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# Probing the resolution of 2-phenylpropanoyl chloride using quasi-enantiomeric Evans' oxazolidinones

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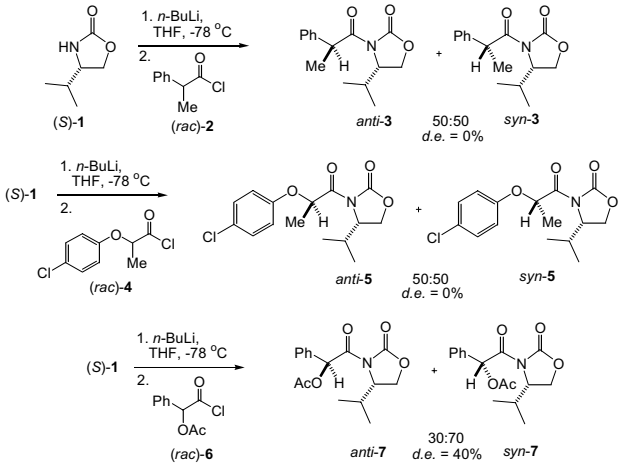
**Abstract**—The parallel kinetic resolution of 2-phenylpropanoyl chloride using quasi-enantiomeric oxazolidinones is discussed. The levels of diastereoselectivity were found to be dependent on the presence of an additional (quasi)-enantiomeric oxazolidinone and its structural nature. The origin of this stereocontrol was believed to be due to hetero-aggregation between (quasi)-enantiomeric oxazolidinone components.


The synthesis of enantiomerically pure profens, like 2-phenylpropanoic acid is very well documented.[1] These compounds have become pharmaceutically important due to their anti-inflammatory and non-steroidal nature.[2] By far, the (*S*)-enantiomer has been shown to have higher anti-inflammatory activity than its corresponding (*R*)-enantiomeric form.[2]

In recent years, the synthesis of enantiomerically pure 2-phenylpropanoic acid has relied on diastereoselective alkylation[3] or derivatisation[4] of substituted oxazolidinones. Of these two approaches, diastereoselective alkylation has been shown to lead to high levels of diastereocontrol with considerable predictability.[5] By comparison, derivatization of lithiated oxazolidinones using racemic acid chlorides have been significantly less documented.[6] This is understandable as the levels of diastereocontrol has been shown to be relatively poor.[6,7] For example, attempted kinetic resolution of 2-phenylpropanoyl chloride (*rac*)-**2**[8] and 2-(4-chlorophenoxy)propanoyl chloride (*rac*)-**4**[9] using Evans' valine derived oxazolidinone (*S*)-**1** gave an equimolar mixture of both diastereoisomeric adducts **3** and **5**, respectively (Scheme 1). However, use of electronically activated acid chlorides[10] such as *O*-acetyl mandelic chloride (*rac*)-**6** has been shown to lead to the corresponding adduct **7** with moderate to good levels of diastereoselectivity (Scheme 1).




**Scheme 1.** Kinetic resolution of racemic acid chlorides **2**, **4** and **6** using (*S*)-**1**.

Davies and co-workers' has recently addressed this problem of poor diastereoselectivity,[10] and has elegantly shown that SuperQuat oxazolidinones, like (*S*)-**8**, are capable of kinetically resolving *O*-acetyl mandelic chloride (*rac*)-**6** and 2-acetoxy-2-cyclohexylacetyl chloride (*rac*)-**10** with good to high levels of diastereoselectivity to give the corresponding adducts **9** and **11** (Scheme 2).

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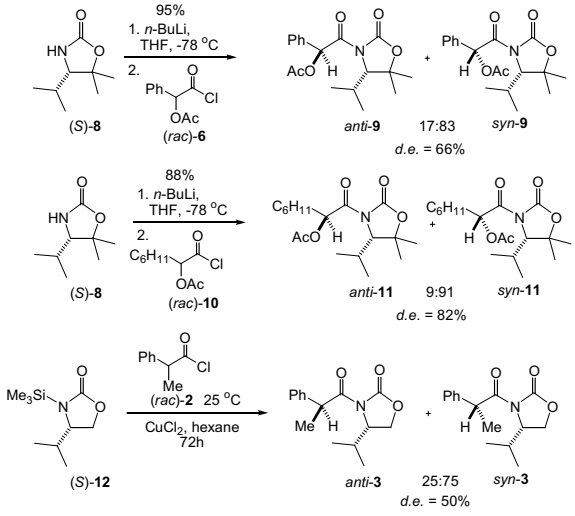
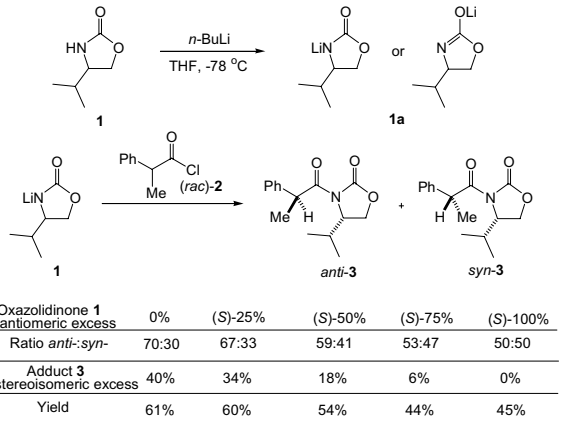



**Scheme 2.** Kinetic resolution of acid chlorides **2**, **6** and **10** using (*S*)-8 and (*S*)-**12**.

By comparison, Fukuzawa[8] has focussed on an alternative coupling strategy[11] to improve the levels of diastereocontrol; by use of a copper(II) chloride mediated coupling of *N*-silylated oxazolidinone (*S*)-**12** and 2-phenylpropanoyl chloride (*rac*)-**2** gave with some success *syn*-**3** (Scheme 2).

We have also attempted[12] to resolve 2-phenylpropanoic acid by addition of the lithiated oxazolidinone (*S*)-**1a** to a solution of 2-phenylpropanoyl chloride (*rac*)-**2** (2 equiv) in THF at −78 °C, and found in line with previous reports[8] that an equimolar mixture of both adducts *anti*- and *syn*-**3** were formed in 45% yield (Scheme 3). The assignment of stereochemistry was easily achieved by individual hydrolysis of each adduct *anti*- and *syn*-**3** using a combination of LiOH and $H_2O_2$[13] to give the corresponding (*S*)- and (*R*)-enantiomers of 2-phenylpropionic acid **13** (Scheme 4). The absolute stereochemistry of these adducts, *anti*- and *syn*-**3**, were assigned by the comparison of the optical rotation of (*S*)-**13** and (*R*)-**13** with their known literature values (Scheme 4).[14]

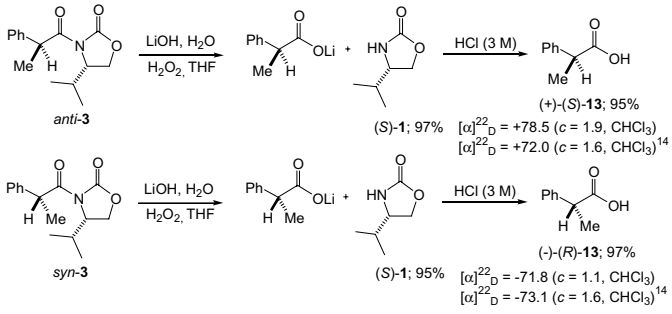
Unperturbed by this non-diastereoselective addition of oxazolidinone (*S*)-**1** to the 2-phenylpropanoyl chloride (*rac*)-**2**, we next investigated whether this stereoselectivity was dependent on the enantiomeric composition



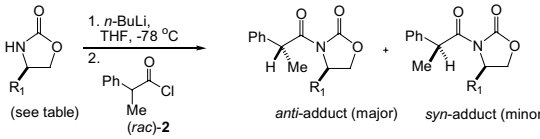

| Oxazolidinone **1** Enantiomeric excess | 0% | (*S*)-25% | (*S*)-50% | (*S*)-75% | (*S*)-100% |
|---|---|---|---|---|---|
| Ratio *anti-*:*syn-* | 70:30 | 67:33 | 59:41 | 53:47 | 50:50 |
| Adduct **3** Diastereoisomeric excess | 40% | 34% | 18% | 6% | 0% |
| Yield | 61% | 60% | 54% | 44% | 45% |

**Scheme 3.** Mutual kinetic resolution of racemic 2-phenylpropanoyl chloride **2**.

of the parent oxazolidinone (Scheme 3). In principle, if the lithiated oxazolidinone **1a** reacted as a monomeric species, the overall diastereoselectivity would be independent of its enantiomeric composition. However, this was found not to be the case. The diastereoselectivity and yield were found to increase with a decrease in the enantiomeric excess of the parent oxazolidinone (*S*)-**1** (Scheme 3). The use of racemic oxazolidinone (*rac*)-**1** gave the highest level of diastereoselectivity favouring formation of the *anti*-adduct **3** with 40% diastereoisomeric excess in 60% yield. This type of behaviour was not limited to the valine derived oxazolidinone (*rac*)-**1**; racemic norephedrine, phenylalanine and serine derived oxazolidinones (*rac*)-**14**, (*rac*)-**15** and (*rac*)-**16** also gave better diastereoselectivity than their corresponding enantiomerically pure derivatives (Scheme 5). The only exception appeared to be the phenylglycine derived oxazolidinone (*rac*)-**17**, which gave similar levels of diastereoselectivity for both the mutual and kinetic resolution of 2-phenylpropanoyl chloride (Scheme 5). From these studies, it was evident that addition of a lithiated oxazolidinone to the 2-phenylpropanoyl chloride **2** did not occur via a monomeric lithiated oxazolidinone like **1a** (Scheme 3), but via a more complex lithium aggregate involving more than one lithiated oxazolidinone. The nature of this lithiated aggregate appears to be dynamic due to the temperature dependence of the diastereoselectivity; changing the temperature from −97 to 50 °C caused a reversal in stereoselectivity from favouring formation of the *anti*-adduct **3** to the corresponding



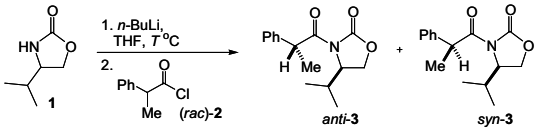

**Scheme 4.** Hydrolysis of *anti*-and *syn*-adducts **3**.




| Oxazolidinones | | 1 | 14 | 15 | 16 | 17 |
|---|---|---|---|---|---|---|
| Using racemic oxazolidinone | *anti*-:*syn*- | **3**; 40% *d.e.* (60%) | **18**; 34% *d.e.* (68%) | **19**; 18% *d.e.* (44%) | **20**; 18% *d.e.* (59%) | **21**; 12% *d.e.* (58%) |
| Using homochiral oxazolidinone | *anti*-:*syn*- | **3**[a]: 0% *d.e.* (52%) | **18**[a]: 0% *d.e.* (68%) | **19**; 0% *d.e.* (70%) | **20**; 0% *d.e.* (59%) | **21**; 0% *d.e.* (69%) |
| | *anti*-:*syn*- | **3**[b]: 4% *d.e.* (47%) | **18**[b]: 0% *d.e.* (70%) | **19**; 4% *d.e.* (70%) | **20**; 0% *d.e.* (69%) | **21**; 14% *d.e.* (71%) |

[a]Using 1 equivalent of (*rac*)-**2**; [b]Using 2 equivalents of (*rac*)-**2**

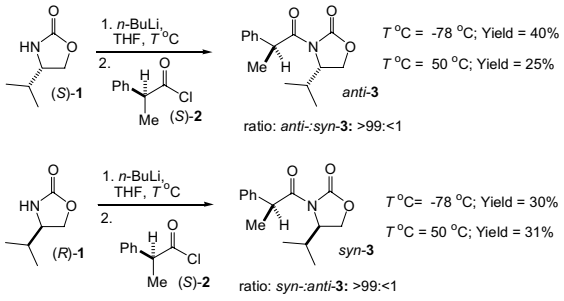
**Scheme 5.** Mutual kinetic resolution of racemic 2-phenylpropanoyl chloride **2** using oxazolidinones **1**, **14**, **15**, **16** and **17**.




| (*rac*)-*anti*-:*syn*-**3** | 70:30 (40%) | 70:30 (60%) | 57:43 (65%) | 45:55 (52%) | 33:67 (49%) | 33:67 (50%) |
|---|---|---|---|---|---|---|
| Temperature *T* °C | -97 °C | -78 °C | -29 °C | 0 °C | 25 °C | 50 °C |

**Scheme 6.** Variation in temperature and diastereoselectivity.

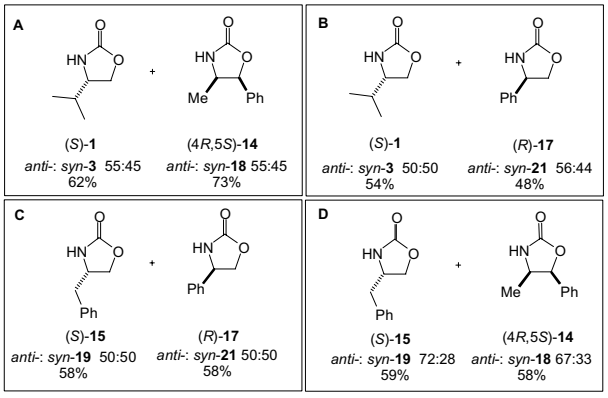
*syn*-adduct **3** at elevated temperatures (Scheme 6). The nucleophilic addition of the oxazolidinone **1** to the 2-phenylpropanoyl chloride (*rac*)-**2** at both −78 and 50 °C occurred with retention of configuration. This was evident from the direct addition of the oxazolidinones (*S*)-**1** and (*R*)-**1** to the enantiomerically pure 2-phenylpropanoyl chloride (*S*)-**2** at −78 and 50 °C, which gave diastereoisomerically pure *anti*- and *syn*-adducts **3**, respectively (>98% de). It is interesting to note that formation of the *anti*-adduct **3** was preferred at −78 °C by addition of the oxazolidinone (*S*)-**1** to acid chloride (*S*)-**2**. Whereas, at 50 °C the complementary *syn*-adduct **3** was favoured, and consequently the addition of (*R*)-**1** to (*S*)-**2** was preferred. These low yields were presumably due to competitive deprotonation of the acid chloride **2** and subsequent re-formation of the parent oxazolidinone **1** and the corresponding ketene. However, it appears that this competitive pathway does not influence the diastereoselective addition of the oxazolidinone **1** to the 2-phenylpropanoyl chloride **2** (Scheme 7).




**Scheme 7.** Stereospecific addition of (*S*)-and (*R*)-**1** to acid chloride (*S*)-**2**.

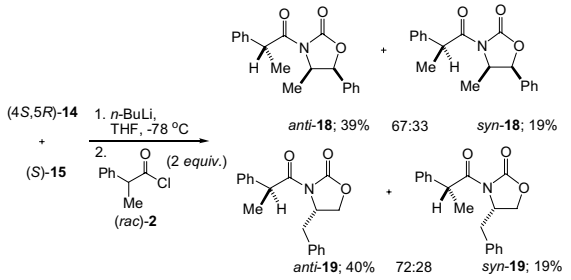
The required adducts *anti*- and *syn*-**3** appear not to be derived from ketene formation.

With this information in hand, we next attempted to resolve 2-phenylpropanoyl chloride (*rac*)-**2** using two complementary quasi-enantiomeric oxazolidinones. We argued that since the mutual kinetic resolution of 2-phenylpropanoyl chloride (*rac*)-**2** gave better diastereoselectivity when using a racemic oxazolidinone (e.g., **1**) than the previously reported kinetic resolution[8] using an enantiomerically pure oxazolidinone (*S*)-**1** (Scheme 3), the use of a complementary quasi-enantiomeric oxazolidinone like (4*R*,5*S*)-**14** (in frame A) or (*R*)-**17** (in frame B) as a surrogate for the (*R*)-enantiomer of **1** should give comparable diastereoselectivity and consequently lead to a more efficient resolution (Scheme 8).[15] However, use of an equimolar mixture of these quasi-enantiomeric

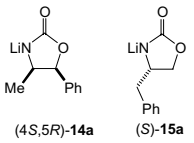



**Scheme 8.** Parrel resolution of (*rac*)-**2** using quasi-enantiomeric oxazolidinones.

oxazolidinones (*S*)-**1** and (4*R*,5*S*)-**14**, and (*S*)-**1** and (*R*)-**17** as a mimic for the racemic oxazolidinone **1** gave poorer diastereoselectivity than the original mutual kinetic resolution. This was presumably due to the oxazolidinones (4*R*,5*S*)-**14** and (*R*)-**17** being non-compatible as a complementary enantiomer to (*S*)-**1**. Probing two further quasi-enantiomeric combinations (*S*)-**15** and (*R*)-**17** (in frame C), and (*S*)-**15** and (4*R*,5*S*)-**14** (in frame D) have revealed that comparable diastereoselectivity can be achieved using this approach (Scheme 8). The combination of the quasi-oxazolidinones (*S*)-**15** and (4*R*,5*S*)-**14** appears to mirror that of each corresponding racemic pair of oxazolidinones **15** and **14**, respectively (Scheme 9). In both cases the diastereocontrol from these parallel resolutions were better than that suggested from their individual mutual kinetic resolutions (Table 1: entries 1–4). These stereoselectivities were clearly dependent on the presence of a surrogate enantiomer for each oxazolidinone, as without it, the overall diastereoselectivity was reduced. In an attempt to promote hetero-aggregation between these lithiated oxazolidinones (4*R*,5*S*)-**14a** and (*S*)-**15a** (Scheme 10), we chose to use an unequal amount of the parent oxazolidinones (Table 1: entries 6 and 7). We argued that if hetero-aggregation between the lithiated oxazolidinones were responsible for improving the diastereocontrol, an increase in stereoselectivity would be expected for the minor oxazolidinone and a decrease in stereoselectivity for the major oxazolidinone. By using an excess of the oxazolidinone (4*R*,5*S*)-**14**, the diastereoselectivity of the minor oxazolidinone (*S*)-**15** improved from 44% to 56% de in favour of the *anti*-adduct **19** (Table 1: entry 6), whereas using an excess of the complementary oxazolidinone (*S*)-**15** improved the diastereoselectivity of the minor oxazolidinone (4*R*,5*S*)-**14** from 34% to 60%




**Scheme 9.** Parallel resolution of (*rac*)-**2** using quasi-enantiomeric oxazolidinones.




**Scheme 10.** Lithiated oxazolidinones (4*S*,5*R*)-**14a** and (*S*)-**15a**.

de in favour of the *anti*-adduct **18** (Table 1: entry 7). Both the major oxazolidinone components (4*R*,5*S*)-**14** (Table 1: entry 6) and (*S*)-**15** (Table 1: entry 7) gave reduced levels of diastereoselectivity.

In conclusion, we have reported an enhancement in the levels of diastereoselective addition of lithiated oxazolidinones [e.g., (4*R*,5*S*)-**14a**] to 2-phenylpropanoyl chloride (*rac*)-**2** by use of a complementary quasi-enantiomeric oxazolidinone [e.g., (*S*)-**15a**]. The origin of this improved diastereoselectivity was thought to be due to the formation of a more diastereoselective hetero-aggregate between both lithiated oxazolidinone components. The use of single enantiomeric oxazolidinones gave little or no diastereoselectivity presumably due to the formation of a less diastereoselective homo-aggregate. The structural nature of these stereoselective aggregates and the role they play on the nucleophilic addition (and deprotonation) of racemic 2-phenylpropanoyl chloride is yet to be determined. However, the closest analogy to this work is that reported by Vedejs et al,[16] Davies et al.[17] and Fox et al.[18] Vedejs et al. has elegantly reported the efficient parallel resolution of 1-phenylethanol using two complementary quasi-enantiomeric chlorocarbonates.[16] Whereas, Davies et al. has elegantly reported the use of two quasi-enantiomeric lithium amides to resolve in parallel a racemic enone.[17] Recently, Fox et al.[18] has superbly demonstrated the use of related quasi-enantiomeric oxazolidinones for efficient resolution of active esters derived from cyclopropene carboxylic acids. It is particularly noteworthy that these (parallel) kinetic resolutions appear to act independently of each other, in an equal and opposite stereochemical sense, and have been shown to give near perfect levels of diastereoselectivity.

## Acknowledgements

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**Table 1.** Parrel resolution of (*rac*)-**2** using quasi-enantiomeric oxazolidinones

| Entry | Oxazolidinone(s) | | *anti*-**18**:*syn*-**18** | De (%) | *anti*-**19**:*syn*-**19** | De (%) |
|---|---|---|---|---|---|---|
| 1 | (*rac*)-**14**[a] | | (*rac*)-67:33 (68%) | 34 | — | |
| 2 | | (*rac*)-**15**[a] | — | | (*rac*)-59:41 (44%) | 18 |
| 3 | (4*R*,5*S*)-**14**[b] | | 50:50 (70%) | 0 | — | |
| 4 | | (*S*)-**15**[b] | — | | 52:48 (70%) | 4 |
| 5 | (4*R*,5*S*)-**14** (1 equiv) | (*S*)-**15** (1 equiv)[c] | 67:33 (58%) | 34 | 72:28 (59%) | 44 |
| 6 | (4*R*,5*S*)-**14** (3 equiv) | (*S*)-**15** (1 equiv)[c] | 64:36 (50%) | 28 | *78:22* (*65%*) | *56* |
| 7 | (4*R*,5*S*)-**14** (1 equiv) | (*S*)-**15** (3 equiv)[c] | *80:20* (*69%*) | *60* | 54:46% (73%) | 8 |

[a] Mutual kinetic resolution.
[b] Kinetic resolution with 2 equiv of (*rac*)-**2**.
[c] Parallel kinetic resolution.

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