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The enantioselective halo aldol reaction utilizing cyclopropyl ketone-derived enolates

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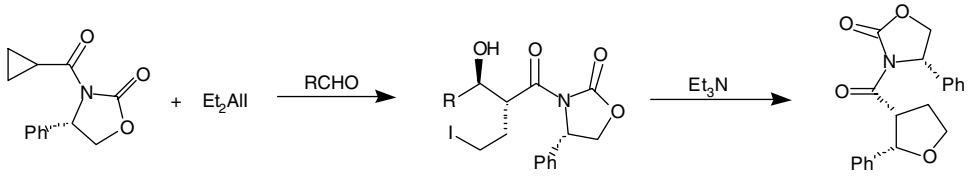
Abstract—A new enantioselective halo aldol reaction is reported using a chiral borane catalyst. The absolute stereochemistry of the product was unambiguously determined by chemical transformations and a preliminary mechanistic study is reported.

Since the inception of asymmetric catalysis, the asymmetric aldol reaction has arguably been one of the most widely studied and widely utilized processes in organic chemistry.[1,2] Numerous elegant reports of both Lewis acid[3] and Lewis base[4] catalyzed versions have appeared in the literature. Since Mukaiyama's findings that silyl enol ethers undergo Lewis acid catalyzed aldol-type transformations, this area of asymmetric synthesis has flourished.[5] While numerous target-oriented syntheses have successfully employed asymmetric aldol reactions, a fundamental limitation lies in the lack of aldol products that are highly functionalized.

To address this limitation, we and others have developed a series of halo aldol reactions in which the aldol side chains are further functionalized by the presence of a halogen.[6] Quite recently, we developed one such reaction utilizing cyclopropyl imides bearing a chiral oxazolidinone auxiliary.[7] Et_2AlI was used as dual purpose Lewis acid promoter and halogen source to provide the corresponding iodo enolates, which were subsequently reacted with aldehydes to furnish the halo aldol products with high diastereoselectivities. Such products were also found to be easily cyclized to furnish the corresponding chiral *cis*-2,3-disubstituted tetrahydrofuran derivatives (Scheme 1).

Although this chiral auxiliary approach produced good results, an inherent limitation is the fact that a stoichiometric amount of the auxiliary must be initially introduced into the starting material and, ultimately, removed in an additional step. In an effort to improve upon this, we sought to develop an enantioselective version of this reaction by employing a suitable chiral Lewis acid promoter. In this letter, we are pleased to report our initial results in this area. This work represents the first enantioselective halo aldol reaction employing enolates derived from cyclopropyl ketones.

The model reaction employed for optimization was that between benzaldehyde and cyclopropyl phenyl ketone. Attempts to perform this transformation with



Scheme 1.

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a stoichiometric amount of BinolTiCl$_2$ and BinolTi(O-*i*-Pr)$_2$ resulted in the opening of the cyclopropyl ketone, but with only trace amounts of aldol product was formed at reasonable reaction times. Similarly, the use of BinolAlI successfully opened the ring, but failed to promote aldol-type addition to the aldehyde. The use of MgI_2 failed to open the ring to any appreciable degree at or below room temperature, so chiral ligand–MgI_2 complexes were not further examined.

With these results in hand, focus was redirected to Mukaiyama-type reactions for this process. When cyclopropyl phenyl ketone was reacted with trimethylsilyl iodide (TMSI) at room temperature, the formation of the corresponding γ-iodo trimethylsilyl enol ether was quantitatively observed within 1 h.[6g] With this in mind, a series of chiral Lewis acid catalysts were screened. Again, the aforementioned Ti and Al complexes worked poorly, affording either low yields or even no products at all. The first encouraging results came when a complex prepared from *N*-heptafluorobutyryl-D-phenylalanine was used. This complex was chosen because it was previously found to be successful in our asymmetric synthesis of β-iodo-Baylis–Hillman adducts.[6a]

Initially, when the reaction between benzaldehyde and the enolate of cyclopropyl phenyl ketone was conducted at −78 °C in CH_2Cl_2, no product was observed when 20% of the above-mentioned catalyst was used. However, when the reaction temperature was raised to 0 °C, the reaction afforded the desired product in 50% yield with an *anti*/*syn* ratio of 7/1. The *anti* isomer was obtained in 10% ee, while the *syn* isomer was essentially racemic. Attempts at performing this reaction at room temperature resulted in the formation of complex product mixtures, while reaction temperatures of −20 °C or lower resulted in the complete recovery of starting materials. Changing the solvent to acetonitrile improved the ee to 35% for the major (*anti* isomer). A screening of other solvents (THF, ether, toluene) showed that no products were formed in any of these cases. Interestingly, the use of freshly distilled propionitrile, which should be quite similar to acetonitrile, repeatedly resulted in inferior yield (ca. 20%), diastereoselectivity (2:1), and ee (20%).

Initial catalyst screening was performed by adding the catalyst via a syringe pump over a 12 h period to a stirring solution of the silyl enol ether and benzaldehyde at 0 °C. Various amino acids and protecting groups were utilized with the results listed in Table 1.

As can be seen from Table 1, only two amino acids, phenylalanine and phenylglycine, were found to induce enantioselectivity to a significant degree. Interestingly, the use of phenylglycine-derived catalyst resulted in significant enantioinduction in the minor (*syn*) diastereomer. However, in light of the superior *anti*/*syn* ratio found in entry 4, the phenylalanine-derived catalyst was ultimately chosen as the catalyst of choice.

Protecting group choice was also found to be crucial. Several acyl groups were screened and were found to be inferior to the heptafluorobutyryl group. It should be noted that the protected amino acids in entries 6 and 9 of Table 2 were only sparingly soluble in acetonitrile and thus failed to be active in this process. Also worthy of mention is that the catalyst with the commonly used 4-Ts protecting group (entry 10) afforded the product in which the enantiomeric excess of the *syn* isomer was much greater than that of the *anti* isomer.

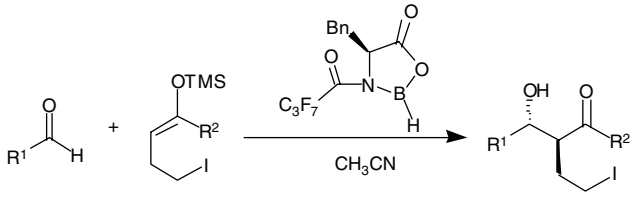
Another variable studied was the effect of the order and manner of addition of the various reaction components. Best results were obtained by fast addition of the catalyst (preformed by heating a CH_3CN solution of

Table 1. Catalyst screening results

Entry	Amino acid	PG	% Catalyst	dr (*anti*:*syn*)[a]	% ee[a,b]
1	R = Bn	C_3F_7CO	20	7.5:1	35 (0)
2	R = Bn	C_3F_7CO	30	6:1	44 (2)
3	R = Bn	C_3F_7CO	40	8:1	49 (6)
4	R = Bn	C_3F_7CO	50	8:1	57 (3)
5	R = Bn	C_3F_7CO	100	8:1	59 (5)
6	R = Bn	CF_3CO	50	No reaction	
7	R = Bn	CH_3CO	50	3:1	13 (2)
8	R = Bn	PhCO	50	2:1	10 (2)
9	R = Bn	C_6F_5CO	50	No reaction	
10	R = Bn	Ts	50	3:1	8.5 (27)
11	R = Ph	C_3F_7CO	50	4:1	51 (45)
12	*s*-Bu	C_3F_7CO	50	3:1	33 (15)
13	*i*-Pr	C_3F_7CO	50	4:1	28 (7)
14	Tryptophan	C_3F_7CO	50	3:2	21 (9)

[a] Determined by analytical HPLC using a Chiracel OD-H column.
[b] Values in parentheses indicate the % ee of the minor isomer.

Table 2. Results of enantioselective halo aldol reaction of cyclopropyl ketone-derived enolates with aldehydes



Entry	R^1	R^2	Yield[a]	dr[b] (*anti*:*syn*)	% ee[c]
1	Ph	Ph	83	>15:1	63 (NA)
2	4-Me-C_6H_5	Ph	81	6:1	54 (10)
3	4-F-C_6H_5	Ph	67	5:1	44 (21)
4	4-Cl-C_6H_5	Ph	79	13:1	59 (NA)
5	4-Br-C_6H_5	Ph	74	6:1	55 (18)
6	2-Me-C_6H_5	Ph	79	5:1	58 (9)
7	Ph	2-Thienyl	66	>15:1	45 (NA)
8	Ph	4-F-C_6H_5	77	5:1	52 (6)[d]

[a] Overall yield for *anti* and *syn* isomers.
[b] Determined by ^{1}H NMR and/or HPLC analysis of the crude reaction mixture.
[c] Determined by analytical HPLC using a Chiracel OD-H column with isopropyl alcohol–hexane 1:20 as the eluent. Values in parentheses refer to the ee of the minor isomer.
[d] Determined using a Chiracel AD column with isopropyl alcohol–hexane 1:20 as the eluent.

borane·THF complex and *N*-heptafluorobutyryl-D-phenylalanine at 40 °C for 1 h) to an ice cold CH_3CN solution of the TMS-enol ether. Subsequent 12 h slow addition of aldehyde (dilute in CH_3CN) was followed by an additional 12 h reaction time before standard acidic workup. In this manner, the % ee was increased from 57% to 63% with benzaldehyde.

With these optimized conditions in hand, we explored the generality of this reaction with a variety of aldehyde and cyclopropyl ketone substrates. The results are reported in Table 2.

As can be seen in Table 2, this reaction exhibits broad scope in both the aromatic aldehyde and cyclopropyl ketone substrates. Unfortunately, several attempts at employing aliphatic aldehydes ($R^1 = n$-Pr, *s*-Bu, and *t*-Bu) repeatedly failed, giving in all cases complex product mixtures and no detectable halo aldol products. Worthy of mention is that the use of heteroaromatic substrate of entry 7 resulted in very high *anti* diastereoselectivity, albeit at a slight decrease in enantioselectivity.

The stereochemistry of the product (Table 2, entry 1) was unambiguously determined by chemical transformation and comparison with a product of known stereochemistry. A chiral 2,3-disubstituted THF derivative was prepared according to our previously published procedure. Base hydrolysis under the conditions reported by Evans et al.[8] afforded the 2-phenyl-3-carboxylic acid derivative, which was directly protected as the methyl ester. Reaction with 2 equiv of PhMgBr provided the corresponding target alcohol. Product 1 of Table 1 was conveniently cyclized in 85% yield by treatment with 5 equiv of Et_3N in CH_2Cl_2 for 24 h. Subsequent treatment with PhMgBr afforded the target alcohol, which had ^1H and ^{13}C NMR spectra that were identical with the alcohol of known stereochemistry. HPLC analysis of these products showed them to be enantiomers. The transformation sequence is illustrated in Scheme 2. In addition, this sequence demonstrates an additional approach to enantiomerically enriched *cis*-2,3-disubstituted tetrahydrofuran derivatives, an important class of heterocycles in biomedicinal and natural product chemistry.

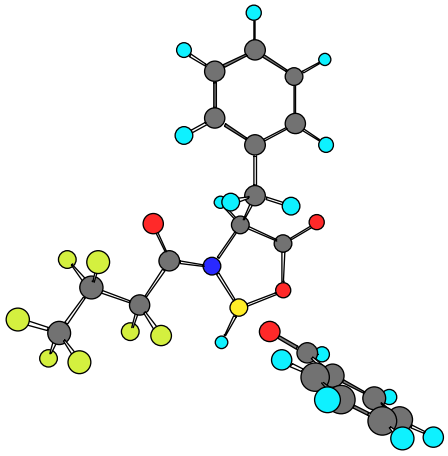


Figure 1.

In an effort to explain the stereochemistry of the reaction, semi-empirical calculations were carried out to determine the nature of the catalyst/aldehyde activated complex.[9] Calculations at the AM1 level of theory found three viable energy minima that are within 3 kcal/mol of each other. The lowest energy conformation is shown in Figure 1. Attack on the *Si*-face of the aldehyde, which is required for the formation of the product with the correct stereochemistry, would require the approach of an *E*-enolate from the side opposite to the heptafluorobutyryl group. The presence of several such energy minima with similar energies could help explain the inability of this system to achieve high enantioselectivities.

In conclusion, a novel asymmetric halo aldol reaction has been developed. Good yields and moderate selectivities were achieved for a variety of substrates. This work represents the first enantioselective halo aldol reaction utilizing cyclopropyl ketone-derived enolates.

Acknowledgments

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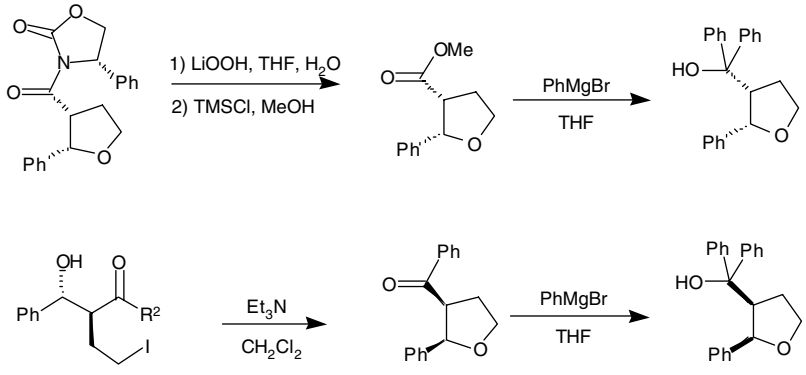

Scheme 2.

Supplementary data

The experimental procedures, ^{1}H NMR, ^{13}C NMR, and FTIR data, HPLC conditions and retention times, and Cartesian coordinates and energies for all calculated energy minima are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.163.

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