectivity. The extra diethylaluminum iodide acts as the Lewis acid catalyst for activating the aldehyde electrophiles. It seems that enolate **A** has a lower activity at low temperatures than nonhalogenated boron enolates, which were well documented by Evans and Heathcock.[12] In those systems, unactivated aldehydes can carry out the aldol reaction smoothly to give syn aldol adducts instead of the anti aldols in our system.

In summary, the first effective asymmetric halo aldol reaction has been established using Et_2AlI as both a halogen source and a Lewis acid. Among the Evans auxiliary series, 4-phenyl-oxazolidinone was found to be the best in controlling the diastereochemistry. Good to excellent yields and complete diastereoselectivity have been achieved. The transformations of halo aldols into other important products will be carried out in our laboratories.

Acknowledgment. We gratefully acknowledge the National Institutes of Health, General Medical Sciences (GM-60261), and the Robert A. Welch Foundation (D-1361, D-1460) for generous support of this work.

Supporting Information Available: X-ray analysis data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027344+

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