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New Asymmetric Halo Aldol Reaction Provides a Novel Approach to Biologically Important Chiral Cyclothers and Cycloamines

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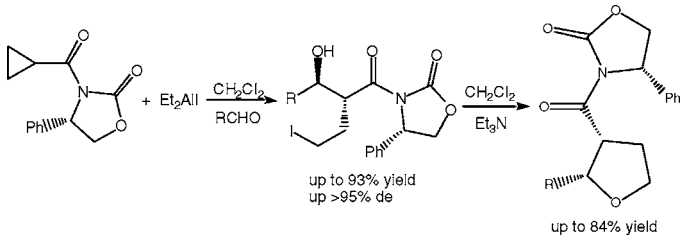
ABSTRACT



A new asymmetric halo aldol reaction has been developed by reacting cyclopropyl carbonyl derived enolates with aldehydes. The absolute structure was unambiguously confirmed by X-ray structural analysis. Eight examples were reported with good yields and up to complete control of diastereomeric excesses. These halo aldol products have been readily cyclized in the presence of weak bases to produce chiral 2,3-disubstituted tetrahydrofuran derivatives in good yield without any observed epimerization.

The asymmetric aldol reaction is among the most important C−C carbon bond formations in organic chemistry and has been an active research topic for several decades.[1−3] Surprisingly, an asymmetric halo aldol reaction has not been established until recently when we became involved in this study.[4,5] The resulting halo aldol products can be used for the synthesis of extended aldols and other numerous important building blocks. The first asymmetric halo aldol reaction was achieved by reacting allenolates with aldehydes in the presence of *N*-C_3F_7CO oxazaborolidine[6] as the catalyst

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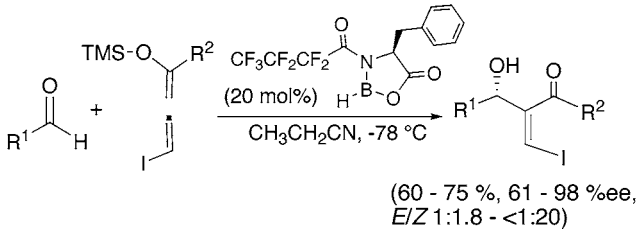
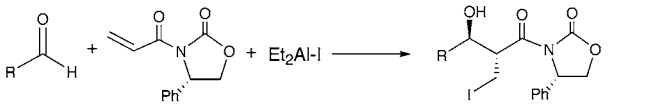
Scheme 1



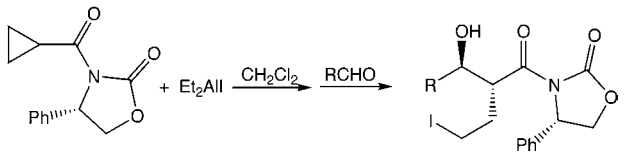
(Scheme 1).[4a] For the catalyst, the fluorinated protecting group was found to be crucial in controlling enantioselectivity. Meanwhile, propionitrile was proven to be the only suitable solvent for multiple in situ preparations for the catalyst and β-iodo TMS-allenolates and subsequent carbonyl addition at −78 °C. The second asymmetric halo aldol reaction was achieved by reacting aldehydes with β-iodo aluminum enolate and by using Evans auxiliary[7] with complete asymmetric control. The β-iodo aluminum enolate was generated by slowly adding the solution of diethylaluminum iodide into the mixture of α,β-unsaturated *N*-acetyl-4-phenyl-2-oxazolidinone in dichloromethane stirring at −20 °C (Scheme 2).

Scheme 2



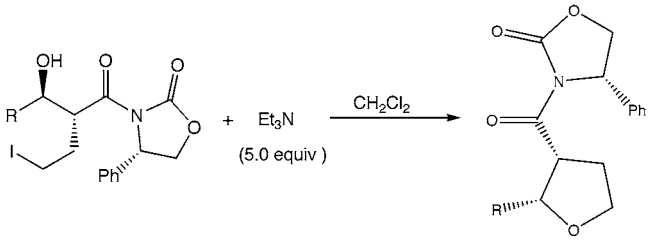
To continue the study of asymmetric halo aldol reaction, we sought to replace the α,β-unsaturated *N*-acyl substrates with cyclopropyl *N*-acyl counterparts since an extra methylene group would be present in the resulting framework of the aldol side chain.[7] In this paper, we wish to report our initial results for this asymmetric process (Scheme 3). More

Scheme 3



significantly, we disclose a concise cyclization by treating the resulting chiral halo aldols with triethylamine to produce biologically important chiral 2,3-disubstituted tetrahydrofuran and tetrahydropyrrole heterocycles (Scheme 4).

Scheme 4



It should be noted that the substituted tetrahydrofuran moiety has been found in a number of natural products and other compounds of interest for bioorganic and medicinal chemistry. Diazonamide,[9] annuionone A,[10] and the leptofuranin series[11] are a few of the many natural products recently synthesized that contain multi-substituted THF units. A number of syntheses have been reported for the preparation of hydroxyl substituted THF derivatives from sugars and other natural sources of chirality.[12] However, to date, very few reports have appeared for the preparation of chiral alkyl-substituted THF derivatives, with even fewer preparations for chiral 2,3-disubstituted THF heterocycles.[13]

First attempts to open the cyclopropyl ring with Et_2AlI at −20 °C proved unfruitful in that most of the starting material was recovered intact after 12 h. However, increasing the temperature to 0 °C proved to be sufficient to completely form the enolate in less than 1 h when dichloromethane was used as a solvent.

Initially, aldehyde (2.0 equiv) and cyclopropyl starting material (1.0 equiv) were premixed in CH_2Cl_2 at 0 °C under N_2 protection. To this solution was added Et_2AlI (1.2 equiv) dropwise over a period of 5 min. The reaction was found to run to completion in 6 h, with very little contamination by the minor isomer. However, it was found that first mixing cyclopropyl starting material and Et_2AlI for 30 min before the addition of the aldehyde resulted in the clean formation of only one isomer, as observed by NMR analysis of the crude reaction mixture. Subsequent purification via column chromatography afforded the product in 80% yield. Toluene and THF were also tested as possible solvents. Toluene was

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comparable to CH_2Cl_2 in both yield and selectivity. When THF was used as a solvent, the yield was slightly diminished (~65−70% as determined by crude NMR analysis). The use of common 4-isopropyl-2-oxazolidinone resulted in the formation of two diastereomers in a 9:1 ratio. The results of the asymmetric halo aldol utilizing cyclopropyl carbonyl starting material are summarized in Table 1.

Table 1. Results of the Asymmetric Halo Aldol Reaction

entry	R	product	time/h	% yield[a]	% de[b]
1	4-BnOC_6H_4−	1	6	82	>95
2	4-FC_6H_4−	2	6	87	>95
3	4-ClC_6H_4−	3	6	92	>95
4	4-BrC_6H_4−	4	6	83	>95
5	3,4-$(CH_3)_2C_6H_3$−	5	6	83	>95
6	PhCHCH−	6	1	93	90
7	PhCHC(Me)−	7	2	84	>95
8	PhCHC(Br)−	8	2	91	>95

[a] Yield after column chromatography. [b] Determined by ^1H NMR analysis of the crude reaction mixture. >95% means that only one isomer was detected.

Unfortunately, none of the above products produced crystals of suitable quality for an X-ray crystallographic structure determination. In an effort to obtain suitable crystals, we sought to protect the hydroxyl group with a 4-nitrobenzenesulfonyl (4-Ns) group. When we performed this reaction using aldol product 1,4-NsCl, Et_3N, and DMAP in dichloromethane, we were surprised to find that the major product was not the nosyl-protected halo aldol product but rather the cyclized tetrahydrofuran derivative. Encouraged by this result, we sought to explore this interesting cyclization.

During the reaction optimization process, it was found that Et_3N alone was sufficient for cyclization. When stirred with 5 equiv of Et_3N in dichloromethane for 12 h, aldol product 1 (Table 1, entry 1) was readily cyclized in 80% yield. Increasing from 5 to 10 equiv of base did not affect the reaction. The use of DMAP showed no improvement in either yield or reaction rate. Potassium carbonate in acetone failed to produce any product after 12 h as detected by NMR analysis of the crude mixture. Using Oshima's condition[13e] of basic alumina provided the product; however, much longer times (>20 h) were required. Interestingly, this reaction was found to be rather solvent dependent. When dichloromethane was replaced with THF, the yield was approximately cut in half for the same reaction time. When toluene was used, no product was obtained at all. The halo aldol products were only sparingly soluble in ether and the reaction was very slow. The optimized yields for the various products are reported in Table 2. For all cases, no epimerization was observed.

Fortunately, the formation of aldol product 9 (Table 2, entry 1) enabled us to recrystallize and get white monoclinic crystals. The structure and absolute stereochemistry of the

Table 2. Results of Cyclization of Halo Aldols

entry	R	product[a]	% yield[b]
1	4-BnOC_6H_4−	9	80
2	4-FC_6H_4−	10	74
3	4-ClC_6H_4−	11	78
4	4-BrC_6H_4−	12	77
5	3,4-$(CH_3)_2C_6H_3$−	13	80
6	PhCHCH−	14	84
7	PhCHC(Me)−	15	66
8	PhCHC(Br)−	16	78

[a] All experiments were performed within 12 h. [b] Yield of analytically pure product after column chromatography.

product were subsequently confirmed by X-ray crystallography. The crystal structure diagram is shown in Figure 1.

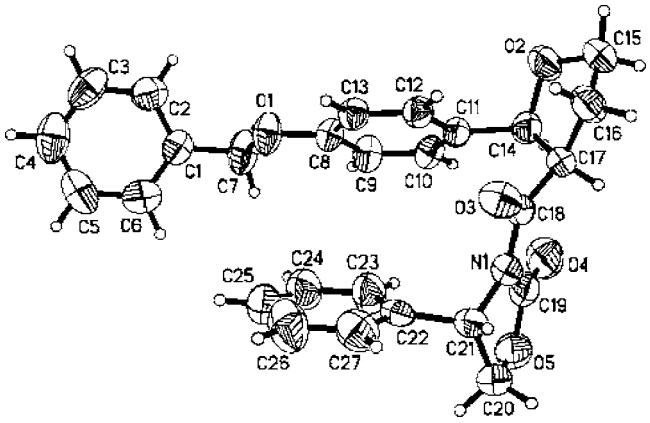


Figure 1. X-ray structure of a disubstituted tetrahydrofuran heterocycle.

This stereochemistry of the initial halo aldol reaction can possibly be explained by the transition state proposed in Figure 2. This open transition state, similar to that proposed by Heathcock,[14] allows for the enolate to remain chelated throughout the reaction, while the aldehyde is activated by the excess Et_2AlI. This is supported by the fact that an excess

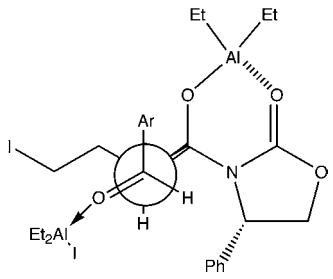


Figure 2. Asymmetric induction manner.

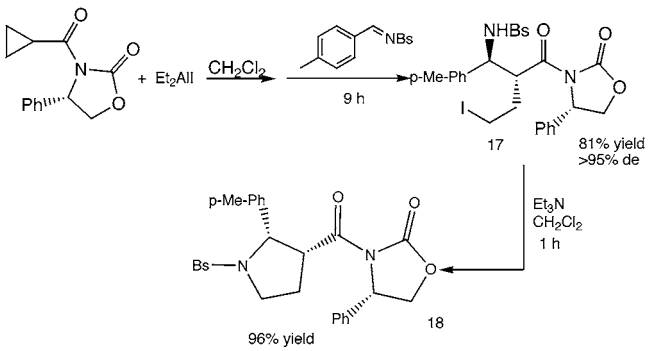
amount of diethylaluminum iodide was found to be necessary for high yields.

The ring formation is interesting from a mechanistic point of view. In a typical iodoetherification reaction, an alkoxide is first formed and then added to an alkyl halide for S_N2 displacement. The fact that a weak base can readily perform the present transformation suggests that the primary alkyl iodide center could be activated by triethylamine, which was followed by subsequent cyclization to give the tetrahydrofuran product.

Work is currently in progress to apply this same methodology using sulfonyl-protected imines to replace aldehydes.[15] At the time of writing, promising results have been obtained for the halo aldol type reaction and subsequent cyclization for one substrate. The results are shown in Scheme 5. A further study will be performed in this laboratory and will be the topic of a future publication.

In summary, the first cyclopropyl carbonyl-based asymmetric halo aldol reaction has been achieved. Good to excellent yields and selectivities have been obtained for a variety of substrates. A concise cyclization is reported by using a weak base to form tetrahydrofuran heterocycles. This is among the most efficient and concise methods reported to date for the formation of chiral 2,3-disubstituted THF derivatives. Furthermore, promising results have been obtained utilizing imines instead of aldehydes. The resulting halo Mannich-type product is also easily cyclized to afford the chiral 2,3-disubstituted pyrrolidine derivative.

Scheme 5



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