Probing Parallel Kinetic Resolution of 1-Phenyethanol using Active Esters as *Quasi*-Enantiomers

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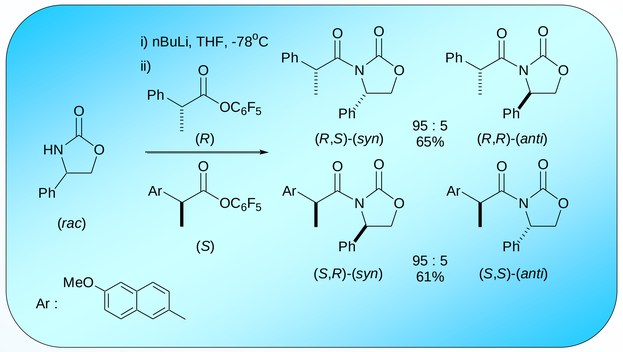
Abstract: The parallel kinetic resolution of racemic secondary arylalkyl alcohols using an equimolar amount of *quasi*-enantiomeric active esters and zinc chloride is discussed. The levels of enantiomeric recognition were high leading to enantiomerically enriched alcohols in good yield.

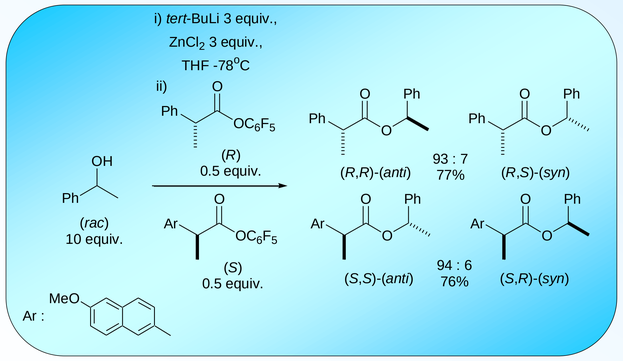
Scheme 1: PKR of Oxazolidin-2-ones



In recent years we have developed a method for using active esters as *quasi*-enatiomers in the parallel kinetic resolution (PKR) of oxazolidin-2-ones (Scheme 1).[1] This method has proven to be both reliable and highly selectivity.

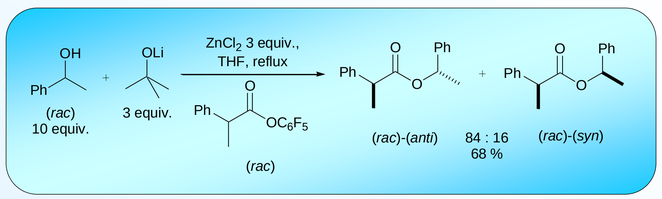
More recently we have extended this methodology towards the PKR of 1-phenyethanol (Scheme 2).[2] This reaction proved to be highly selective; however, the use of *tert*-BuLi as a base, made the reaction extremely sensitive to trace amounts of water.

Scheme 2: PKR of 1-Phenylethanol using *tert*-BuLi



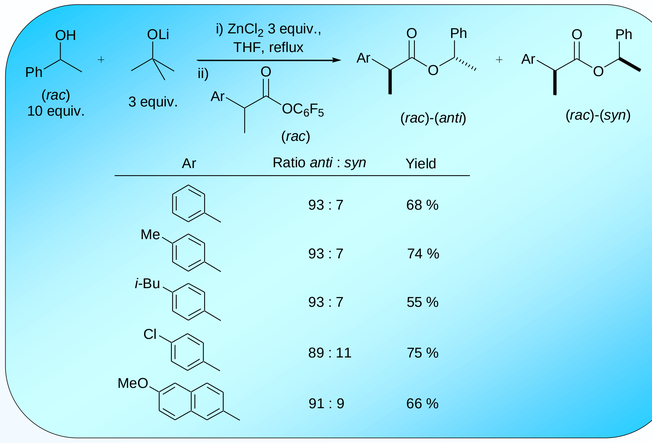
We have since found that this method can be made more robust by using the less reactive lithium *tert*-butoxide instead of *tert*-BuLi for the mutual kinetic resolution (MKR) of 1-phenyethanol with a pentafluorophenyl active ester (Scheme 3) . In order for this less reactive akoxide to form the appropriate salt with 1-phenylethanol and zinc chloride, the first step of the reaction was carried out at an elevated temperature in refluxing THF. The addition of the active ester is carried out at room temperature, so that the reaction can proceed under kinetic control.[3]

Scheme 3: MKRs of 1-phenyethanol using lithium alkoxide



With a more robust method in hand, we chose to screen a variety of structurally related active esters that contained different aryl substituents (Scheme 4). Interestingly changing the aryl group of these active esters appeared to have very little impact on the diastereoselectivity of these reactions (highest selectivity 93:7, lowest is 89:11).

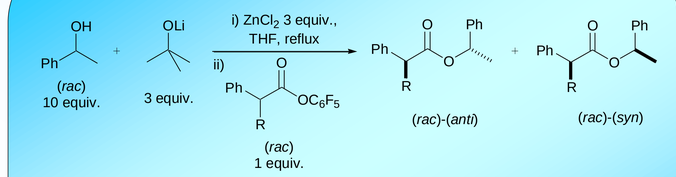
Scheme 4: MKRs with alternative aromatic groups



Ar	Ratio *anti* : *syn*	Yield
	93 : 7	68 %
Me	93 : 7	74 %
i-Bu	93 : 7	55 %
Cl	89 : 11	75 %
MeO	91 : 9	66 %

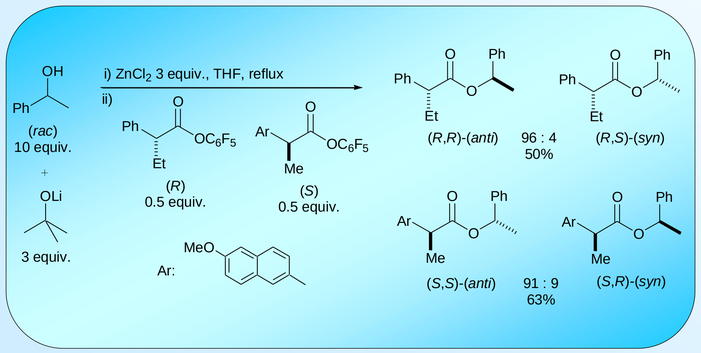
We next chose to investigate the use of two pentafluorophenyl butanoates to probe the size of their aliphatic groups (Scheme 5). This affected the resolution dramatically; the larger aliphatic groups reduced the rate of the reaction. It would also appear that a moderate sized aliphatic group (Et) gives improved levels of selectivity over its smaller (Me) and larger (*i*-Pr) counterparts.

Scheme 5: MKR with alternative aliphatic groups



Entry	R	Ratio *anti* : *syn*	Yield
1	Me	93 : 7	68 %
2	Et	96 : 4	60 %
3	*i* -Pr	~ 90 : 10	~1 %

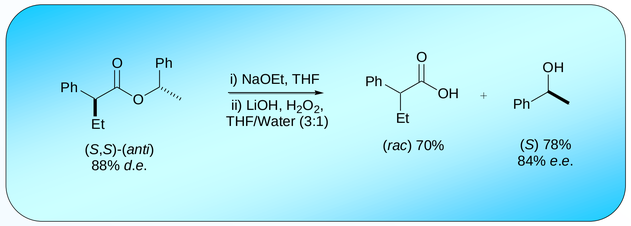
Scheme 6: PKR of 1-Phenylethanol



This improved method has been shown to work successfully for the PKR of 1-phenyethanol using a pair of *quasi*-enantiomeric active ester (Scheme 6). This pair of active ester were chosen from those screened because of their high levels of selectivity (in their corresponding MKRs) and their difference in polarity, so that separation of the required products could be easily achieved.

Access to the resolved 1-phenylethanol was achieved, without any loss of optical purity,[4] by transesterification using sodium ethoxide followed by hydrolysis using lithium hydroxide and hydrogen peroxide.

Scheme 7: Hydrolysis of the Esters



To conclude, we have improved our previous highly selective PKR so that it is more robust. This new method has been used to screen a wide range of alterative active esters.

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References

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4. J. Eames and E. Coulbeck, *Tetrahedron: Asymmetry*, **2009**, *20*, 635-640.