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Parallel kinetic resolution of racemic 1-phenylethanol using quasi-enantiomeric combinations of carboxylic acids mediated by *N,N′*-dicyclohexylcarbodiimide and 3,5-lutidine

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ABSTRACT

The parallel kinetic resolution of racemic 1-phenylethanol using an equimolar combination of quasi-enantiomeric 2-arylpropionic and butanoic acids mediated by a *N,N′*-dicyclohexylcarbodiimide (DCC)/3,5-lutidine coupling is discussed. The levels of diastereoselectivity were high leading to separable quasi-enantiomeric esters in good yield.

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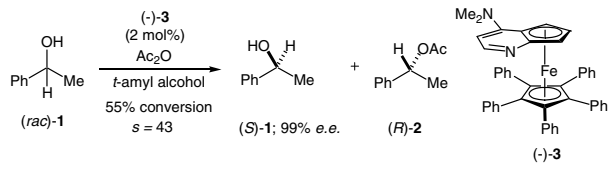
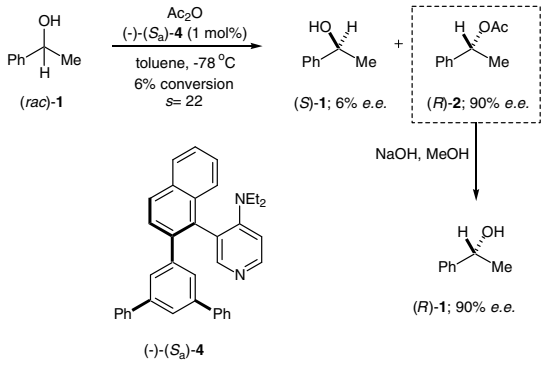
The kinetic resolution of secondary alcohols by enantioselective alkyl and arylcarbonyl transfer involving stoichiometric and sub-stoichiometric chiral mediators is well documented.[1] One non-enzymatic approach that has attracted significant attention has been the use of chiral 4-dimethylaminopyridine (DMAP) equivalents[2] as sub-stoichiometric mediators.[3] Fu and co-workers have reported the use of a planar-chiral iron complex (−)-**3**[4] as a sub-stoichiometric chiral mediator for the kinetic resolution of 1-phenylethanol (*rac*)-**1** using acetic anhydride as an acyl transfer motif (Scheme 1).[5] This process was shown to be highly enantiomer-selective when performed in *t*-amyl alcohol (2-methylbutan-2-ol) allowing the unreacted 1-phenylethanol (*S*)-**1** to be isolated with 99% ee by enantioselective acetylation of its (*R*)-enantiomer [(*R*)-**1**] to give the corresponding acetate (*R*)-**2** (selectivity factor, $s = 43$ at 55% conversion)[6] (Scheme 1).[5]

In comparison, Spivey and co-workers have developed a related resolution for 1-phenylethanol (*rac*)-**1** using a chiral atropisomeric DMAP equivalent (−)-(S_a)-**4** (Scheme 2).[7] However, they chose to resolve (*rac*)-**1** by sequential enantioselective acetylation of its (*R*)-enantiomer **1** [to give the enantiomerically enriched acetate



Scheme 1. Kinetic resolution of 1-phenylethanol (*rac*)-**1** using the chiral mediator (−)-**3**.



Scheme 2. Kinetic resolution of 1-phenylethanol (*rac*)-**1** using the chiral mediator (−)-(S_a)-**4**.

(*R*)-**2** (with 90% ee) and the partially resolved 1-phenylethanol (*S*)-**1** (6% ee)], followed by simple hydrolysis/transesterification with NaOH in MeOH to give the target 1-phenylethanol (*R*)-**1** with 90% ee ($s = 22$ at 6% conversion) (Scheme 2).[7] The low enantiomeric excess for the resolved 1-phenylethanol (*S*)-**1** was due to the low percentage conversion for this resolution.

Vedejs and co-workers focused[8] their attention on the use of a stoichiometric chiral pyridinium chloride (*R*)-**6** as an efficient activated chiral DMAP equivalent for the resolution of (*rac*)-**1** in the presence of anhydrous zinc chloride (as a Lewis acid) and triethylamine (as the Brønsted base) (Scheme 3). However, this methodology relied on the pre-formation of the active pyridinium chloride (*R*)-**6** [formed by addition of trichlorobutyl chloroformate to the chiral DMAP equivalent (*R*)-**5**] prior to the resolution of (*rac*)-**1**.[8] This acyl transfer reagent was shown to be highly (*S*)-enantiomer selective towards (*rac*)-**1**, giving the corresponding ester (*S*)-**7** with 93% ee ($s = 38$ at 25% conversion) (Scheme 3).[8]

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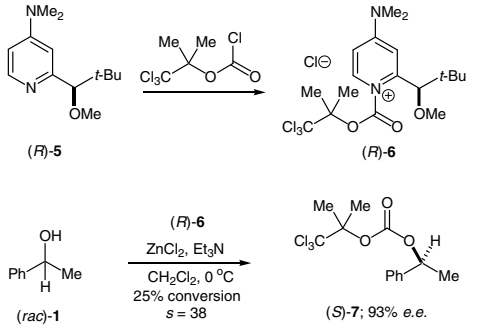
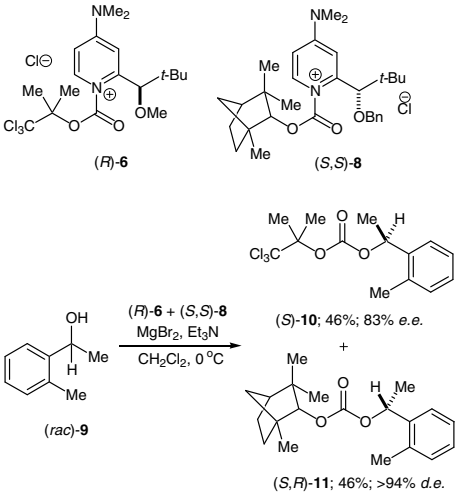


Scheme 3. Kinetic resolution of 1-phenylethanol (*rac*)-**1** using the pyridinium chloride (*R*)-**6**.

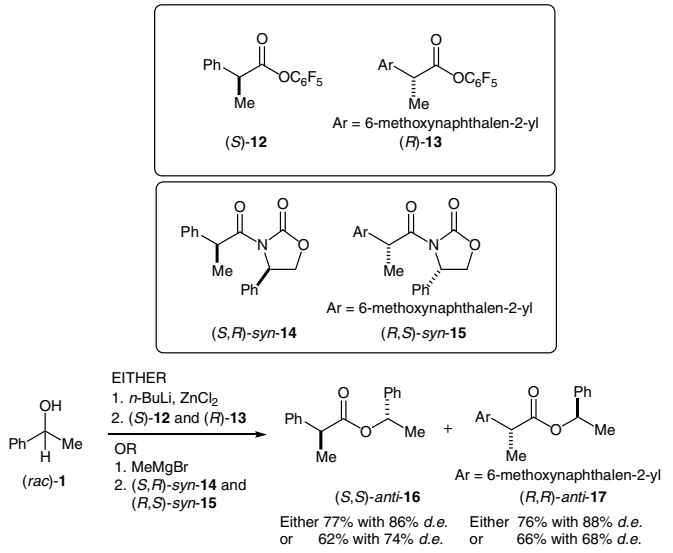
As a way of increasing the levels of enantiomer selection, Vedejs devised a novel parallel kinetic resolution strategy[9] for the removal of both enantiomers in parallel by using a combination of two complementary chiral pyridinium chlorides (*R*)-**6** and (*S*,*S*)-**8** (Scheme 4).[10] Addition of these two quasi-enantiomeric[11] pyridinium chlorides (*R*)-**6** and (*S*,*S*)-**8** to a stirred solution of a racemic secondary alcohol [e.g., 1-(1-methylphenyl)ethanol (*rac*)-**9**] in the presence of magnesium dibromide and triethylamine gave two complementary esters (*S*)-**10** and (*S*,*R*)-**11**, respectively, in good yield with excellent levels of enantiomeric/diastereoisomeric excess (Scheme 4). By performing this double kinetic resolution in situ, this process removed the inherent concentration effect (present in a single kinetic resolution) thereby improving the relative enantio- and diastereoisomeric outcomes.[10]

Over the last few years, we have been interested in the parallel kinetic resolution of 1-phenylethanol (*rac*)-**1** using quasi-enantiomeric combinations of stoichiometric active esters (*S*)-**12** and (*R*)-**13**,[12] and oxazolidin-2-ones (*S*,*R*)-*syn*-**14** and (*R*,*S*)-*syn*-**15**[13] as complementary acyl transfer reagents to give the corresponding esters (*S*,*S*)-*anti*-**16** and (*R*,*R*)-*syn*-**17** with some success (Scheme 5).

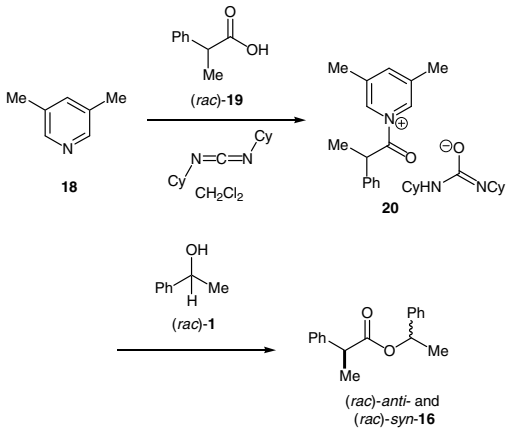
In an attempt to improve these levels of diastereoselection, we were interested in developing a diastereoselective *N*,*N*′-dicyclohexylcarbodiimide (DCC) coupling procedure[14] for the synthesis of esters, such as **16**, which utilised the in situ formation of (quasi-enantiomeric) chiral pyridinium salts, such as **20**, derived from the corresponding chiral carboxylic acid, for example, 2-phenylpropionic acid (*rac*)-**19** and achiral pyridine **18** (Scheme 6). To this end, we report our study into the use of quasi-enantiomeric 2-aryl-



Scheme 4. Parallel kinetic resolution of 1-(1-methylphenyl)ethanol (*rac*)-**9** using pyridinium chlorides (*R*)-**6** and (*S*,*S*)-**8**.



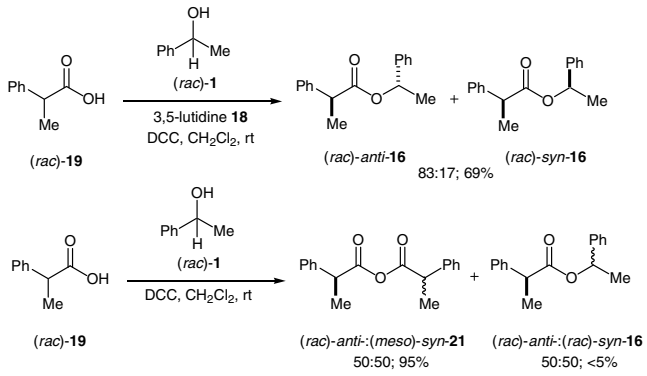
Scheme 5. Parallel kinetic resolution of 1-phenylethanol (*rac*)-**1** using quasi-enantiomeric combinations of stoichiometric active esters (*S*)-**12** and (*R*)-**13**, and oxazolidin-2-ones (*S*,*R*)-*syn*-**14** and (*R*,*S*)-*syn*-**15**.



Scheme 6. Proposed mutual kinetic resolution of 1-phenylethanol (*rac*)-**1** using 2-phenylpropionic acid (*rac*)-**19** mediated by DCC and 3,5-lutidine **18**.

propionic and butanoic acids as complementary *diastereoselective* alkyl-carbonyl transfer components for the parallel kinetic resolution of 1-phenylethanol (*rac*)-**1** using a DCC coupling procedure[15] involving 3,5-lutidine **18** as a covalent nucleophilic mediator and stereochemical directing *pro*-leaving group.

For our study, we first probed the mutual kinetic resolution of 2-phenylpropionic acid (*rac*)-**19** with an equimolar amount of racemic 1-phenylethanol **1** using our proposed DCC/3,5-lutidine coupling protocol in order to determine the relative levels of complementary recognition (Schemes 6 and 7). Addition of (*rac*)-**1** to a stirred solution of (*rac*)-**19**, DCC and 3,5-lutidine **18**[16] in dichloromethane gave after 12 h an inseparable diastereoisomeric mixture of esters (*rac*)-*anti*- and (*rac*)-*syn*-**16** in 69% yield with 66% de (Scheme 7).[17] The levels of stereocontrol were determined by ^{1}H NMR spectroscopy (400 MHz) by integration of the corresponding methyl doublets in (*rac*)-*anti*- and (*rac*)-*syn*-**16**.[18] Interestingly, without the addition of **18**, self-coupling of (*rac*)-**19** occurs predominantly to give the corresponding anhydrides (*rac*)-*anti*- and (*meso*)-*syn*-**21** as an inseparable equimolar mixture in 95% yield (Scheme 7). The formation of the esters (*rac*)-*anti*- and (*rac*)-*syn*-**16** must proceed either via addition of 3,5-lutidine **18** to the



Scheme 7. Mutual kinetic resolution of 1-phenylethanol (*rac*)-**1** using 2-phenylpropionic acid (*rac*)-**19** mediated by DCC and 3,5-lutidine **18**.

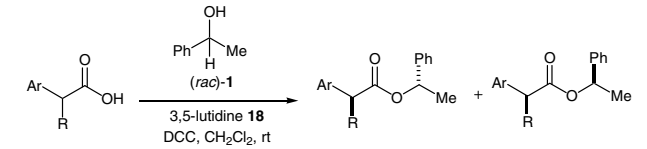
intermediate isourea [derived from addition of DCC to (*rac*)-**19**] and/or the anhydride **21**. This reaction does not proceed via intermediate ketene formation, as each diastereoisomer [e.g., (*S*,*S*)-*anti*-**16**] can be synthesised stereospecifically (~94% de) by coupling 2-phenylpropionic acid (*S*)-**19** (96% ee) with 1-phenylethanol (*S*)-**1** (>97% ee) in 48% yield.

Our attention next turned to finding a complementary partner for our original carboxylic acid, 2-phenylpropionic acid **19**. For this study, we chose to investigate the mutual kinetic resolution of a small series of structurally related racemic 2-aryl-propionic and butanoic acids (*rac*)-**22**, (*rac*)-**23**, (*rac*)-**24**, (*rac*)-**25**, (*rac*)-**26** and (*rac*)-**27** with 1-phenylethanol (*rac*)-**1** under our standard DCC/3,5-lutidine conditions (Scheme 8). Treatment of these 2-aryl-propionic and butanoic acids with 1-phenylethanol in the presence of DCC and 3,5-lutidine gave the corresponding esters (*rac*)-*anti*- and (*rac*)-*syn*-**28** [in 59% yield with 70% de (ratio 85:15)], (*rac*)-*anti*- and (*rac*)-*syn*-**29** [in 64% yield with 70% de (ratio 85:15)], (*rac*)-*anti*- and (*rac*)-*syn*-**30** [in 60% yield with 70% de (ratio 85:15)], (*rac*)-*anti*- and (*rac*)-*syn*-**31** [in 63% yield with 58% de (ratio 79:21)], (*rac*)-*anti*- and (*rac*)-*syn*-**32** [in 56% yield with 68% de (ratio 84:16)] and (*rac*)-*anti*- and (*rac*)-*syn*-**33** [in 50% yield with 64% de (ratio 82:18)] with near equal levels of diastereoselection (Scheme 8). The only exception was the carboxylic acid (*rac*)-**25** which was less diastereoselective (58% de) (Scheme 8).

With this information at hand, we next turned our attention to probing the parallel kinetic resolution of (*rac*)-**1** using two combinations of enantiomerically pure quasi-enantiomeric carboxylic acids (*R*)-**22** and (*S*)-**19**, and (*R*)-**22** and (*S*)-**26** as shown in Schemes 9 and 10, respectively. Treatment of a solution of (*rac*)-**1**, DCC and 3,5-lutidine in dichloromethane with an equimolar amount of carboxylic acids (*R*)-**22** and (*S*)-**19**, and (*R*)-**22** and (*S*)-**26** gave the corresponding inseparable mixtures of diastereoisomeric esters (*R*,*R*)-*anti*- and (*R*,*S*)-*syn*-**28** [in 71% yield with 68% de (ratio 84:16) for (*R*)-**22**] and (*S*,*S*)-*anti*- and (*S*,*R*)-*syn*-**16** [in 72% yield with 66% de (ratio 83:17) for (*S*)-**19**], and (*R*,*R*)-*anti*- and (*R*,*S*)-*syn*-**28** [in 55% yield with 66% de (ratio 83:17) for (*R*)-**22**] and (*S*,*S*)-*anti*- and (*S*,*R*)-*syn*-**32** [in 67% yield with 68% de (ratio 84:16) for (*S*)-**26**], respectively, in good yields, with good to excellent levels of diastereocontrol (up to 68% de) (Schemes 9 and 10). These levels of complementary stereocontrol were near identical to their corresponding mutual kinetic resolution (as shown in Scheme 8).

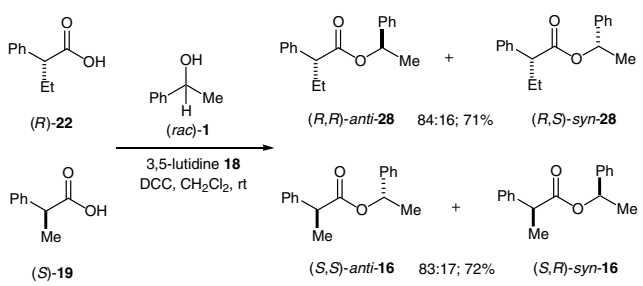
For the remainder of our study, we chose to use the more polar naproxen (*S*)-**27** as a complementary component due to its known separability from related profen-derived adducts.[12,13] Treatment of an equimolar combination of (*R*)-**22** and (*S*)-**27** with (*rac*)-**1**, DCC and 3,5-lutidine in dichloromethane gave a separable mixture of diastereoisomeric adducts (*R*,*R*)-*anti*- and (*R*,*S*)-*syn*-**28** [in 64% yield with 72% de (ratio 86:14) for (*R*)-**22**] and (*S*,*S*)-*anti*- and (*S*,*R*)-*syn*-**33** [in 58% yield with 64% de (ratio 82:18) for (*S*)-**27**] (Scheme 11). The complementary esters (*R*,*R*)-*anti*- and (*R*,*S*)-*syn*-**28** were separated efficiently from the more polar naproxen-derived esters (*S*,*S*)-*anti*- and (*S*,*R*)-*syn*-**33**, by flash column chromatography on silica gel, eluting with light petroleum ether (bp 40–60 °C)/diethyl ether (1:1) ($\Delta R_F = 0.16$) (Scheme 11).

The configurational stability of this molecular recognition process was studied using a pair of quasi-enantiomeric alcohols,

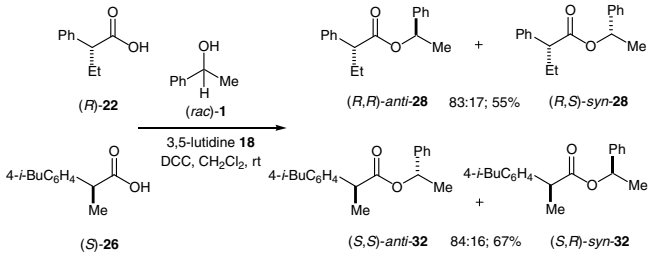


Carboxylic acid	(*rac*)-Ester	Yield	Ratio *anti*-:*syn*-	D.e.
(*rac*)-**22**	(*rac*)-*anti*-**28** and (*rac*)-*syn*-**28**	59%	85:15	70%
(*rac*)-**23**	(*rac*)-*anti*-**29** and (*rac*)-*syn*-**29**	64%	85:15	70%
(*rac*)-**24**	(*rac*)-*anti*-**30** and (*rac*)-*syn*-**30**	60%	85:15	70%
(*rac*)-**25**	(*rac*)-*anti*-**31** and (*rac*)-*syn*-**31**	63%	79:21	58%
(*rac*)-**26**	(*rac*)-*anti*-**32** and (*rac*)-*syn*-**32**	56%	84:16	68%
Ar = 6-methoxynaphthalen-2-yl (*rac*)-**27**	(*rac*)-*anti*-**33** and (*rac*)-*syn*-**33**	50%	82:18	64%

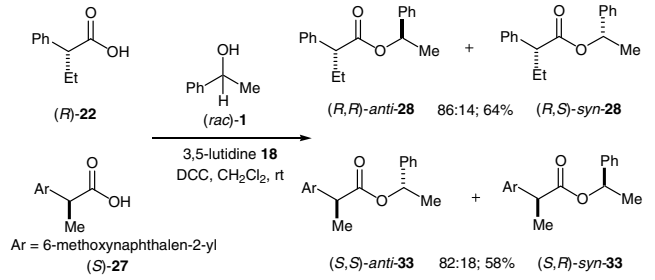
Scheme 8. Mutual kinetic resolution of 1-phenylethanol (*rac*)-**1** using carboxylic acids (*rac*)-**22–27** mediated by DCC and 3,5-lutidine.



Scheme 9. Parallel kinetic resolution of 1-phenylethanol (*rac*)-**1** using carboxylic acids (*R*)-**22** and (*S*)-**19** mediated by DCC and 3,5-lutidine.



Scheme 10. Parallel kinetic resolution of 1-phenylethanol (*rac*)-**1** using carboxylic acids (*R*)-**22** and (*S*)-**26** mediated by DCC and 3,5-lutidine.

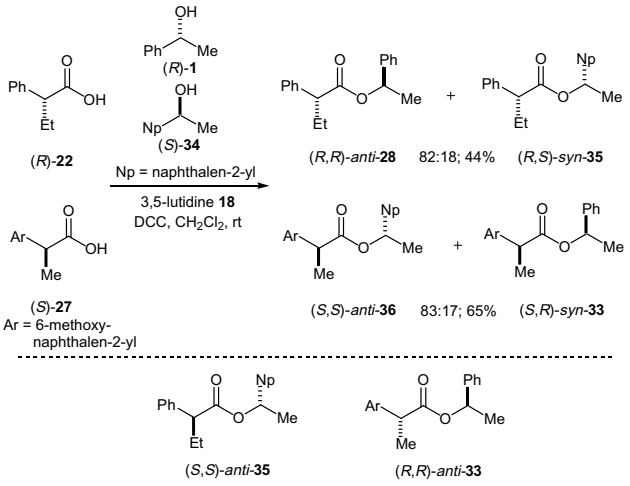


Scheme 11. Parallel kinetic resolution of 1-phenylethanol (*rac*)-**1** using carboxylic acids (*R*)-**22** and (*S*)-**27** mediated by DCC and 3,5-lutidine.

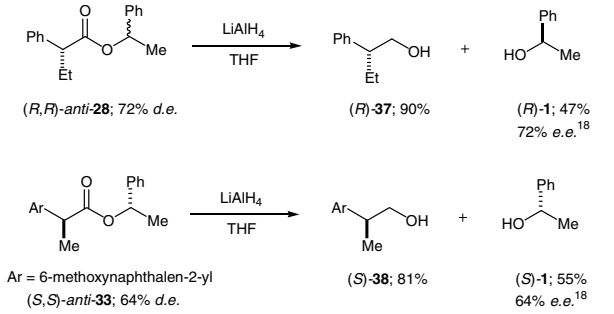
1-phenylethanol (*R*)-**1** and 1-(naphthalen-2-yl)ethanol (*S*)-**34** for the mutual kinetic separation of 2-phenylbutanoic acid (*R*)-**22** and 2-(6-methoxynaphthalen-2-yl)propionic acid (*S*)-**27** (Scheme 12). Treatment of an equimolar mixture of quasi-enantiomeric carboxylic acids (*R*)-**22** and (*S*)-**27** with DCC and 3,5-lutidine in dichloromethane, followed by the addition of a quasi-enantiomeric mixture of alcohols (*R*)-**1** and (*S*)-**34**, gave a mixture of distinct and diastereoisomerically pure esters (*R*,*R*)-*anti*-**28** and (*R*,*S*)-*syn*-**35** [ratio 82:18 relative to the (*R*)-configuration in **22**], and (*S*,*S*)-*anti*-**36** and (*S*,*R*)-*syn*-**33** [ratio 83:17 relative to the (*S*)-configuration in **27**] (Scheme 12). These relative levels of mutual selectivity were determined by 400 MHz ^{1}H NMR spectroscopy. From this study it was evident that no racemisation of the carboxylic acids (*R*)-**22** and (*S*)-**27** had occurred [due to the absence of the diastereoisomeric esters (*S*,*S*)-*anti*-**35** and (*R*,*R*)-*anti*-**33**] and that no epimerisation of the products had occurred [due to the absence of (*S*,*R*)-*syn*-**28** and (*R*,*S*)-*syn*-**36**] (Scheme 12).

Access to both enantiomers of 1-phenylethanol **1** were achieved by $LiAlH_4$ reduction of the inseparable esters (*R*,*R*)-*anti*- and (*R*,*S*)-*syn*-**28** (ratio 86:14; 72% de), and (*S*,*S*)-*anti*- and (*S*,*R*)-*syn*-**33** (ratio 82:18; 64% de) to give the enantiomerically enriched 1-phenylethanol (*R*)-**1**[19] (in 47% yield with 72% ee) and (*S*)-**1**[19] (in 55% yield with 64% ee), respectively (Scheme 13). The complementary primary alcohol (*S*)-**38** was separated efficiently by flash column chromatography on silica gel from 1-phenylethanol (*S*)-**1** {ΔR_F [light petroleum ether (bp 40–60 °C)/diethyl ether (9:1)] = 0.20}, whereas, the remaining alcohol (*R*)-**37** was only partially separable from (*R*)-**1**.

In conclusion, we have developed a diastereoselective parallel kinetic resolution approach for the resolution of 1-phenylethanol (*rac*)-**1**, using an equimolar combination of quasi-enantiomeric carboxylic acids [e.g., (*R*)-**22** and (*S*)-**27**]. The levels of diastereocontrol were found to be excellent favouring the formation of the corresponding esters (*R*,*R*)-*anti*-**28** and (*S*,*S*)-*anti*-**33** in good yields.[20] Simple reduction of adducts (*R*,*R*)-*anti*-**28** and (*S*,*S*)-*anti*-**33** using $LiAlH_4$ gave the corresponding enantiomerically enriched (*R*)- and (*S*)-enantiomers of 1-phenylethanol **1**. The nearest analogy to this study is the kinetic resolution of racemic secondary



Scheme 12. Parallel kinetic separation of alcohols (*R*)-**1** and (*S*)-**34** using carboxylic acids (*R*)-**22** and (*S*)-**27** mediated by DCC and 3,5-lutidine.



Scheme 13. Reduction of esters (*R*,*R*)-*anti*-**28** and (*S*,*S*)-*anti*-**33** to give enantiomerically enriched 1-phenylethanol **1**.

alcohols using enantiomerically pure carboxylic acids mediated by a *N*,*N*′-dicyclohexylcarbodiimide and DMAP coupling reported by Yus and Heuman.[14,21] They have shown that 1-phenylethanol **1** could be resolved to give modest enantiomeric excess (43% ee) using (*R*)-2,4-dichlorophenoxypropionic acid as resolving component. We are currently exploring the scope and a limitation of our diastereoselective DCC coupling reaction and the outcomes will be reported in due course.

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15. We assume that the chirality present in DCC plays no stereochemical role in these reactions.
16. Using a sub-stoichiometric amount of 3,5-lutidine **18** (0.2 equiv) gave after 12 h the corresponding esters (*rac*)-*anti*- and (*rac*)-*syn*-**16** in a combined 57% yield with a diastereoisomeric ratio of 82:18.
17. Replacing 3,5-lutidine with 4-dimethylaminopyridine (DMAP) gave the corresponding ester (*rac*)-(*anti*)-**16** in 69% yield with lower diastereocontrol [54% de (ratio 77:23 *anti*-:*syn*-)].
18. For (*rac*)-*anti*-**16**, the methyl doublets appear at 1.43 ppm (3H, d, J = 7.2 Hz, PhC*H*CH_3O) and 1.42 ppm (3H, d, J = 6.6 Hz, PhC*H*CH_3). Whereas, for (*rac*)-*syn*-**16**, the methyl doublets appear at 1.41 ppm (3H, d, J = 7.2 Hz, PhC*H*CH_3O) and 1.35 ppm (3H, d, J = 6.6 Hz, PhC*H*CH_3).
19. The enantiomeric excess of 1-phenylethanol was determined by (400 MHz) ^{1}H NMR spectroscopy by derivatisation with (*R*)-Mosher's acid (2-methoxy-2-phenyl-2-trifluoroacetic acid) using a DCC/DMAP (0.2 equiv) coupling procedure.
20. Representative experimental procedure: *N*,*N*′-dicyclohexylcarbodiimide (DCC) (0.27 g, 1.34 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of 2-phenylbutanoic acid (*R*)-**22** (0.20 g, 1.22 mmol) and 2-(6-methoxynaphthalen-2-yl)propionic acid (*S*)-**27** (0.28 g, 1.22 mmol) in CH_2Cl_2 (20 mL) at rt. 3,5-Lutidine (0.13 g, 1.22 mmol) was added and the resulting solution was stirred for 2 min. 1-Phenylethanol (*rac*)-**1** (0.29 g, 2.44 mmol) in CH_2Cl_2 (2 mL) was added and the resulting solution was stirred for 12 h. The solution was filtered (to remove DCU). Brine (10 mL) was added and solution was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried (over $MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum ether (bp 40–60 °C)/diethyl ether (1:1) to give an inseparable mixture (86:14) of (*R*,*R*)-*anti*- and (*R*,*S*)-*syn*-**28** (0.21 g, 64%) as a colourless oil; R_F [light petroleum ether (bp 40–60 °C)/diethyl ether (1:1)] = 0.68; $[\alpha]_D^{25}$ +2.55 (*c* 4.4, $CHCl_3$) {theoretical—$[\alpha]_D^{25}$ +2.51 for (*R*,*R*)-*anti*-**28**:(*R*,*S*)-*syn*-**28** in the ratio 86:14} and an inseparable mixture of (*S*,*S*)-*anti*- and (*S*,*R*)-*syn*-**33** (0.24 g, 58%) as a white solid; mp 94–100 °C; R_F [light petroleum ether (bp 40–60 °C)/diethyl ether (1:1)] = 0.52; $[\alpha]_D^{25}$ +23.88 (*c* 6.6, $CHCl_3$) {theoretical—$[\alpha]_D^{25}$ +2.51 for (*S*,*S*)-*anti*-**33**:(*S*,*R*)-*syn*-**33** in the ratio 82:18}.
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