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[A0010]

Parallel Kinetic Resolution of 1-Phenylethanol Using *Quasi*-Enantiomeric Active Esters

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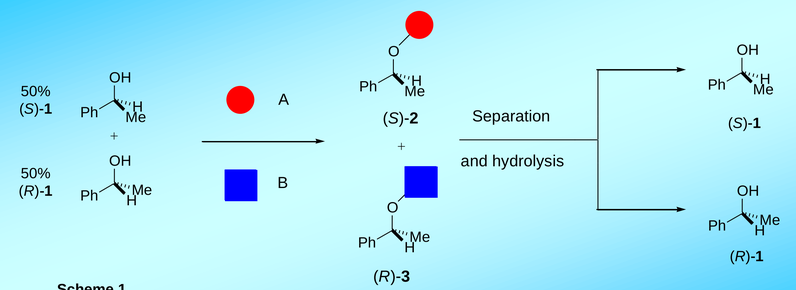
Introduction

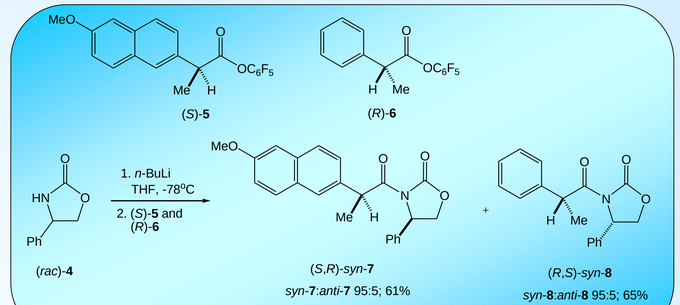


Scheme 1

Parallel Kinetic Resolutions (PKRs) involves the parallel separation of enantiomers under kinetic control as outlined in Scheme 1.[1]

We have recently reported the parallel kinetic resolution of racemic oxazolidinone (*rac*)-**4** using a combination of *quasi*-enantiomeric active esters (*S*)-**5** and (*R*)-**6** (Scheme 2).[2] These processes proceeded efficiently to give separable diastereoisomeric adducts (*S*,*R*)-*syn*-**7** and (*R*,*S*)-*syn*-**8** in good yields with excellent levels of stereocontrol (>90% *d.e.*) (Scheme 2).

Previous Parallel Kinetic Resolutions

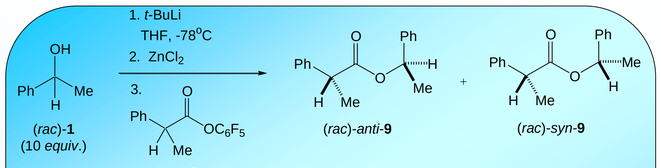


Scheme 2

Preliminary MKR study

We now report an extension of this methodology towards the resolution of 1-phenylethanol (*rac*)-**1** using an equimolar combination of active esters.[3]

For this study, we chose to use lithium 1-phenylethoxide [formed by addition of *t*-BuLi to 1-phenylethanol (*rac*)-**1**] as our nucleophilic source of 1-phenylethanol. Under our standard mutual kinetic conditions, addition of lithium 1-phenylethoxide (*rac*) to a solution of active ester (*rac*)-**6**, gave an inseparable mixture of esters (*rac*)-*anti*- and *syn*-**9** in 72% yield with poor diastereoselection (24% *d.e.*) (Scheme 3: Entry 1). However, the diastereocontrol was found to improve significantly by the simple addition of $ZnCl_2$ from 24% *d.e.* to 94% *d.e* (Scheme 3: Entry 1→4). The optimum amount required was found to use 3 equivalents of $ZnCl_2$ and *t*-BuLi and 10 equivalents 1-phenylethanol.

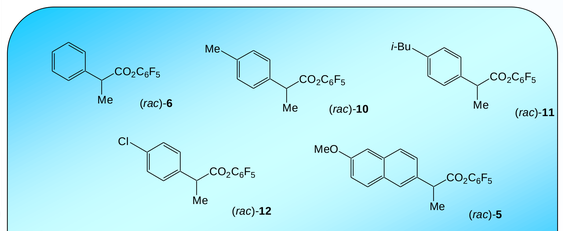


Entry	*t*-BuLi (*equiv.*)	$ZnCl_2$ (*equiv.*)	ratio *anti*-:*syn*-**9**	*d.e.*	Yield
1	3.0	0.0	62:38	24%	72%
2	3.0	1.5	72:28	44%	72%
3	3.0	3.0	94:6	88%	71%
4	3.0	6.0	97:3	94%	32%

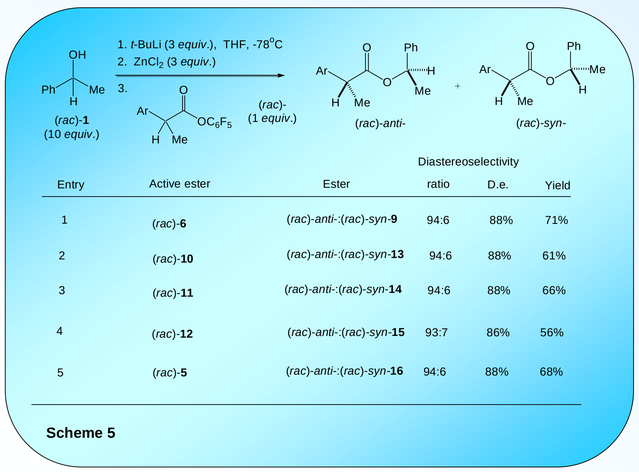
Scheme 3

Probing Different Active Esters

With this information at hand, we turned our attention to probing the use of structurally related active esters (Schemes 4 and 5). From this study, it was shown that the substitution pattern of the aryl ring had little or no effect on the stereochemical outcome of these processes.



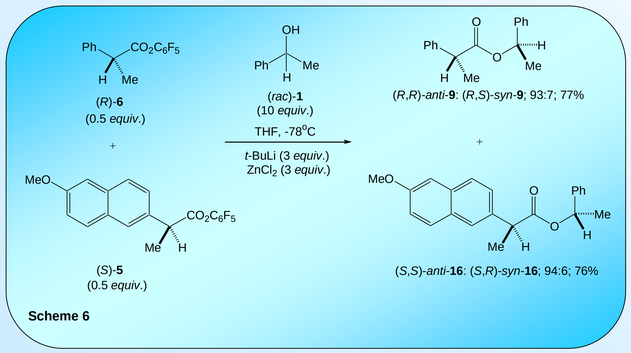
Scheme 4



Entry	Active ester	Ester	ratio	D.e.	Yield
1	(*rac*)-**6**	(*rac*)-*anti*-:(*rac*)-*syn*-**9**	94:6	88%	71%
2	(*rac*)-**10**	(*rac*)-*anti*-:(*rac*)-*syn*-**13**	94:6	88%	61%
3	(*rac*)-**11**	(*rac*)-*anti*-:(*rac*)-*syn*-**14**	94:6	88%	66%
4	(*rac*)-**12**	(*rac*)-*anti*-:(*rac*)-*syn*-**15**	93:7	86%	56%
5	(*rac*)-**5**	(*rac*)-*anti*-:(*rac*)-*syn*-**16**	94:6	88%	68%

Scheme 5

PKR of 1-Phenylethanol

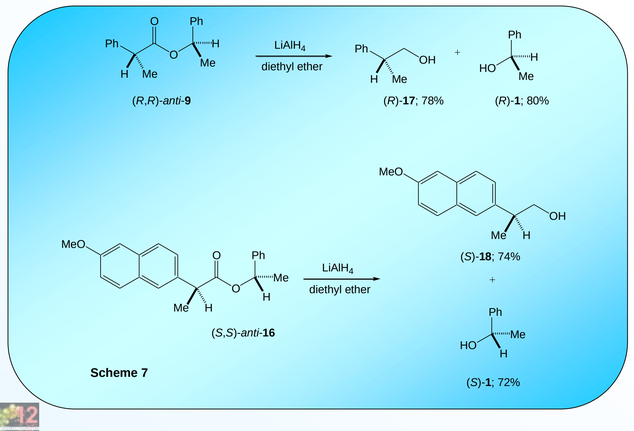


Scheme 6

We next chose to investigated the parallel kinetic resolution (PKR) of 1-phenylethanol (*rac*)-**1** using an equimolar combination of active esters (*R*)-**5** and (*S*)-**6** which were known to be separable {by flash column chromatography - ΔR_F [light petroleum 40-60ºC: diethyl ether (9:1)] = 0.19}. This resolution proceeded efficiently to give esters *anti*- and *syn*-**9** in 77% yield with 86% *d.e.* (93:7) and *anti*- and *syn*-**16** in 76% yield with 88% *d.e.* (94:6).

Access to the resolved 1-phenylethanol **1** was achieved by simple $LiAlH_4$ reduction of esters **9** and **16** to give (*R*)- and (*S*)-1-phenyethanol **1** in good yield (Scheme 7). We are currently studying the mechanism of this process and the outcomes will be reported in due course.

Reduction of the Esters



Scheme 7

Conclusion and Acknowledgments

We have shown that 1-phenylethanol **1** can be resolved efficiently using a combination of *quasi*-enantiomeric active ester giving access to both enantiomers of 1-phenylethanol **1** in 86% *e.e.*[4]

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References

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3. Coulbeck, E; Eames, J. *Tetrahedron Asymmetry*, **2007**, 18, 2313.
4. Coulbeck, E; Eames, J. *Synlett*, **2008**, 333.