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Tetrahedron Letters 46 (2005) 2897–2902
Tetrahedron Letters

Efficient parallel resolution of an active ester of 2-phenylpropionic acid using quasi-enantiomeric Evans' oxazolidinones

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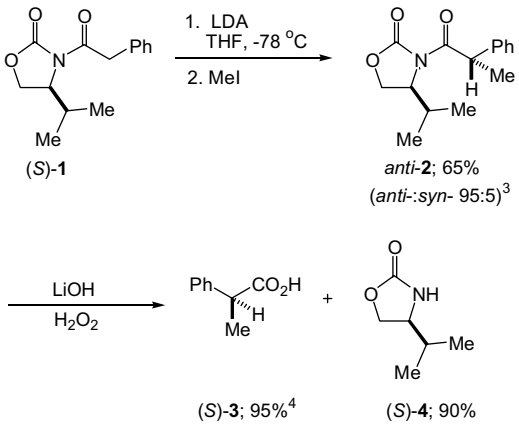
Received 13 January 2005; revised 11 February 2005; accepted 18 February 2005

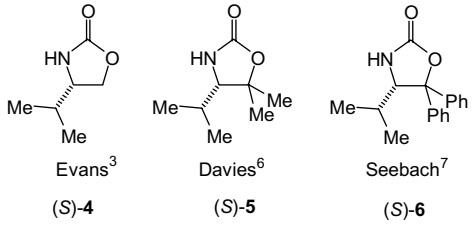
Abstract—The parallel kinetic resolution of pentafluorophenyl 2-phenylpropionate using an equimolar combination of quasi-enantiomeric oxazolidinones is discussed. The levels of diastereocontrol were excellent leading to separable quasi-enantiomeric *syn*-oxazolidinone adducts in good yield.

The use of chiral auxiliaries to synthesise enantiomerically pure α-substituted carboxylic acid derivatives is very well documented.[1] One common strategy has utilised Evans' diastereoselective alkylation of an intermediate chiral lithium enolate to control the overall stereochemical outcome.[2] For example, simple deprotonation of a phenylacetyl oxazolidinone, like (*S*)-**1**, using a suitably hindered lithium amide, such as lithium diisopropylamide (LDA) and subsequent alkylation of the intermediate chelated (*Z*)-lithium enolate with methyl iodide gave the required adduct *anti*-**2** in good yield and high diastereoselectivity (Scheme 1).[3] Hydrolysis of this *anti*-adduct **2** with lithium hydroxide liberates the recyclable oxazolidinone (*S*)-**4** and the all-important enantiomerically pure α-substituted carboxylic acid, 2-phenylpropionic acid (*S*)-**3** in high yield and optical purity (Scheme 1).[3–5]

Over the last decade or so, this particular methodology has been extended with the advent of more efficient and diastereoselective oxazolidinones developed notably by Davies and co-workers[6] (e.g., **5**) and Seebach and Hintermann (e.g., **6**)[7] (Scheme 2).



Scheme 1. Evans' oxazolidinone alkylation methodology.



Scheme 2. Three generations of oxazolidinones developed by Evans, Davies and Seebach.

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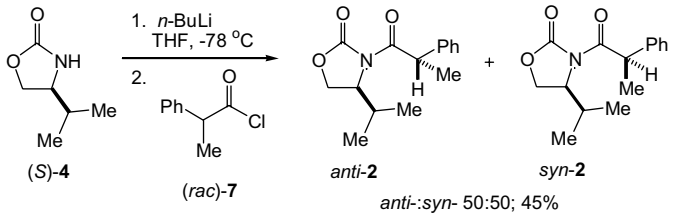
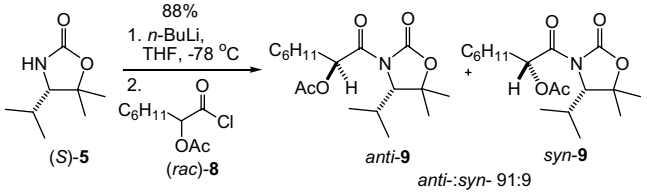
doi:10.1016/j.tetlet.2005.02.139



Scheme 3. Attempted kinetic resolution of 2-phenylpropanoyl chloride (*rac*)-**7**.

In principle, oxazolidinone adducts like **2** could have been formed by kinetic resolution of an appropriate racemic carboxylic acid derivative using an enantiomerically pure lithiated oxazolidinone (Scheme 3).[4,5,8] We have recently reported the resolution of racemic 2-phenylpropanoyl chloride **7**[4,8] using an Evans oxazolidinone [e.g., (*S*)-**4**] to give an equimolar mixture of both diastereoisomeric adducts *anti*- and *syn*-**2** in 45% yield.[4,8] Davies has previously addressed this problem[9] and has superbly demonstrated that the use of Superquat oxazolidinones, like (*S*)-**5**, leads to higher levels of diastereoselectivity for the kinetic resolution of 2-acetoxy-substituted acid chlorides such as (*rac*)-**8** (to give adducts *anti*- and *syn*-**9**) than the corresponding Evans oxazolidinone (*S*)-**4** (Scheme 4). We have additionally investigated the diastereoselectivity of these processes, and we have recently shown[4] that the levels of diastereoselectivity can be improved by use of a combination of quasi-enantiomeric Evans' oxazolidinones such as (4*S*,5*R*)-**10** and (*S*)-**11** to give the corresponding oxazolidinone adducts **12** and **13** with moderate diastereoselectivity (Scheme 5).

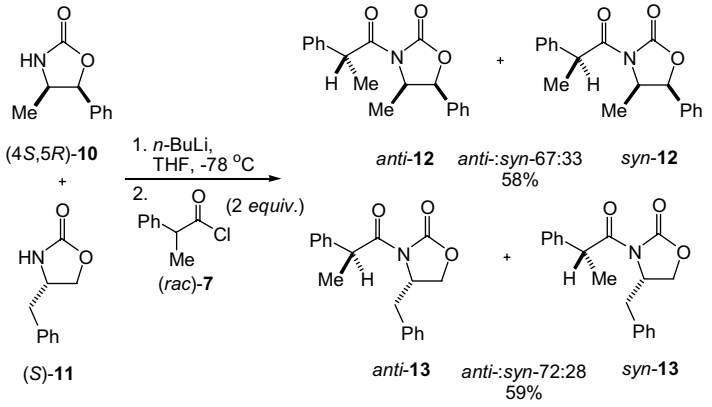


Scheme 4. Kinetic resolution of acid chloride (*rac*)-**8** using Davies' oxazolidinone (*S*)-**4**.

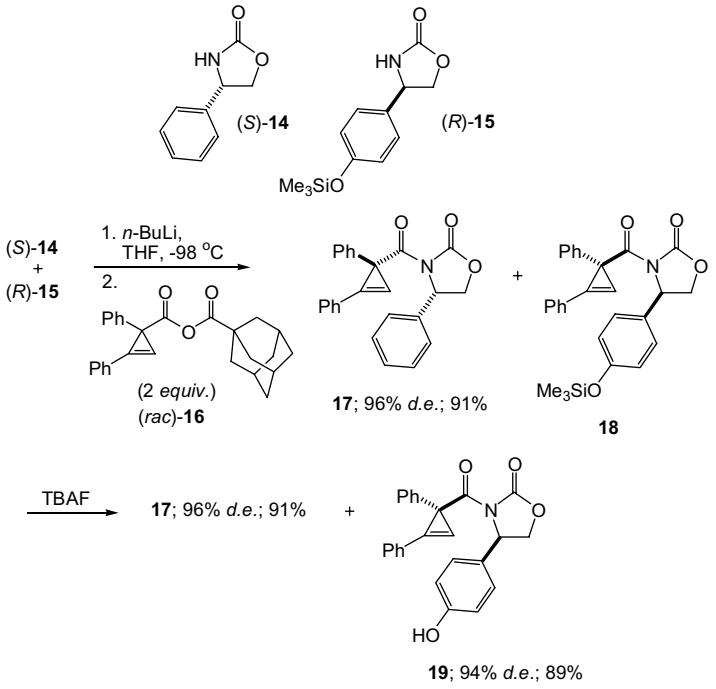
The use of quasi-enantiomeric components as parallel resolving agents is becoming an increasingly popular area.[10] Fox has elegantly reported[11] an efficient parallel kinetic resolution of a mixed anhydride (*rac*)-**16** (derived from a cyclopropene carboxylic acid) using a combination of quasi-enantiomeric oxazolidinones (*S*)-**14** and (*R*)-**15** (Scheme 6). Addition of this mixed anhydride (*rac*)-**16** to a stirred solution of lithiated oxazolidinones derived from (*S*)-**14** and (*R*)-**15** in THF at −98 °C gave two single quasi-enantiomeric oxazolidinone adducts **17** and **18** in high yield and with near perfect stereocontrol (Scheme 6). These adducts were efficiently separated by column chromatography after treatment of the crude adducts **17** and **18** with a solution of TBAF in THF to give the more separable components **17** and **19** (Scheme 6).[11]

We now wish to report our study into the resolution of a related active ester, pentafluorophenyl 2-phenylpropionate (*rac*)-**21**, using a combination of quasi-enantiomeric oxazolidinones. In our study, we chose to focus on the use of pentafluorophenol **20** as a *pro*-leaving group due to its ease of incorporation,[12] large conformational size[13] and reliability as an efficient leaving group.[14] The required active ester (*rac*)-**21** was efficiently synthesised in 92% yield by addition of DCC to a stirred solution of 2-phenylpropionic acid (*rac*)-**3** and pentafluorophenol **20** in dichloromethane (Scheme 7).

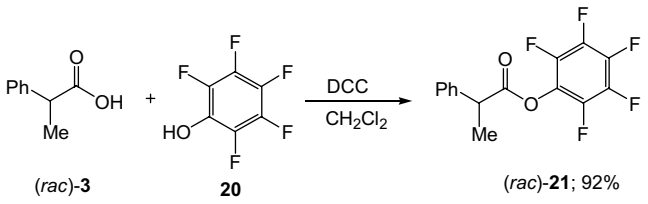
We first screened the mutual resolution of this active ester (*rac*)-**21** using a series of racemic oxazolidinones (*rac*)-**4**, (*rac*)-**10**, (*rac*)-**11**, (*rac*)-**14** and (*rac*)-**22** to probe their efficiency (Scheme 8). The valine, phenylglycine and serine derived oxazolidinones (*rac*)-**4**, (*rac*)-**14** and (*rac*)-**22** were shown to be particularly diastereoselective



Scheme 5. Parallel resolution of 2-phenylpropanoyl chloride (*rac*)-**7** using a combination oxazoldinones (4*S*,5*R*)-**10** and (*S*)-**11**.



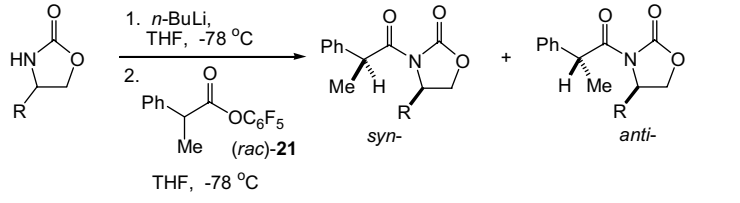
Scheme 6. Parallel resolution of cyclopropene carboxylic ester (*rac*)-**16** using quasi-enantiomeric oxazolidinones (*S*)-**14** and (*R*)-**15**.



Scheme 7. Synthesis of pentafluorophenyl 2-phenylpropionate (*rac*)-**21**.

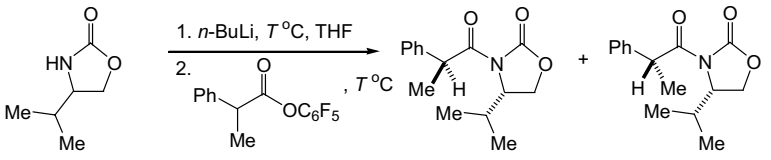
favouring formation of the diastereoisomeric adducts *syn*-**2**, *syn*-**23** and *syn*-**24**, respectively (determined by ^{1}H NMR spectroscopy) (Scheme 8, entries 1, 4 and 5). The remaining oxazolidinones (*rac*)-**10** and (*rac*)-**11** (derived from norephedrine and phenylalanine, respectively), were found to be less diastereoselective (Scheme 8, entries 2 and 3).

We next probed the temperature dependence of this mutual recognition by the addition of a solution of lithiated oxazolidinone derived from (*rac*)-**4** (in THF) to a solution of active ester (*rac*)-**21** (in THF) at a variety of temperatures ranging from −78 to 50 °C (Scheme 9). The overall levels of diastereoselectivity were found to be temperature dependent; for high yield and mutual recognition between the auxiliary (*rac*)-**4** and substrate



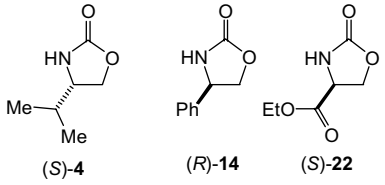
	(*rac*)-**4**	(*rac*)-**10**	(*rac*)-**11**	(*rac*)-**14**	(*rac*)-**22**
Entry	1	2	3	4	5
Adduct	*anti*-**2**:*syn*-**2**	*anti*-**12**:*syn*-**12**	*anti*-**13**:*syn*-**13**	*anti*-**23**:*syn*-**23**	*anti*-**24**:*syn*-**24**
	5:95	32:68	30:70	3:97	5:95
Yield	58%	63%	71%	70%	63%

Scheme 8. Mutual kinetic resolution of active ester (*rac*)-**21** using quasi-enantiomeric oxazolidinones (*rac*)-**4**, (*rac*)-**10**, (*rac*)-**11**, (*rac*)-**14** and (*rac*)-**22**.



Temperature, T	-78 °C	-29 °C	0 °C	50 °C
Entry	1	2	3	4
ratio *anti*-:*syn*-	5:95	5:95	10:90	14:86
Yield	58%	67%	55%	40%

Scheme 9. Variation in temperature and diastereoselectivity.



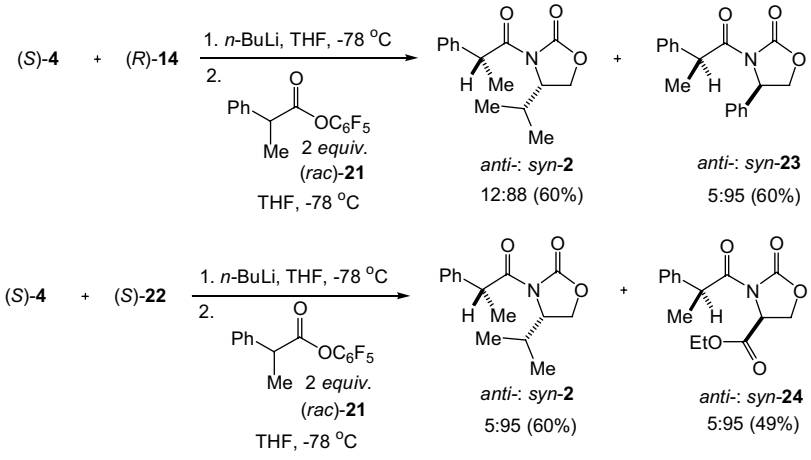
Scheme 10. Quasi-enantiomeric oxazolidinones (*S*)-**4**, and (*R*)-**14** and (*S*)-**22**.

(*rac*)-**21**, the reaction temperature was required to be below −29 °C (Scheme 9).

With this information in hand, we next investigated the parallel kinetic resolution of racemic oxazolidinone (*rac*)-**21** using a combination of quasi-enantiomeric oxazolidinones (Scheme 10). For this study, we chose to screen two quasi-enantiomeric combinations involving the valine derived oxazolidinone (*S*)-**4** as one component and the phenylglycine and serine derived oxazolidinones (*R*)-**14** and (*S*)-**22**, respectively, as its complementary quasi-enantiomeric component. These oxazolidinones were chosen due to their excellent mutual kinetic recognition with the active ester (*rac*)-**21** (see Scheme 8).

We first probed the addition of an equimolar mixture of lithiated quasi-enantiomeric oxazolidinones [derived from (*S*)-**4** and (*R*)-**14**] to a stirred solution of active ester (*rac*)-**21** (2 equiv) in THF at −78 °C (Scheme 11). This resolution gave the required pair of quasi-enantiomeric adducts *syn*-**2**[15] and *syn*-**23**[15] in good yield and excellent diastereoselectivity (Scheme 11). These adducts were separated by trituration in light petroleum (40–60 °C):diethyl ether (1:1) to give the diastereoisomerically pure adducts *syn*-**2** in 60% and *syn*-**23** in 60% yields, respectively. Using the remaining combination of quasi-enantiomeric oxazolidinones (*S*)-**4** and (*S*)-**22**, this gave, similarly, a pair of quasi-enantiomeric adducts *syn*-**2**[15] in 60% and *syn*-**24**[15] in 49% yields, respectively (Scheme 11). The stereochemistry of these adducts *syn*-**23** and *syn*-**24** were determined by single crystal X-ray structure determination (Figs. 1 and 2).[16]

In conclusion, we report an efficient parallel kinetic resolution of pentafluorophenyl 2-phenylpropionate (*rac*)-**21** using a combination of quasi-enantiomeric oxazolidinones. This methodology appears to be efficient for a variety of structurally related oxazolidinones [e.g., (*S*)-**4** and (*R*)-**14**] and predictably gives the required separable, diastereoisomerically pure, *syn*-adducts **2** and **23** in good yield. This reaction is evidently complementary to Evans' original alkylation of oxazolidinones[3] as this methodology favours formation of related *anti*-adducts with near perfect diastereocontrol.



Scheme 11. Parallel resolution of active ester (*rac*)-**21** using a combination of oxazolidinones (*S*)-**4**, (*R*)-**14** and (*S*)-**22**.

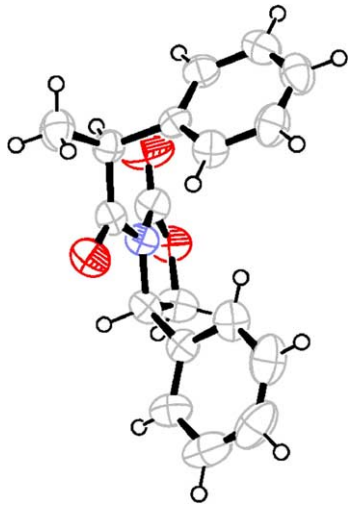


Figure 1. ORTEP diagram of oxazolidinone adduct *syn*-**23**.

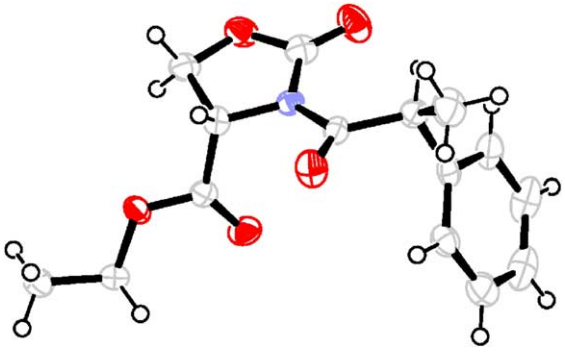


Figure 2. ORTEP diagram of oxazolidinone adduct *syn*-**24**.

*Representative experimental procedure. Parallel kinetic resolution of active ester (rac)- **21** using oxazolidinones syn- **2** and syn- **23***: *n*-BuLi (0.25 mL, 2.5 M in hexane, 0.62 mmol) was added to a stirred solution of oxazolidinones (*S*)-**4** (40 mg, 0.31 mmol) and (*R*)-**14** (51 mg, 0.31 mmol) in THF (2 mL) at −78 °C. After stirring for 1 h, a solution of pentafluorophenyl 2-phenylpropionate (*rac*)-**21** (0.2 g, 0.62 mmol) in THF (2 mL) was slowly added. The resulting solution was stirred for a further 2 h at −78 °C. The reaction was quenched with water (10 mL) and extracted with ether (2 × 20 mL). The combined organic layers were dried (over $MgSO_4$) and evaporated under reduced pressure. The residue was purified by trituration using light petroleum (40–60 °C):diethyl ether (1:1), which gave, after filtration, the (*S*,*R*)-oxazolidinone *syn*-**23**[15] (55 mg, 60%) as a white solid; mp = 140–142 °C; R_f [light petroleum (40–60 °C):ether (1:1)] 0.42; $[\alpha]_D^{27}$ 88.5 (*c* 4.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1778 (CO), 1701 (CO) and 1601 (Ph); δ_H (270 MHz; $CDCl_3$) 7.29–7.21 (10H, m, 10 × CH; 2 × Ph), 5.45 (1H, dd, *J* 9.0 and 5.1, CHN), 5.09 (1H, q, *J* 6.9, C*H*CH_3), 4.63 (1H, t, *J* 9.0, CH_AH_BCH), 4.08 (1H, dd, *J* 9.0 and 5.1, CH_AH_BCH) and 1.39 (3H, d, *J* 6.9, CH_3CH); δ_C (62.9 MHz; $CDCl_3$) 173.7 (C=O), 153.2 (C=O), 139.9 (*i*-CH; Ph), 138.3 (*i*-CH; Ph), 128.9, 128.7, 128.5, 128.2, 127.1 and 125.9 (6 × CH; Ph), 69.6 (NCH), 57.9 (CH_2O), 43.9 (*C*HCO) and 18.6 (CH_3), found MH^+, 296.1286; $C_{18}H_{18}NO_3$ requires 296.1287. Evaporation of the resulting organic solution gave the (*R*,*S*)-oxazolidinone *syn*-**2**[15] (49 mg, 60%) as an oil; R_f [light petroleum (40–60 °C):ether (1:1)] 0.50; $[\alpha]_D^{22}$ −24.7 (*c* 0.73, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1774 (CO), 1703 (CO), 1601 (Ph), 1559 (Ph) and 1489 (Ph); δ_H(250 MHz; $CDCl_3$) 7.39–7.19 (5H, m, 5 × CH; Ph), 5.14 (1H, q, *J* 7.0, CHCO), 4.92–4.46 (1H, m, CHN), 4.24 (1H, t, *J* 8.8, CH_AH_BO), 4.10 (1H, dd, *J* 8.8 and 3.5, CH_AH_BO), 2.24–2.12 (1H, m, C*H*$(CH_3)_2$), 1.47 (3H, d, *J* 6.9, CH_3CHCO), 0.79 (3H, d, *J* 7.0, CH_3CHCH_3) and 0.46 (3H, d, *J* 6.9, CH_3CHCH_3); δ_C (62.9 MHz; $CDCl_3$) 174.5 (C=O), 153.5 (C=O), 140.5 (*i*-CH; Ph), 128.6, 128.1 and 127.2 (3 × CH; Ph), 62.9 (CHN), 58.1 (CH_2O), 43.3 (*C*HCO), 27.9 (*C*H$(CH_3)_2$), 18.7, 17.8 and 14.1 (3 × CH_3), found MH^+, 262.1432; $C_{15}H_{20}NO_3$ requires 262.1443.

Acknowledgements

We are grateful to the EPSRC for a studentship (to Y.Y.), The Royal Society and The University of London Central Research Fund for their financial support (to J.E.), Pfizer for a summer studentship and the EPSRC National Mass Spectrometry Service (Swansea) for accurate mass determinations.

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