Solvent- or Temperature-Controlled Diastereoselective Aldol Reaction of Methyl Phenylacetate

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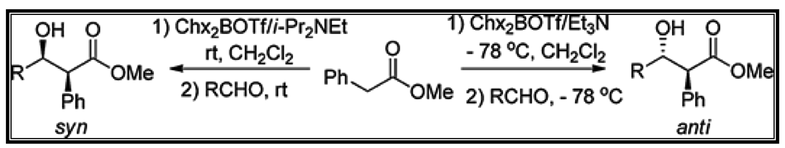
Introduction

Previous studies of Boron-mediated Aldol reactions included the investigation of numerous phenylacetates; primarily Methyl Phenylacetate with n-Bu_2BOTf and Ethyl Phenylacetate with Chx_2BI. However, Chx_2BI is unstable and is very sensitive to ethereal solvents. Examination was refocused on a Phenylacetate with Chx_2BOTf because of its ease to prepare. The research also has allowed complete control of diastereoselectivity by changing the solvent or temperature and by keeping the same reagents.



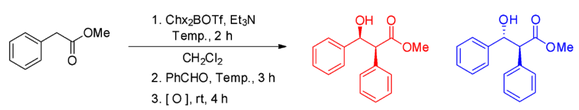
Solvent & Temperature Controlled Diastereoselectivity

In the literature, investigation was started by changing alkoxy group of ester. Less bulky alkoxy group provided syn-aldols, more bulky group produced anti-aldols. However, t-butoxy group did not provide aldol products. Then investigation was focused on the examination of effects of solvent and temperature on diastereoselectivity of aldol reactions. The examination of the diastereoselectivity of the reaction was tested by changing the solvent. Enolization of the methyl ester in CCl_4 happened to yield 90% *anti*. The same reaction was ran using pentane and ether and the reactions yielded between 79% and 84% anti. The solvent CH_2Cl_2 favored the *syn* selectivity We concluded that less polar solvents favor ***anti*** selectivity.

The effect of temperature was examined next and the results demonstrated a pattern. The CH_2Cl_2 favored the *syn* selectivity and anti selectivity at low temperature. This concluded that thermodynamic enolate is formed at high temperature and kinetic enolate is formed at low temperature.

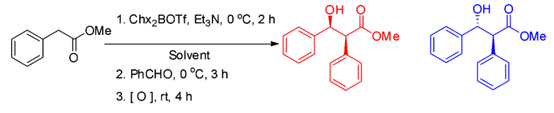
Temperature Optimization

Entry	Enolization Temp.	Aldolization Temp.	Yield (%)	*syn*:*anti*
1	-78 °C	-78 °C	91	2:98
2	-30 °C	-30 °C	85	18:82
3	0 °C	0 °C	88	80:20
4	rt	rt	78	88:12
5	reflux	reflux	84	88:12



Solvent Optimization

Entry	Solvent	Yield (%)	*syn*:*anti*
1	CH_2Cl_2	88	80:20
2	CCl_4	82	12:88
3	Pentane	79	9:91
4	Et_2O	84	10:90



Conclusions

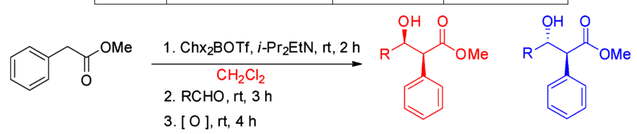
The aldol reaction of Methyl Phenylacetate can generate *syn*-selective or *anti*-selective product by incorporating the required solvent and temperature. Low temperature provides anti aldols and room temperature provides syn aldols. Non polar solvents provide anti aldols and polar solvents provide syn aldols.

Acknowledgements

I thank Dr. Chanda for giving me another opportunity to work in his research group for another semester.

Syn-Selective Aldol Reactions

Entry	R	Yield (%)	*syn*:*anti*
1	Ph	79	90:10
2	*p*-$CH_3C_6H_4$	83	85:15
3	*p*-$MeOC_6H_4$	88	79:21
4	*p*-FC_6H_4	83	87:13
5	*p*-$NO_2C_6H_4$	79	85:15
6	*E*-PhCH=CH	89	81:19
7	thiophene-2-yl	87	76:24
8	*n*-Pr	87	89:11
9	*i*-Pr	82	85:15
10	*t*-Bu	89	62:38



Anti-Selective Aldol Reactions

Entry	R	Yield (%)	*syn*:*anti*
1	Ph	91	2:98
2	*p*-$CH_3C_6H_4$	87	2:98
3	*p*-$MeOC_6H_4$	81	3:97
4	*p*-FC_6H_4	81	4:96
5	*p*-$NO_2C_6H_4$	93	4:96
6	*E*-PhCH=CH	82	5:95
7	thiophen-2-yl	92	4:96
8	*n*-Pr	96	2:98
9	*i*-Pr	86	4:96
10	*t*-Bu	89	4:96