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Probing the Parallel Kinetic Resolution of Racemic Oxazolidinones using *Quasi*-enantiomeric Profens

[c003]

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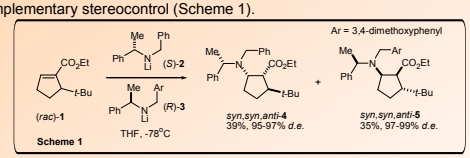
Introduction

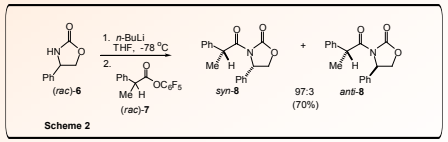
The separation of enantiomeric substrates using a parallel kinetic resolution is becoming increasingly popular.[1] In recent years, attention has focussed on the use of traditional chiral auxiliaries as complementary *quasi*-enantiomeric resolving agents.[2] In particular, Davies,[3] has elegantly shown 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

Mutual kinetic resolution (MKR)

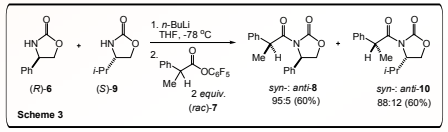
We have recently reported[4] the mutual kinetic resolution of a racemic active ester (*rac*)-**7** (derived from 2-phenyl propionic acid) using a racemic oxazolidinone, like (*rac*)-**6**, to give the corresponding racemic *syn*-adduct **8** with high diastereocontrol (Scheme 2).



Scheme 2

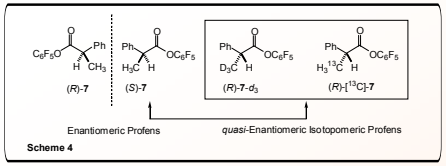
Parallel kinetic resolution (PKR)

We have extended this approach[4] by resolving the active ester, **7**, by employing two complementary enantiomerically pure *quasi*-enantiomeric oxazolidinones (*R*)-**6** and (*S*)-**9** to give the corresponding enantiomerically pure *syn*-adducts **8** and **10** in good yields and with high levels of diastereoselectivity (Scheme 2).



Scheme 3

Proposed resolution of oxazolidinones

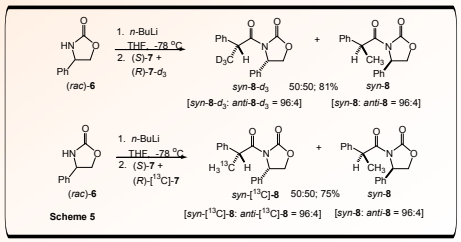


Scheme 4

We report an extension of this methodology for the resolution of racemic Evans' oxazolidinones, like (*rac*)-**6**, using two complementary *quasi*-enantiomeric profens (Schemes 3 and 4). We chose to use the enantiomeric isotopomers (*R*)-**7**-d_3 and (*R*)-[^{13}C]-**7** as surrogates for their non-labelled (*R*)-enantiomer **7** as this would lead to distinguishable stereoisomeric adducts (Scheme 3).

PKR of oxazolidinones using isotopomers

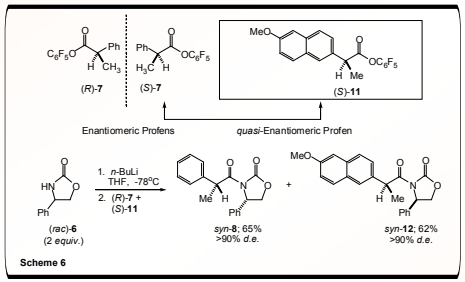
We studied two combinations of *quasi*-enantiomeric isotopomers, namely (*S*)-**7**/(*R*)-**7**-d_3 and (*S*)-**7**/(*R*)-[^{13}C]-**7**, for the resolution of oxazolidinone, (*rac*)-**6**, as this would closely match our original mutual resolution (Schemes 1 and 5). Using an equimolar amount of these *quasi*-enantiomeric profens gave, a distinguishable pair of single diastereoisomeric adducts *syn*-**8**/**8**-d_3 and *syn*-**8**/[^{13}C]-**8**, respectively, with high diastereoselectivity (>92% *d.e.* in all cases) (Scheme 5).



Scheme 5

Proposed PKR using differential profens

With this information in-hand, we next focussed on the use of the naproxen derived active ester (*S*)-**11** as a surrogate for the (*S*)-enantiomer of **7** within our mutual resolution due to their potential separability (Scheme 6).



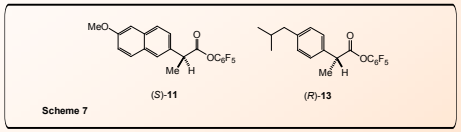
Scheme 6

PKR using *quasi*-enantiomeric profens

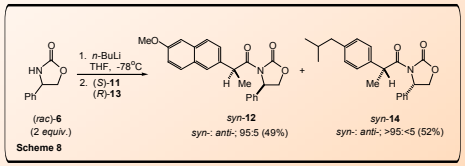
Addition of an equimolar mixture of these active esters (*R*)-**7** and (*S*)-**11** to the lithiated *quasi*-enantiomeric oxazolidinone [derived from (*rac*)-**6** (2 equivalents)] under our standard conditions, gave a separable *quasi*-enantiomeric mixture of *syn*-**8** and *syn*-**12** in good yield and excellent diastereoselectivity (Scheme 6).

Our attention next turned to the use of naproxen (*S*)-**11** and ibuprofen (*R*)-**13** as complementary *quasi*-enantiomeric resolving agents (Scheme 7). Simple addition of the lithiated racemic oxazolidinone [derived from (*rac*)-**6**] to the active esters (*S*)-**11** and (*R*)-**13**, gave the required pair of complementary *quasi*-enantiomeric *syn*-adducts **12** and **14** with excellent stereocontrol (Scheme 8). These adducts were efficiently separated by column chromatography to give the corresponding diastereoisomerically pure adducts in good yields.

PKR using *quasi*-enantiomeric profens



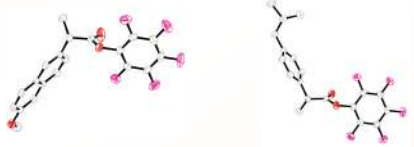
Scheme 7



Scheme 8

Conformation of active esters

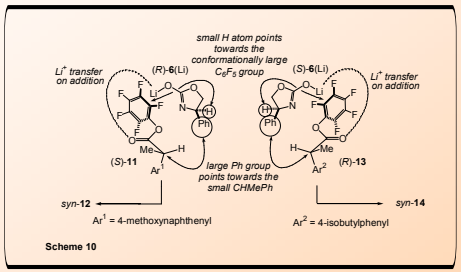
The origin of this stereocontrol is intriguing. We were originally interested in the use of a pentafluorophenol as a *pro*-leaving group due to its ease of incorporation, large conformational size and reliability as an efficient leaving group. Closer inspection of these active esters (*S*)-**11** and (*R*)-**13** reveals the pentafluorophenyl ring and neighbouring carbonyl group to be positioned near orthogonal to each other (Scheme 9).


Scheme 9 (*S*)-**11** (*R*)-**13**

Origin of stereocontrol

Formation of these adducts, *syn*-**12** and *syn*-**14**, was achieved by the preferential addition of (*R*)-**6**(Li) to (*S*)-**11**, and (*S*)-**6**(Li) to (*R*)-**13**, respectively (Scheme 10). In addition, these oxazolidinones (*R*)-**6**(Li) and (*S*)-**6**(Li) must be oriented (relative to the active esters) to allow efficient lithium cation transfer from themselves to form the intermediate alkoxides (not shown). The favoured pathway appears to be preferred when the large Ph group (rather than the small H atom) in **6** is oriented away from the conformationally large pentafluorophenyl group[5] and towards the smaller Ar^{1}CHMe and Ar^{2}CHMe motifs (Scheme 10). This particular arrangement is very interesting as it suggests a stereochemical interaction between the stereogenicity on the active ester and in-coming lithiated oxazolidinone - this presumably accounts for the increased stereocontrol over other *pro*-leaving groups.[5]

Proposed mnemonic for stereocontrol



Scheme 10

Conclusion

We have shown an efficient parallel kinetic resolution of racemic Evans' oxazolidinones using a combination of *quasi*-enantiomeric profens. This methodology appears to be efficient for a variety of structurally related oxazolidinones [*e.g.*, (*rac*)-**6**] and *quasi*-enantiomeric profens [*e.g.*, (*S*)-**11** and (*R*)-**13**] leading predictably to the required separable, diastereoisomerically pure, *syn*-adducts **12** and **14** in good yield.

Reference

1. Eames, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 885 and references therein; Vedejs, E.; Rozners, E. *J. Am. Chem. Soc.* **2001**, *123*, 2428.
2. Liao, L.; Zhang, F.; Dmitrenko, O.; Bach, R.D.; Fox, J.M. *J. Am. Chem. Soc.* **2004**, *126*, 4490.
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4. Coumbarides, G.S.; Dingjan, M.; Eames, J.; Flinn, A.; Northen, J.; Yohannes, Y. *Tetrahedron Lett.* **2005**, *46*, 2897; and references therein.
5. Coumbarides, G.S.; Eames, J.; Flinn, A.; Northen, J.; Yohannes, Y. *Tetrahedron Lett.* **2005**, *46*, 849; and references therein.