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[c002]

Probing The Resolution of 2-Alkoxy and 2-Aryloxy Carboxylic Acids

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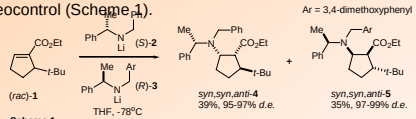
Introduction

The separation of enantiomeric substrates using a parallel kinetic resolution strategy is becoming increasingly popular.[1] In recent years,
attention has focussed on the use of traditional chiral auxilaries as complementary *quasi*-enantiomeric resolving agents.[2] In particular, Davies,[3] has elegantly shown the parallel kinetic resolution of the racemic enone (*rac*)-**1** using a pair of *quasi*-enantiomeric lithium amides (*S*)-**2** and (*R*)-**3** to give the corresponding *syn*,*syn*,*anti*-adducts **4** and **5** with near perfect levels of complementary stereocontrol (Scheme 1).



Scheme 1

Concept of Parallel Kinetic Resolution (PKR)

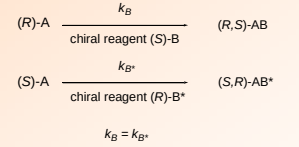
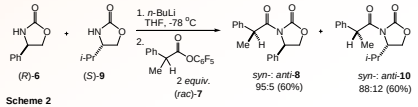


Figure 1

For an efficient parallel kinetic resolution (PKR), the complementary *quasi*-enantiomer is used to remove the unwanted enantiomer in parallel during the reaction.[1] Ideally the reaction rates for both enantiomers (k_B and k_{B*}) are identical.

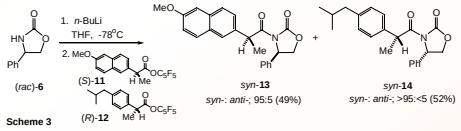
Our Aim:

We have recently become interested in the complementary resolution of profen esters, like pentafluorophenyl 2-phenylpropionate (*rac*)-**7**[4] using two complementary Evans' *quasi*-enantiomeric oxazolidinones (*R*)-**6** and (*S*)-**9** to give the separable adducts *syn*-**8** and *syn*-**10**, respectively (Scheme 2). The levels of mutual recognition between these substrates (*R*)-**6** and (*S*)-**7**, and (*S*)-**9** and (*R*)-**7** were excellent (>76 % *d.e*).



Scheme 2

Interestingly, more recently we have also shown that the PKR can also be conducted using two complementary *quasi*-enantiomeric profen esters such as **11** and **12** along with the racemic oxazolidinone **6** (Scheme 3).[5]

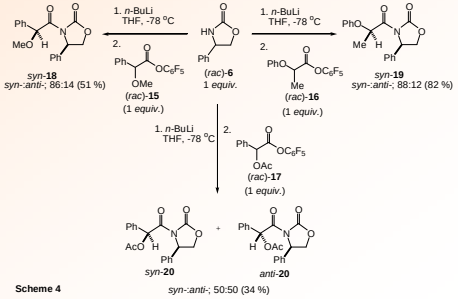


Scheme 3

In order to further investigate this methodology, we probed the resolution of 2-hydroxy carboxylic acid derivatives, such as (*rac*)-**15**, (*rac*)-**16** and (*rac*)-**17** as we were curious to see whether the excellent levels of mutual recognition could be maintained (Figure 2).

Mutual Kinetic Resolution

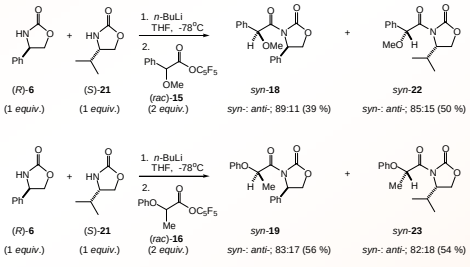
We first chose to investigate the mutual kinetic resolution (MKR) of active esters (*rac*)-**15**, (*rac*)- **16** and (*rac*)-**17** using racemic oxazolidinones (Scheme 4). This is good model for our PKR, because the reaction rates for both enantiomers are the same. It was found thqt (*rac*)-**15** and (*rac*)-**16** gave good levels of diastereoselectivity using MKR favouring the formation of the *syn*-adduct whilst (*rac*)-**17** gave no diastereoselectivity at all.



Scheme 4

PKR of pentafluorophenyl ester derivatives

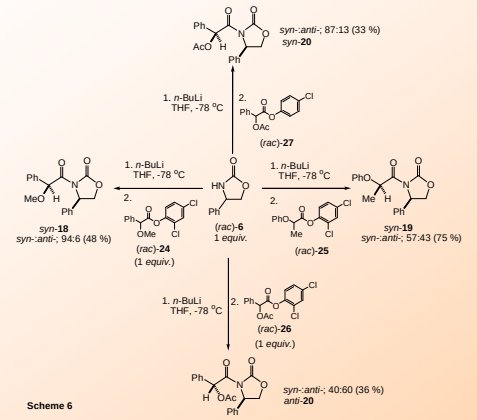
With this information in hand, we next chose to probe the PKR of active esters (*rac*)-**15** and (*rac*)-**16** using oxazolidinone (*R*)-**6** and its complementary partner (*S*)-**21**. In both cases, the syn adducts **18**, **22** (for (*rac*)-**15**) and **19** and **23** (for (*rac*)-**16**) were obtained in good diastereoselectivity (Scheme 5).



Scheme 5

Effect of different leaving groups on diastereoselectivity

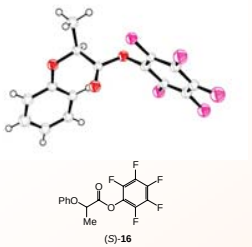
We were next interested to see what effect a different leaving group would have on the diastereoselectivity for our mutual kinetic resolution. We chose to screen the 2,4-dichlorophenyl variants of **15**, **16** and **17** (**24**, **25** and **26** in scheme 6) as this particular leaving was shown to be of similar sterically demanding nature as that of the pentafluorophenyl group in our previous study. The diastereoselectivities for the MKRs of oxazolidinone (*rac*)-**6** against (*rac*)-**24** and **25** remained in favour of the *syn* adduct. However, the MKR of (*rac*)-**26** showed an improvement in diastereoselectivity favouring formation of *anti*-**20** (*d.e.* 20 %) compared to that of the pentafluorophenyl ester (*rac*)-**17** (*d.e* 0%). Furthermore, using the 4-chlorophenyl ester variant of **26** ((*rac*)-**27**, scheme 6) gave a dramatic reversal in diastereoselectivity favouring the syn adduct **20** (*d.e*. 74 %). This clearly indicates that the nature of the leaving group has an effect on the diastereoselective outcome of these processes, especially for the *O*-acetylmandelic acid ester derivatives **17**, **26** and **27**.



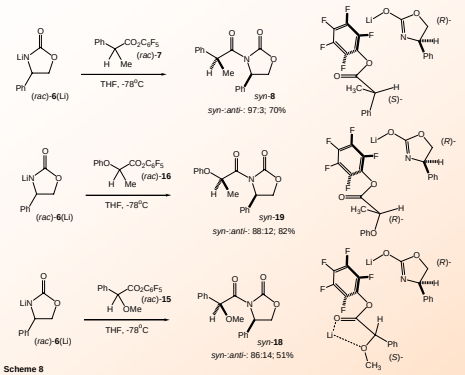
Scheme 6

Potential Mechanistic Pathways

Closer inspection of active ester (*S*)-**16** (Scheme 7) reveals the pentafluorophenol ring and neigbouring carbonyl group appear to be positioned near orthogonal to each other. Addition of lithiated oxazolidinone such as (*R*)-**6**(Li) (see Scheme 8) to the (*S*)-enantiomer of **7** and **15** can occur by addition to the most reactive Felkin-Anh conformer. The incoming lithiated oxazolidinone must be oriented in such a way to allow for efficient lithium cation transfer to the intermediate alkoxide. This addition proccess appears to be controlled by the sterically demanding pentafluorophenoxy group, elimination of the intermediate alkoxide ($LiOC_6F_5$) (not illustrated) leads to the *syn* adducts **8** and **18**. (*R*)-**6**(Li) reacts similarly with the (*R*) enantiomer of pentafluorophenoxy ester **16** to give *syn*-**19**. For the *O*-acetylmandelic acid phenyl esters, **17**, **26** and **27**, we believe that another competing mechanistic pathway involving chelation of the heteroatom at *C*(2)- of the *pro*-leaving group as well as the acetoxy group may be responsible for the diastereoselectivities observed.



Scheme 7



Scheme 8

Conclusion

Overall, we have shown that 2-alkyloxy and 2-aryloxy acids can be resolved using *quasi*-enantiomeric oxazolidinones. The levels of diastereoselectivity were shown to be moderate to excellent.

Acknowledgements

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[5] Coumbarides, G.S.; Dingjan, M., Eames, J.; Flinn, A.; Northen, J.; Yohannes, Y. *Synlett* **2006**, 101.