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Resolution of pentafluorophenyl esters using oxazolidin-2-ones

Najla Al Shaye, Jason Eames *

Department of Chemistry, University of Hull, Cottingham Road, Kingston Upon Hull HU6 7RX, UK

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ABSTRACT

A series of structurally related racemic pentafluorophenyl active esters were resolved using an equimolar amount of (*S*)-4-phenyloxazolidin-2-one. The levels of diastereocontrol were found to be excellent (80-96% de) at ~40% conversion.

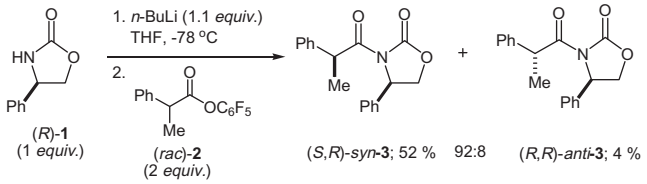
The resolution and synthesis of pharmaceutically important 2-aryl- and 2-phenylpropanoic acids are well documented.[1] Since 2000, we have been interested in the resolution[2] of pentafluorophenyl active esters derived from 2-aryl- and 2-phenylpropanoic acids, such as (*rac*)-**2**, using Evans' 4-phenyloxazolidin-2-one (*R*)-**1** (Scheme 1).[3] For example, treatment of oxazolidin-2-one (*R*)-**1** with *n*-BuLi at −78 °C, followed by the addition of an excess of pentafluorophenyl 2-phenylpropanoate (*rac*)-**2** in THF, gave after 2 h, the corresponding oxazolidin-2-one adducts (*S*,*R*)-*syn*- and (*R*,*R*)-*anti*-**3** in 52% and 4% yields, respectively, in a diastereoisomeric ratio of 92:8 (84% de) (Scheme 1).[4] However, using one equivalent or less of this (*rac*)-**2**, resulted in lower levels of diastereocontrol (40% de) due to competitive oxazolidin-2-one in addition to the less reactive (*R*)-enantiomer of **2** to give the minor diastereoisomer (*R*,*R*)-*anti*-**3** (Scheme 1).[4]

We now report the scope and limitation of this methodology for the efficient resolution of pentafluorophenyl 2-aryl- and 2-phenylpropanoates, such as (*rac*)-**2**, using a variety of structurally related oxazolidin-2-ones as the resolving agent.

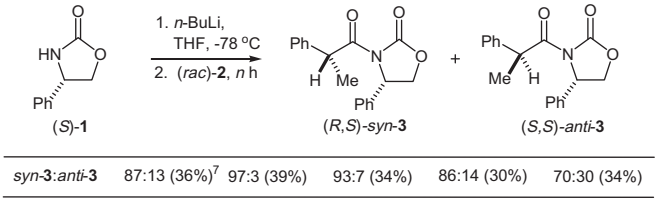
We first investigated the time dependence for an efficient resolution of pentafluorophenyl 2-phenylpropanoate (*rac*)-**2** using an equimolar amount of 4-phenyloxazolidin-2-one (*S*)-**1** (Scheme 2). Treatment of oxazolidin-2-one (*S*)-**1** with *n*-BuLi in THF at −78 °C, followed by addition of the active ester, (*rac*)-**2**, and stirring the resulting solution from 1 min to 2 h, gave the corresponding oxazolidin-2-one (*R*,*S*)-*syn*-**3**[5] in moderate yield (30–39%) with poor to excellent levels of diastereocontrol (40–94% de) (Scheme 2).

The remaining active ester **2** was isolated by column chromatography in good yield, and was found to have (*S*)-configuration (Scheme 2).[6,7] The optimum reaction time was found to be 5 min, leading to the formation of oxazolidin-2-one (*R*,*S*)-*syn*-**3** in 39% yield (out of a possible 50% yield) with 94% de (Scheme 2). With this information at hand, we next investigated the relative stoichiometry of this active ester (*rac*)-**2**, from 0.25 to 2 equiv, in an attempt to improve the levels of diastereocontrol. For a short reaction time (5 min), the relative diastereoselectivity remained constant (94% de) from 2 to 0.25 equiv; however, the yields were reduced from 57% to 3% (Scheme 3).[8] For longer reaction times (2 h), the diastereoselectivity was reduced by unavoidable addition of (*S*)-**1** to the less reactive (*S*)-enantiomer of **2**, to give the minor diastereoisomeric oxazolidin-2-one (*S*,*S*)-*anti*-**3** (Scheme 1).

We next turned our attention to study a series of structurally related active esters (*rac*)-**2**, (*rac*)-**4**, (*rac*)-**6**, (*rac*)-**8**, (*rac*)-**10**, (*rac*)-**12** and (*rac*)-**14** using our optimum reaction conditions [oxazolidin-2-one (*S*)-**1**, −78 °C, 5 min] (Scheme 4). Treatment of the oxazolidin-2-one (*S*)-**1** in THF at −78 °C, with *n*-BuLi, followed by the addition of active esters (*rac*)-**4**, (*rac*)-**8**, (*rac*)-**10**, (*rac*)-**12** and (*rac*)-**14** in THF, gave the corresponding oxazolidin-2-one adducts (*R*,*S*)-*syn*-**5**, (*R*,*S*)-*syn*-**9**, (*R*,*S*)-*syn*-**11**, (*R*,*S*)-*syn*-**13** and (*R*,*S*)-*syn*-**15** in good yields (36–54%) with good to excellent levels of diastereoisomeric excesses (52–96% de) (Scheme 4, entries 2 and 4–7).[9,10] From this study, there



Scheme 1. Resolution of active ester (*rac*)-**2** using oxazolidin-2-one (*R*)-**1**.



Scheme 2. Change in diastereoisomeric excess versus reaction time.

* Corresponding author. Tel.: +44 1482 466401; fax: +44 1482 466410.
E-mail address: j.eames@hull.ac.uk (J. Eames).

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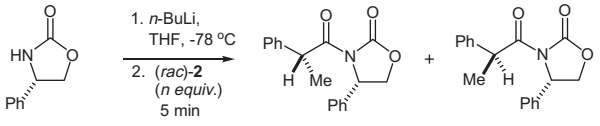
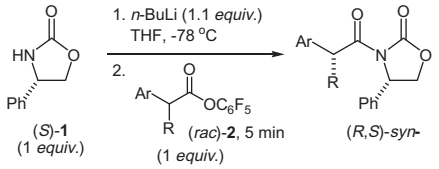


syn-**3**:*anti*-**3**	97:3 (57%)	97:3 (39%)[8]	97:3 (7%)	97:3 (3%)
(*rac*)-**2** *n* equiv.	2 *equiv.*	1 *equiv.*	0.5 *equiv.*	0.25 *equiv.*

Scheme 3. Resolution of active ester (*rac*)-**2** using oxazolidin-2-one (*S*)-**1**.

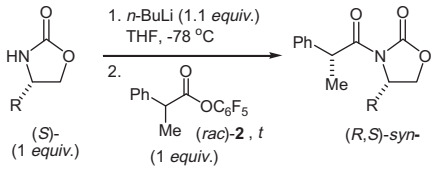


Entry	Active ester	Product	d.e.	Yield
1	(*rac*)-**2**	(*R*,*S*)-*syn*-**3**	94% *d.e.*	39%
2	(*rac*)-**4**	(*R*,*S*)-*syn*-**5**	96% *d.e.*	43%
3	(*rac*)-**6**	(*R*,*S*)-*syn*-**7**	—	0%
4	(*rac*)-**8**	(*R*,*S*)-*syn*-**9**	84% *d.e.*	36%
5	(*rac*)-**10**	(*R*,*S*)-*syn*-**11**	82% *d.e.*	44%
6	(*rac*)-**12**	(*R*,*S*)-*syn*-**13**	52% *d.e.*	54%
7	Ar = 6-methoxynaphthyl (*rac*)-**14**	(*R*,*S*)-*syn*-**15**	80% *d.e.*	43%

Scheme 4. Resolution of active esters (*rac*)-**2**, **4**, **8**, **10**, **12** and **14** using oxazolidin-2-one (*S*)-**1**.

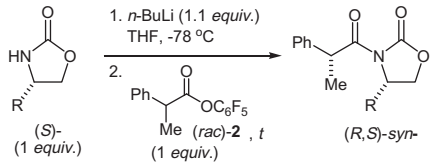
appears to be a steric threshold as the most sterically demanding active ester, (*rac*)-**6**, was unreactive under these reaction conditions (−78 °C, 5 min). By comparison, the less sterically demanding pentafluorophenyl 2-phenylbutanoate (*rac*)-**4** gave the corresponding oxazolidin-2-one (*R*,*S*)-*syn*-**5** in 43% yield with the highest level of diastereocontrol (96% de) (Scheme 4, entry 2). The relatively and less sterically demanding pentafluorophenyl 2-phenylpropanoate (*rac*)-**2**, gave the corresponding oxazolidin-2-one (*R*,*S*)-*syn*-**3** in 39% yield with marginally lower levels of diastereocontrol (94% de). The remaining pentafluorophenyl propanoates (*rac*)-**8**, (*rac*)-**10** and (*rac*)-**14** were comparable to the parent pentafluorophenyl 2-phenylpropanoate (*rac*)-**2** (Scheme 4, entries 4, 5 and 7). However, the active ester, pentafluorophenyl 4-chlorophenyl propanoate (*rac*)-**12**, was notably less stereoselective presumably due to the electron-withdrawing 4-chlorophenyl group (Scheme 4, entry 6).[11] The unreacted active esters, (*S*)-**4**, (*S*)-**8**, (*S*)-**10**, (*S*)-**12** and (*S*)-**14**, were recovered in good yields (20–43%) with moderate to good levels of enantiomeric excesses (46–80% ee) (Scheme 4).[9]

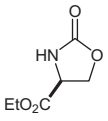
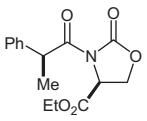
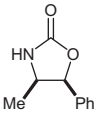
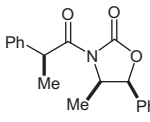
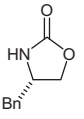
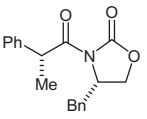
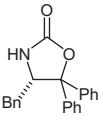
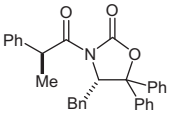
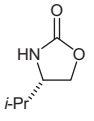
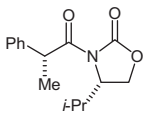
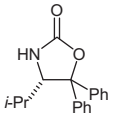
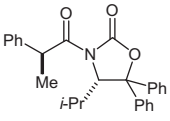
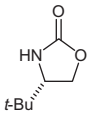
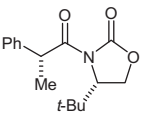
In an attempt to increase the levels of diastereoisomeric control, we next chose to probe the use of other structurally related 4-aryl/phenyl oxazolidin-2-ones, such as (*S*)-**16**, (*R*)-**18** and (*R*,*S*)-**20** (Scheme 5).[12] Treatment of these 4-aryl/phenyl oxazolidin-2-ones (*S*)-**16**, (*R*)-**18** and (*R*,*S*)-**20** in THF at −78 °C, with *n*-BuLi, followed by the addition of our standard active ester, pentafluorophenyl 2-phenylpropanoate (*rac*)-**2**, gave after 5 min the corresponding oxazolidin-2-ones (*R*,*S*)-*syn*-**17**, (*S*,*R*)-*syn*-**19** and (*S*,*R*,*S*)-*syn*-**21** in poor to good yields (12–43%), but with excellent levels of diaste-



Entry	*t*	Oxazolidin-2-one	Product	d.e.	Yield
1	5 min	(*S*)-**1**	(*R*,*S*)-*syn*-**3**	94% *d.e.*	39%
2	2 h			40% *d.e.*	34%
3	5 min	(*S*)-**16**	(*R*,*S*)-*syn*-**17**	90% *d.e.*	12%
4	2 h			82% *d.e.*	30%
5	5 min	(*R*)-**18** R = TBDMS	(*S*,*R*)-*syn*-**19** R = TBDMS	84% *d.e.*	36%
6	2 h			38% *d.e.*	53%
7	5 min	(*R*,*S*)-**20**	(*S*,*R*,*S*)-*syn*-**21**	90% *d.e.*	43%
8	2 h			58% *d.e.*	54%

Scheme 5. Resolution of active ester (*rac*)-**2** using oxazolidin-2-ones (*S*)-**1**, (*S*)-**16**, (*R*)-**18** and (*R*,*S*)-**20**.



Entry	t	Oxazolidin-2-one	Product	d.e.	Yield
1	5 min			56% *d.e.*	27%
2	2 h			28% *d.e.*	65%
		(*S*)-**22**	(*S*,*S*)-*syn*-**23**		
3	5 min			28% *d.e.*	54%
4	2 h			8% *d.e.*	68%
		(*R*,*S*)-**24**	(*S*,*R*,*S*)-*syn*-**25**		
5	5 min			14% *d.e.*	65%
6	2 h			2% *d.e.*	68%
		(*S*)-**26**	(*R*,*S*)-*syn*-**27**		
7	5 min			—	0%
8	2 h			66% *d.e.*	26%
		(*S*)-**28**	(*S*,*S*)-*anti*-**29**		
9	5 min			72% *d.e.*	26%
10	2 h			20% *d.e.*	33%
		(*S*)-**30**	(*R*,*S*)-*syn*-**31**		
11	5 min			—	0%
12	2 h			66% *d.e.*	22%
		(*S*)-**32**	(*S*,*S*)-*anti*-**33**		
13	5 min			—	0%
14	2 h			32% *d.e.*	14%
		(*S*)-**34**	(*R*,*S*)-*syn*-**35**		

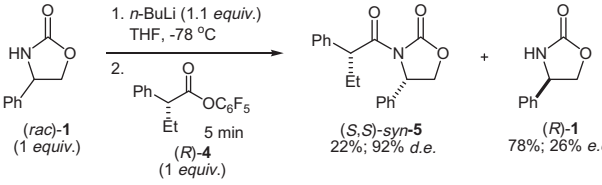
Scheme 6. Resolution of active ester (*rac*)-**2** using oxazolidin-2-ones (*S*)-**22**, (*R*,*S*)-**24**, (*S*)-**26**, (*S*)-**28**, (*S*)-**30**, (*S*)-**32** and (*S*)-**34**.

reocontrol (80–90% de) (Scheme 5, entries 3, 5 and 7).[12] Under these reaction conditions (−78 °C, 5 min), the oxazolidin-2-one (*R*,*S*)-**20** gave the optimum levels of yield and diastereoselectivity (43%; 90% de) (Scheme 5). As expected from our previous study, a longer reaction time (2 h), gave lower levels of diastereocontrol (Scheme 5, entries 2, 4, 6 and 8). However, for less reactive oxazolidin-2-ones, such as (*S*)-**16**, the levels of diastereocontrol still remained high (82% de) primarily due to their lower percentage conversion (Scheme 5, entries 3 vs 4).

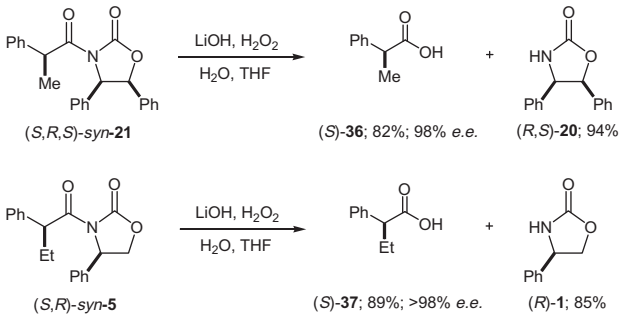
With this information at hand, we next investigated the structural nature of the oxazolidin-2-one by probing the resolution of (*rac*)-**2** using a series of 4-alkylsubstituted oxazolidin-2-ones, (*S*)-**22**, (*R*,*S*)-**24**, (*S*)-**26**, (*S*)-**28**, (*S*)-**30**, (*S*)-**32** and (*S*)-**34** (Scheme 6).[13] Under our standard reaction conditions (−78 °C, 5 min), the oxazolidin-2-ones, (*S*)-**22** and (*S*)-**30**, gave the corresponding oxazolidin-2-ones (*S*,*S*)-*syn*-**23** and (*R*,*S*)-*syn*-**31** in moderate yields, 27% and 26%, respectively, with high levels of diastereocontrol, 56% de and 72% de, respectively (Scheme 6, entries 1 and 9). From this study, it appears that the less sterically demanding oxazolidin-2-ones, (*R*,*S*)-**24** and (*S*)-**26**, gave the corresponding oxazolidin-2-ones (*S*,*R*,*S*)-*syn*-**25** and (*R*,*S*)-*syn*-**27** in good yields, 54% and 65%, respectively, but with low levels of diastereocontrol, 28% de and 14% de, respectively (Scheme 6, entries 3 and 5). By comparison, the more sterically demanding oxazolidin-2-ones (*S*)-**28**, (*S*)-**32** and (*S*)-**34** were unreactive under these reaction conditions (−78 °C, 5 min) (Scheme 6, entries 7, 11 and 13).

Increasing the reaction time, from 5 min to 2 h, unsurprisingly lowered the diastereoselectivity for the oxazolidin-2-ones (*S*)-**22**, (*R*,*S*)-**24**, (*S*)-**26** and (*S*)-**30** (Scheme 6, entries: 2, 4, 6 and 10). However, for the more sterically demanding oxazolidin-2-ones (*S*)-**28** and (*S*)-**32**, the relative diastereoselection was reversed, favouring formation of the *anti*-diastereoisomeric adducts[14] (*S*,*S*)-*anti*-**29** and (*S*,*S*)-*anti*-**33** in moderate yields, 26% and 22%, respectively (Scheme 6, entries 8 and 12). This is somewhat surprising as their less sterically demanding counterparts, oxazolidin-2-ones (*S*)-**26** and (*S*)-**30**, preferred formation of the complementary *syn*-adducts, (*R*,*S*)-*syn*-**27** and (*R*,*S*)-*syn*-**31** (Scheme 6, entries 5–12). For the remaining sterically demanding oxazolidin-2-one, 4-*tert*-butyl-oxazolidin-2-one (*S*)-**34**, this favoured formation of the *syn*-diastereoisomer (*R*,*S*)-*syn*-**35** in a low (14%) yield with moderate diastereoselectivity (32% de) (Scheme 6, entry 14). Interestingly, Evans-type oxazolidin-2-ones (*S*)-**1**, (*S*)-**22**, (*R*,*S*)-**24**, (*S*)-**26**, (*S*)-**30** and (*S*)-**34** preferred formation of the *syn*-diastereoisomeric adducts (*R*,*S*)-**3**, (*S*,*S*)-**23**, (*S*,*R*,*S*)-**25**, (*R*,*S*)-**27**, (*R*,*S*)-**31** and (*R*,*S*)-**35**, whereas, Seebach-type oxazolidin-2-ones, (*S*)-**28** and (*S*)-**32**, preferred formation of the complementary *anti*-diastereoisomeric adduct (*S*,*S*)-*anti*-**29** and (*S*,*S*)-*anti*-**33** (Schemes 5 and 6). The only exception being the less sterically demanding 4,5,5-triphenyloxazolidin-2-one (*S*)-**16**, which favoured formation of the corresponding *syn*-adduct (*R*,*S*)-**17** (Scheme 5, entries 3 and 4). This addition process also occurred in a shorter reaction time (5 min), whereas, for the more steric demanding Seebach oxazolidin-2-ones, (*S*)-**28** and (*S*)-**32**, no addition occurred (Scheme 5, entry 3 vs Scheme 6, entries 7 and 11).

Attempts at forming these *syn*-oxazolidin-2-one adducts, such as (*R*,*S*)-*syn*-**33**, through stereospecific addition of oxazolidin-2-one (*S*)-**32** to pentafluorophenyl 2-phenylpropanoate (*R*)-**2**, were unsuccessful. Addition of a solution of pentafluorophenyl 2-phenylpropanoate (*R*)-**2** in THF, to a stirred solution of lithiated oxazolidin-2-one (*S*)-**32** in THF at −78 °C, gave after 2 h, an inseparable diastereoisomeric mixture of oxazolidin-2-ones (*S*,*S*)-*anti*- and (*R*,*S*)-*syn*-**33** (ratio 66:34) in 20% yield. By comparison, stereospecific formation of the complementary oxazolidin-2-one (*S*,*S*)-*anti*-**33** [by addition of oxazolidin-2-one (*S*)-**32** to pentafluorophenyl 2-phenylpropanoate (*S*)-**2**] was more diastereoselective, leading to the required oxazolidin-2-one (*S*,*S*)-*anti*-**33** in 35% yield with 82% de. From this study, it appears that addition of the sterically demanding oxazolidin-2-



Scheme 7. Resolution of oxazolidin-2-one (*rac*)-**1** using active ester (*R*)-**4**.



Scheme 8. Formation of enantiomerically pure 2-phenyl-propanoic acid (*S*)-**36** and butanoic acid (*S*)-**37**.

one **32** to the active ester **2** is not stereospecific and probably proceeds via a deprotonation/deprotonation ketene mechanism.

In an attempt to probe the complementarity of this resolution, we next investigated the resolution of 4-phenyl-oxazolidin-2-ones (*rac*)-**1** using an enantiomerically pure active ester, pentafluorophenyl 2-phenylbutanoate (*R*)-**4** (Scheme 7). Treatment of the oxazolidin-2-one (*rac*)-**1** in THF at −78 °C, with *n*-BuLi, followed by the addition of pentafluorophenyl 2-phenylbutanoate (*R*)-**4** in THF, and stirring the resulting solution for 5 min, gave the oxazolidin-2-one (*S*,*S*)-*syn*-**5** in 22% yield with 92% de (Scheme 7). The remaining oxazolidin-2-one (*R*)-**1** was recovered with 26% ee (Scheme 7).

Simple hydrolysis of these enantiomerically pure oxazolidin-2-one adducts, such as (*S*,*R*,*S*)-*syn*-**21** and (*S*,*R*)-*syn*-**5**, using a combination of LiOH and $H2O_2$ in THF/H_2O (3:1), gives access to the resolved 2-phenylpropanoic acid (*S*)-**36** and 2-phenylbutanoic acid (*S*)-**37** in good yields with excellent enantiomeric excesses (Scheme 8).[6]

In conclusion, we have reported the kinetic resolution of a series of pentafluorophenyl active esters, such as (*rac*)-**2**, using 4-aryl/phenyl-substituted oxazolidin-2-ones, such as (*R*,*S*)-**20**, to give the corresponding oxazolidin-2-one adduct (*S*,*R*,*S*)-*syn*-**21** in good yield (43%) with high levels of diastereocontrol (90% de). The levels of diastereocontrol were found to be highly dependent on the structural nature of the 4-substituted oxazolidin-2-one. Those oxazolidin-2-ones that contained a 4-aryl/phenyl-substituted ring gave higher levels of diastereoselectivity than those contained a simple 4-alkyl substituent. Increasing the steric demand of these oxazolidin-2-ones, by using 5,5-diphenyl substitution[15] [in the case of oxazolidin-2-ones (*S*)-**28** and (*S*)-**32**] increased the likelihood of non-stereospecific addition pathways. The recovered active esters were isolated in good yield (9–90%) and were found to be enantiomerically enriched with up to 80% ee.

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5. The level of diastereocontrol was found to be excellent [measured by ^{1}H NMR (400 MHz) spectroscopy]. For oxazolidin-2-one (*S*,*S*)-*anti*-**3**, the PhCHN double doublet is at 5.32 ppm (1H, dd, J = 8.8 and 3.2). Whereas, for oxazolidin-2-one (*R*,*S*)-*syn*-**3**, the PhCHN double doublet is 5.45 ppm (1H, dd, J = 9.0 and 5.1).
6. The enantiomeric excess was determined through hydrolysis of the active ester to give the corresponding carboxylic acid. The enantiomeric excess of this carboxylic acid was determined through statistical anhydride formation by treatment with DCC. For further information, see: Coulbeck, E.; Eames, J. *Tetrahedron: Asymmetry* **2009**, *20*, 635.
7. After 1 min—the active ester (*S*)-**2** was recovered in 30% yield with 90% ee. The enantiomeric excess was confirmed by specific rotation and self-coupling; see Ref. 6.
8. For 1 equiv—the active ester (*S*)-**2** was recovered in 35% yield with 44% ee. The enantiomeric excess was confirmed by specific rotation and self-coupling; see Ref. 6.
9. The following enantiomerically enriched active esters were isolated; Scheme 4, entry 1—(*S*)-**2**; 35%; 46% ee; entry 2—(*S*)-**4**; 43%; 80% ee; entry 3—(*rac*)-**6**; 90%; entry 4—(*S*)-**8**; 42%; 55% ee; entry 5—(*S*)-**10**; 42%; 74% ee; entry 6—(*S*)-**12**; 20%; 65% ee; entry 7—(*S*)-**14**; 37%; 63% ee.
10. The% ee of the recovered active esters were comparable (within experimental error) to the theoretical value based on the %yield (±10%) and %de of the oxazolidin-2-one adduct.
11. Addition of the lithiated oxazolidin-2-one (*S*)-**1** to the active ester (*rac*)-**12** is stereospecific as addition to the enantiomerically pure active ester (*R*)-**12** gave exclusively the major diastereoisomeric oxazolidin-2-one (*R*,*S*)-*syn*-**13** in 54% yield with >98% de.
12. The enantiomerically enriched active ester **2** was isolated; Scheme 5, entry 1—35%; (*S*)-54% ee; entry 2—14%; (*S*)-23% ee; entry 3—59%; (*S*)-17% ee; entry 4—32%; (*S*)-53% ee; entry 5—24%; (*R*)-56% ee; entry 6—15%; (*R*)-54% ee; entry 7—37%; (*R*)-66% ee; entry 8—17%; (*R*)-64% ee.
13. The enantiomerically enriched active ester **2** was isolated; Scheme 6, entry 1—25%; (*R*)-32% ee; entry 2—17%; (*R*)-68% ee; entry 3—32%; (*R*)-37% ee; entry 4—15%; (*R*)-19% ee; entry 5—14%; (*S*)-44% ee; 4%; (*S*)-4% ee; entry 8—31%; (*R*)-36% ee; entry 9—37%; (*S*)-36% ee; entry 10—9%; (*S*)-16% ee; entry 12—19%; (*R*)-33% ee; entry 14—50%; 6% ee.
14. The stereochemistry of the Seebach adducts, (*R*,*S*)-*syn*-**17**, (*S*,*S*)-*anti*-**29** and (*S*,*S*)-*anti*-**33**, were confirmed by stereospecific synthesis.
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