Enantioselective Cross Aldol Reactions of Aldehydes

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Introduction

The enantioselective cross-aldol reaction using proline catalysis pioneered by MacMillan et al.[1] is a successful tool for synthesizing stereospecific β-hydroxyaldehydes. While the use of proline catalysis overcomes aldehyde polymerization common with metal catalysis and the need to isolate nonequivalent aldehydes during the reaction, this modification of the Hajos-Parrish-Barbas-List reaction[2,3,4] relies heavily upon a 10:1 ratio of electrophilic acceptor to nucleophilic donor for success. In the laboratory, this practice can be financially costly when using expensive electrophilic acceptor aldehydes for the cross-aldol reaction.

This goal of this project was to determine the minimum ratio of electrophilic acceptor to nucleophilic donor necessary to afford the best yields of the MacMillan enantioselective cross-aldol reaction. To achieve this goal, a series of reactions were set up following the conditions outlined by MacMillan, with variations to the electrophilic acceptor/nucleophilic donor ratio to improve yield and reduce hazardous waste by performing this reaction at close to molar equivalence. A series of six different electrophilic acceptors were chosen, four of which had not been previously tested by MacMillan and were chosen to expand the effectiveness of the reaction on electrophilic acceptors aldehydes with α–hydrogens while the identity of the nucleophilic donor was kept constant as propionaldehyde. The ultimate goal of this research project is to determine the effectiveness of these reaction conditions for coupling an electrophilic acceptor aldehyde that contains an acid sensitive α–hydrogen with propionaldehyde.

Methods

General procedures: To a 100 mL round bottom flask was combined the electrophilic aldehyde (10 mmol, 10 eq.) and L-proline (0.100 mmol, .1 eq.) in DMF (4.5 mL) and allowed to cool to 3 °C with magnetic stirring under an Ar atmosphere. Then, a solution of propionaldehyde (1 mmol, 1 eq.) in DMF (0.500 mL) was added via a syringe pump over 24 h at 3° C. The mixture was left to stir for another 24 h at 3° C.

Reaction

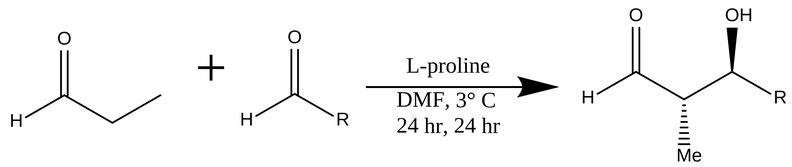
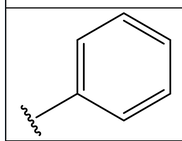
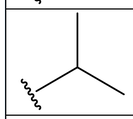
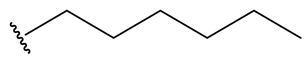
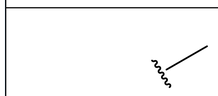
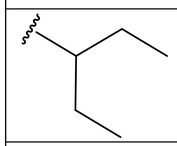
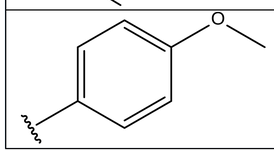


Figure 1: Example of Enantioselective Cross Aldol Reaction

Results

Table 1: Percent Yields of R-groups at Molar Ratios.

R-group	Molar Ratio Aldehyde:Propionaldehyde	Yield
	10:1	75.0%
	5:1	80.0%
	1:1	3.80%
	2:1	48.9%
	1:1	20.1
	10:1	3.00%
	5:1	43.3%
	1:1	9.4%
	10:1	17.6%
	5:1	35.1%
	1:1	35.9%
	10:1	28.6%
	5:1	38.0%
	1:1	30.4%
	10:1	16.6%
	5:1	20.7%
	1:1	15.2%

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Methods

The reaction mixture was diluted with EtOAc (50 mL) and the organic layer was washed with H_2O (15 mL) and brine (15 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The organic layers were combined, dried with $MgSO_4$ (anhydrous), and concentrated *in vacuo*.

Purification via flash chromatography (8:1 Hexanes : EtOAc, then 1:1 Hexanes : EtOAc) afforded the desired cross-aldol product. Glass backed TLC plates were stained with PMA. Characterization of the product was performed by FT-IR and ^{1}H NMR analysis.

For each electrophilic aldehyde tested, the molar ratios listed in **Table 1** were followed.

Conclusion

After examining the results, it appears that there was difficulty creating the desired products when testing with electrophilic acceptors aldehydes with α–hydrogens. This can be seen by the low percent yields obtained in most of the trials. An interesting point to note was that the percent yield did tend to increase from 10:1 to 5:1 ratios. However, going from 5:1 (or 2:1 in the case of Isobutyraldehyde) to 1:1 did not seem to have the same success outside of the Acetaldehyde trials.

References

1. Northrup, A. B.; MacMillan D. W. C. *J. Am. Chem. Soc.* **2002,** 124, 6798-6799.
2. (a) Kandasamy, S.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) Cordova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301.
3. (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (c) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
4. (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *10*, 496. (c) Agami, C.; Platzer, N.; Sevestre, H. *Bull. Chim. Soc. Fr.* **1987**, *2*, 358.