Efficient Parallel Resolution of Racemic Evans' Oxazolidinones Using *quasi*-Enantiomeric Profens

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Abstract: Racemic Evans' oxazolidinones were efficiently resolved using a combination of *quasi*-enantiomeric profens. The levels of stereocontrol were high, giving products with predictable configurations.

Key words: chiral auxiliaries, chiral resolution, kinetic resolution, molecular recognition, stereoselectivity

The separation of enantiomeric substrates using a parallel kinetic resolution is becoming an increasingly popular method of resolution.[2] In recent years, attention has focussed on the use of traditional chiral auxiliaries as complementary *quasi*-enantiomeric resolving agents.[3] In particular, Fox[4] has elegantly shown the use of a pair of Evans' oxazolidinones (*S*)-**1** and (*R*)-**2** to efficiently resolve racemic cyclopropene carboxylic acids, like (*rac*)-**3**, to give the corresponding oxazolidinone adducts **4** and **5** with near perfect levels of stereocontrol (Scheme 1). These adducts were efficiently separated using Vedejs' post-modification strategy[5] by treatment with TBAF to give the more separable adducts **4** and **6** (Scheme 1).

By comparison, Davies[6] has superbly demonstrated the use of *quasi*-enantiomeric lithium amides, (*S*)-**7** and (*R*)-**8** (Figure 1), to resolve racemic methyl 3-*tert*-butylcyclopentene carboxylate (*rac*)-**9** to give *quasi*-enantiomeric β-amino esters *syn*,*syn*,*anti*-**10** and *syn*,*syn*,*anti*-**11** with excellent stereocontrol (Scheme 2). More importantly, these adducts were separable, without post-modification, by simple column chromatography.[6]

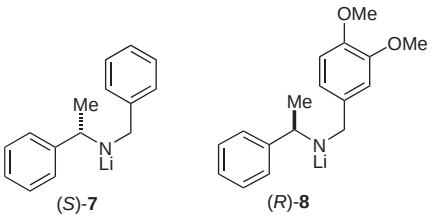
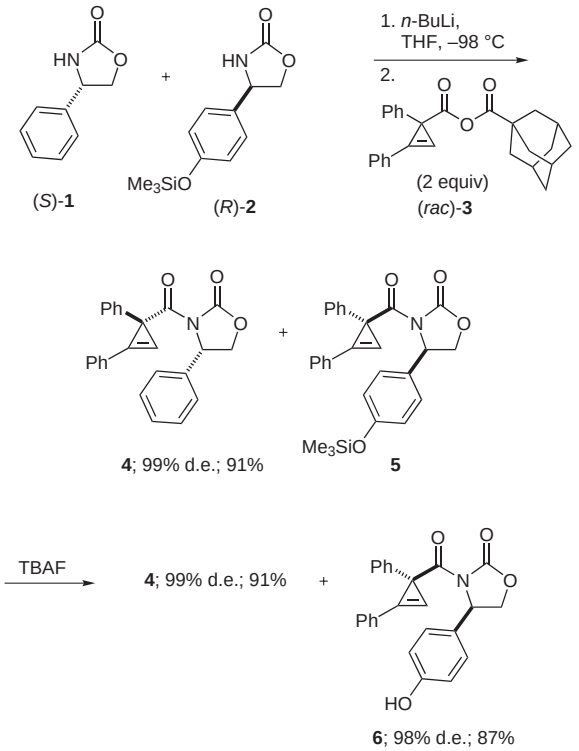


Figure 1 *quasi*-Enantiomeric Davies' lithium amides (*S*)-**7** and (*R*)-**8**



Scheme 1 Parallel kinetic resolution of anhydride (*rac*)-**3** using *quasi*-enantiomeric oxazolidinones (*S*)-**1** and (*R*)-**2**

We have previously reported[7] the mutual kinetic resolution of racemic pentafluorophenyl 2-phenylpropionate **12** using a racemic oxazolidinone, such as (*rac*)-**1**, to give the racemic *syn*-adduct **13** with high diastereocontrol (Scheme 3).

We have also extended this approach[7] for the resolution of racemic pentafluorophenyl 2-phenylpropionate **12** by employing two complementary enantiomerically pure *quasi*-enantiomeric oxazolidinones (*R*)-**1** and (*S*)-**14** (Scheme 4). Simple addition of an equimolar mixture of lithiated oxazolidinones, derived from (*R*)-**1** and (*S*)-**14**, to a solution of racemic pentafluorophenyl 2-phenylpropionate **12** in THF at –78 °C, gave the corresponding enantiomerically pure *syn*-adducts **13** and **15** in good yields and with high levels of diastereoselectivity (Scheme 4).[7]

We now report an extension of our methodology for the resolution of racemic Evans' oxazolidinones **1**, **14** and **16** by the use of complementary *quasi*-enantiomeric profens

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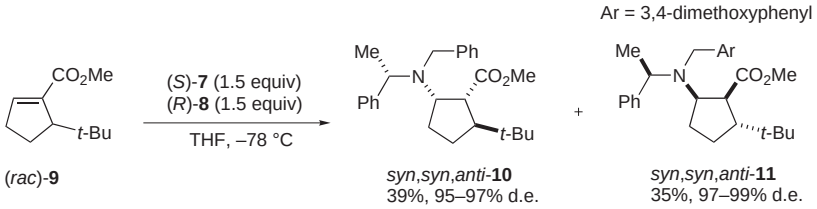
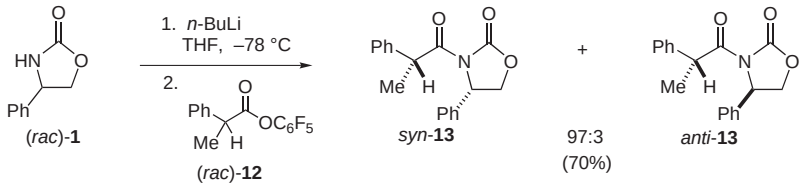
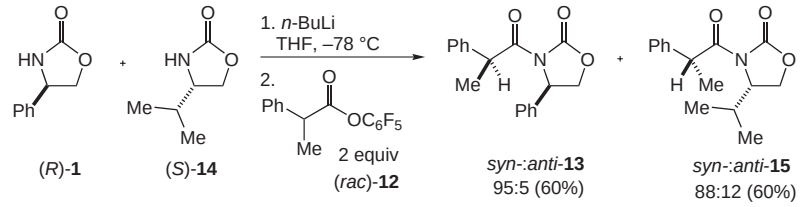


Scheme 2 Parallel kinetic resolution of methyl 3-*tert*-butylcyclopentene carboxylate (*rac*)-**9** using *quasi*-enantiomeric lithium amides (*S*)-**7** and (*R*)-**8**



Scheme 3 Mutual kinetic resolution of active ester (*rac*)-**12** using oxazolidinone (*rac*)-**1**



Scheme 4 Parallel kinetic resolution of active ester (*rac*)-**12** using *quasi*-enantiomeric oxazolidinones (*R*)-**1** and (*S*)-**14**

(Figure 2). We primarily focussed on the use of the naproxen derived active ester (*S*)-**17** as a surrogate for the *S*-enantiomer of pentafluorophenyl 2-phenylpropionate **12** within our mutual resolution due to their potential separability (Figure 3). These required pentafluorophenyl active esters (*R*)-**12** and (*S*)-**17** were synthesised in 78% and 84% yields, by addition of DCC to a stirred solution of pentafluorophenol and the corresponding profens, 2-phenylpropionic acid [(*R*)-**18**] and naproxen [(*S*)-**19**], respectively, in dichloromethane (Scheme 5).

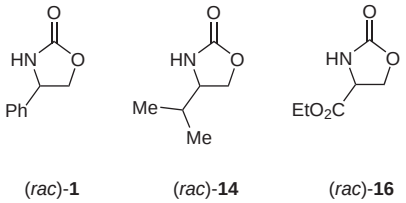


Figure 2 Racemic oxazolidinone (*rac*)-**1**, (*rac*)-**14** and (*rac*)-**16**

We first probed the kinetic resolution of racemic oxazolidinones **1**, **14** and **16** using these active esters (*R*)-**12** and (*S*)-**17** (Scheme 6 and Scheme 7). For this study, we chose to use two equivalents of racemic oxazolidinone, as this would mirror our standard parallel kinetic resolution conditions. These active esters (*R*)-**12** and (*S*)-**17** proved to be moderately diastereoselective favouring formation of the corresponding *syn*-adducts **13**, **15** and **20** [for (*R*)-**12**] and **21**, **22** and **23** [for (*S*)-**17**] as the major diastereoisomers (Scheme 6 and Scheme 7). The stereochemistry of these adducts was assigned by comparison with known derivatives.[8]

With this information in hand, we next probed the parallel resolution of Evans' oxazolidinones (*rac*)-**1**, (*rac*)-**14** and (*rac*)-**16** using an equimolar combination of *quasi*-enantiomeric active esters (*R*)-**12** and (*S*)-**17** (Scheme 8). We first probed the addition of an equimolar mixture of active esters (*R*)-**12** and (*S*)-**17** to a stirred solution of the lithiated racemic oxazolidinone derived from (*rac*)-**1** (2 equiv) in THF at –78 °C (Scheme 8, entry 1). This resolution gave the required pair of *quasi*-enantiomeric oxazolidinones *syn*-**13** and *syn*-**21** in good yield and excellent

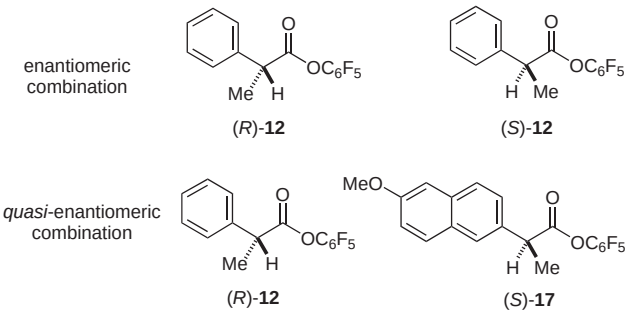
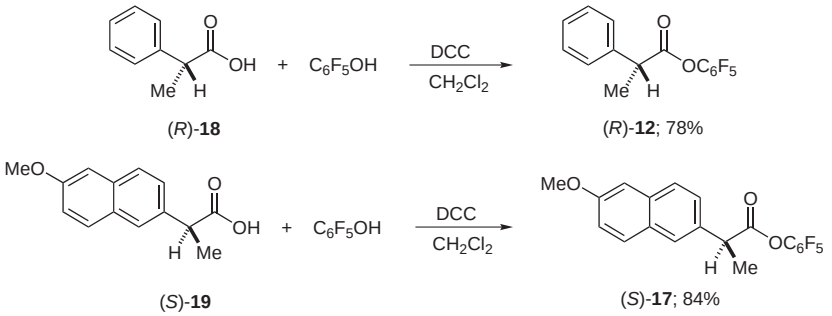
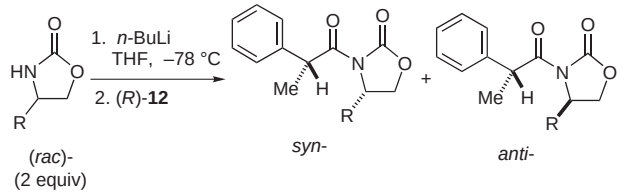


Figure 3 *quasi*-Enantiomeric profens (*R*)-**12** and (*S*)-**17**



Scheme 5 Synthesis of *quasi*-enantiomeric esters (*R*)-**12** and (*S*)-**17**



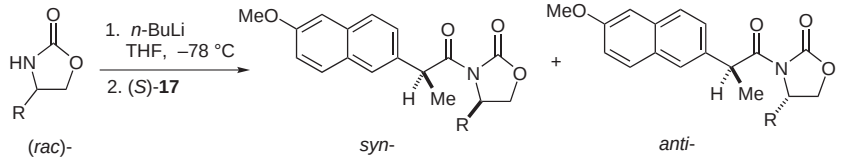
Entry	1	2	3
Oxazolidinones	(*rac*)-**1**; R = Ph	(*rac*)-**14**; R = *i*-Pr	(*rac*)-**16**; R = CO_2Et
Adducts	*syn*-**13**:*anti*-**13**	*syn*-**15**:*anti*-**15**	*syn*-**20**:*anti*-**20**
Ratio	80:20	74:26	78:22
Yield	61%	60%	59%

Scheme 6 Kinetic resolution of racemic oxazolidinones **1**, **14** and **16** using active ester (*R*)-**12**

diastereoselectivity (Scheme 8). These oxazolidinones were efficiently separated by column chromatography to give the diastereoisomerically pure adducts *syn*-**13** in 65% yield and *syn*-**21** in 61% yield, respectively. For the remaining *quasi*-enantiomeric oxazolidinones (*rac*)-**14** and (*rac*)-**16**, these gave similar pairs of *quasi*-enantiomeric adducts *syn*-**15** and *syn*-**22** in 57% and 59% yields, and *syn*-**20** and *syn*-**23** in 55% and 59% yields, respectively, with high levels of diastereoselectivity (Scheme 8, entries 2 and 3).

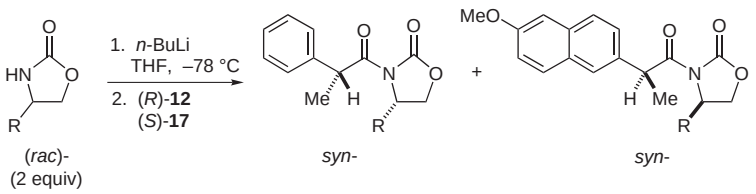
Our attention next turned to the use of naproxen (**19**) and ibuprofen (**24**) as complementary *quasi*-enantiomeric resolving agents (Scheme 9). We chose to use a *quasi*-enantiomeric combination of active esters (*S*)-**17** and (*R*)-**25**, as this would be structurally similar to our previous study (Scheme 8 and Scheme 9). The required active ester, (*R*)-**25**, was efficiently synthesised in 79% yield by addition of DCC to a stirred solution of pentafluorophenol and (*R*)-ibuprofen (**24**) in dichloromethane (Scheme 9). Addition of the lithiated racemic oxazolidinone, derived from (*rac*)-**1** (2 equiv), to a stirred solution of active esters (*S*)-**17** and (*R*)-**25** in THF at –78 °C, gave the required pair of complementary *quasi*-enantiomeric *syn*-adducts **21** and **26** with high stereocontrol (Scheme 9). These adducts were efficiently separated by column chromatography to give the corresponding diastereoisomerically pure adducts in good yields.

In conclusion, we report an efficient parallel kinetic resolution of racemic Evans' oxazolidinones using a combination of *quasi*-enantiomeric profens. This methodology[9] appears to be efficient for a variety of structurally related oxazolidinones (e.g., **1**) and *quasi*-enantiomeric profens [e.g., (*S*)-**17** and (*R*)-**25**)], and is predictable leading to the required separable, diastereoisomerically pure, *syn*-adducts **21** and **26** in good yield. We are now in the process of investigating the origin of these diastereoselective addition–elimination processes and this study will be reported in due course.



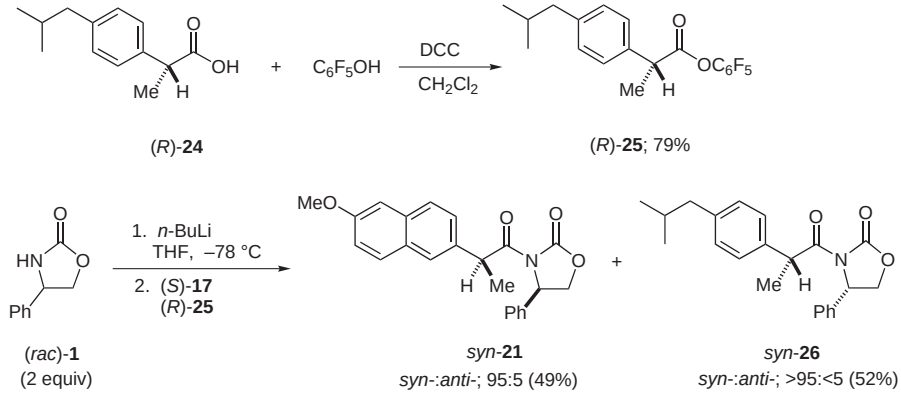
Entry	1	2	3
Oxazolidinones	(*rac*)-**1**; R = Ph	(*rac*)-**14**; R = *i*-Pr	(*rac*)-**16**; R = CO_2Et
Adducts	*syn*-**21**:*anti*-**21**	*syn*-**22**:*anti*-**22**	*syn*-**23**:*anti*-**23**
Ratio	79:21	82:18	79:21
Yield	67%	69%	78%

Scheme 7 Kinetic resolution of racemic oxazolidinones **1**, **14** and **16** using active ester (*S*)-**17**



Entry	Oxazolidinones	Adducts derived from (*R*)-**12**	Adducts derived from (*S*)-**17**
1	(*rac*)-**1**; R = Ph	*syn*-:*anti*-**13**; 95:5 (65%)	*syn*-:*anti*-**21**; 95:5 (61%)
2	(*rac*)-**14**; R= *i*-Pr	*syn*-:*anti*-**15**; 95:5 (57%)	*syn*-:*anti*-**22**; 95:5 (59%)
3	(*rac*)-**16**; R = CO_2Et	*syn*-:*anti*-**20**; 95:5 (55%)	*syn*-:*anti*-**23**; 95:5 (59%)

Scheme 8 Parallel kinetic resolution of racemic oxazolidinones **1**, **14** and **16** using *quasi*-enantiomeric active esters (*R*)-**12** and (*S*)-**17**



Scheme 9 Parallel kinetic resolution of racemic oxazolidinone **1** using *quasi*-enantiomeric active esters (*S*)-**17** and (*R*)-**25**

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References and Notes

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(9) **Experimental Section: Representative Procedure for the Parallel Kinetic Resolution of Oxazolidinone (*rac*)-1 Using *quasi*-Enantiomeric Profen Esters (*S*)-17 and (*R*)-25.**
n-BuLi (0.61 mL, 2.5 M in hexane, 1.52 mmol) was added to a stirred solution of oxazolidinone (*rac*)-**1** (0.18 g, 1.08 mmol) in THF (2 mL) at –78 °C. After stirring for 1 h, a solution of active esters (*S*)-**17** (0.22 g, 0.55 mmol) and (*R*)-**25** (0.20 g, 0.55 mmol) in THF (2 mL) were slowly added. The resulting solution was stirred for a further 2 h at –78 °C. The reaction was quenched with H_2O (10 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried (over $MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography eluting with light PE (40–60 °C)–Et_2O (1:1) to give oxazolidinone *syn*-**21** (101 mg, 49%) as a white solid and oxazolidinone *syn*-**26** (99 mg, 52%) as a white solid. Oxazolidinone *syn*-**21**: mp 168–170 °C; R_f = 0.19 [light PE (40–60 °C)–Et_2O (1:1)]; $[\alpha]_D^{24}$ +166.2 (*c* 1.5, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 1780 and 1706 (CO), 1632, 1605 and 1500

(Ar) cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.64 (1 H, d, *J* = 7.7 Hz, C*H*, Ar), 7.52 (1 H, d, *J* = 7.7 Hz, C*H*, Ar), 7.35 (1 H, br s, C*H*, Ar), 7.30–7.05 (5 H, m, 6 × C*H*, Ar and Ph), 6.88 (2 H, d, *J* = 7.7 Hz, 2 × C*H*, Ar), 5.46 (1 H, dd, *J* = 9.2, 5.2 Hz, C*H*N), 5.20 (1 H, q, *J* = 6.9 Hz, C*H*CO), 4.63 (1 H, t, *J* = 8.9 Hz, CH_AH_BO), 4.05 (1 H, dd *J* = 8.9, 5.2 Hz, CH_AH_BO), 3.92 (3 H, s, CH_3, CH_3O), 1.44 (3 H, d, *J* = 6.9 Hz, CH_3CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.3 (C=O), 157.7 (C=O), 153.1 (*i*-$COCH_3$, Ar), 138.2 (*i*-C, Ar), 135.2 (*i*-C, Ar), 133.7, 129.4, 128.9, 128.5, 127.4, 127.1, 126.4, 126.0, 118.8 and 105.5 (10 × C, Ar and Ph), 69.6 (CHN), 57.9 (CH_2O), 55.3 (CH_3O), 43.9 (CHCO), 18.8 (CH_3). MS: *m/z* calcd for $C_{23}H_{22}NO_4$: 376.1549; found: 376.1553 [MH^+].

Oxazolidinone *syn*-**26**: mp 97–99 °C; R_f = 0.47 [light PE (40–60 °C)–Et_2O (1:1)]; $[\alpha]_D^{24}$ –99.1 (*c* 0.4, $CHCl_3$). IR ($CHCl_3$): ν_{max} = 1779 and 1705 (CO), 1514 (Ar) cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 7.28–7.15 (3 H, m, 3 × C*H*, Ph), 7.0 (4 H, s, 4 × CH, Ar), 6.90 (2 H, d, *J* = 7.9 Hz, 2 × C*H*, Ph), 5.44 (1 H, dd, *J* = 9.2, 5.2 Hz, C*H*N), 5.09 (1 H, q, *J* = 6.9 Hz, C*H*CO), 4.63 (1 H, t, *J* = 9.2 Hz, CH_AH_BO), 4.06 (1 H, dd, *J* = 8.9, 5.2 Hz, CH_AH_BO), 2.43 (2 H, d, *J* = 7.4 Hz, CH_2CHCH_3), 1.89–1.79 [1 H, m, $CH(CH_3)_2$], 1.38 (3 H, d, *J* = 6.9 Hz, CH_3CHCO), 0.90 [6 H, d, *J* = 6.7 Hz, 2 × CH_3, $(CH_3)_2CH$)]. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.3 (C=O), 153.3 (C=O), 140.7, 139.4 and 137.4 (3 × *i*-C, Ar and Ph), 129.3, 129.2, 128.7, 127.9, 125.8 (5 × CH, Ar and Ph), 69.7 (NCH), 58.1 (CH_2O), 45.1 (CHCO), 42.7 (CH_2Ar), 30.2 [$CH(CH_3)_2$], 22.4 [$CH(CH_3)_2$], 19.4 [CH_3CH]. MS: *m/z* calcd for $C_{22}H_{26}NO_3$: 352.1913; found: 352.1909 [MH^+].).