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Resolution of secondary arylalkyl alcohols using pentafluorophenyl 2-phenylbutanoate and zinc chloride

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ABSTRACT

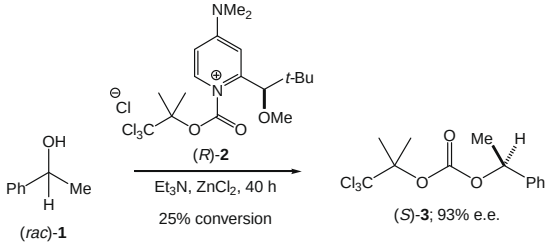
The resolution of racemic secondary arylalkyl alcohols using pentafluorophenyl 2-phenylbutanoate and zinc chloride is discussed. The levels of enantiomeric recognition were high leading to enantiomerically enriched alcohols in good yield.

Since the mid-1990s, the kinetic resolution of secondary alcohols using non-enzymatic methods has been well documented.[1] In particular, resolution through enantioselective alkyl and aryl acyl transfer involving stoichiometric and sub-stoichiometric reagents has attracted much of this attention.[2] Vedejs reported the kinetic resolution of 1-phenylethanol (*rac*)-**1** using an activated stoichiometric acyl transfer reagent, (*R*)-**2**, in the presence of $ZnCl_2$ and Et_3N, to give the corresponding carbonate (*S*)-**3** with 93% enantiomeric excess (at 25% conversion) (Scheme 1).[3] Recently, Davies has reported an Evans-style[4] resolution of (*rac*)-**1** using an enantioselective benzoyl transferring oxazolidin-2-one (*S*)-**4** to give the corresponding benzoate (*R*)-**5** in high yield with 91% ee (Scheme 2).[5]

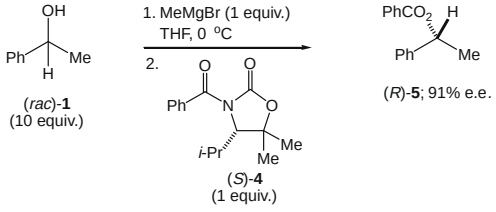
Over the last few years, we have become interested in the parallel kinetic resolution of 1-phenylethanol (*rac*)-**1**[6–8] using an equimolar combination of *quasi*-enantiomeric[9] active esters (*R*)-**6** and (*S*)-**7** as mutual resolving partners (Scheme 3). Within this resolution, these active esters (*R*)-**6** and (*S*)-**7** behaved as enantiomer selective alkyl transfer reagents leading to the formation of a separable mixture of diastereoisomeric esters (*R*,*R*)-*anti*-**8** (in 77% yield with 86% de) and (*S*,*S*)-*anti*-**9** (in 76% yield with 88% de) (Scheme 3). However, there are two significant limitations with this methodology; firstly *tert*-butyllithium is needed to form lithium 1-phenylethoxide in the absence of more nucleophilic alkoxides,[10] and secondly, separation of the *quasi*-enantiomeric ester products can be problematic.[11]

In an attempt to address these deficiencies, we now report an extension of this methodology for the resolution of secondary alkylaryl alcohols using lithium *tert*-butoxide, as a surrogate Brønsted base, and a single active ester, (*S*)-pentafluorophenyl 2-phenylbutanoate, to simplify product separation.

We had originally focused our attention on the use of lithium *tert*-butoxide as a surrogate base for the generation of lithium 1-phenylethoxide (by simple acid-base equilibration with 1-phenylethanol) because of its larger sterically demanding nature and less nucleophilic character (relative to lithium 1-phenylethoxide).[12,13] The active zinc 1-phenylethoxide salt was prepared[14] by refluxing a solution of (*rac*)-**1**,[15] lithium *tert*-butoxide, and anhydrous zinc chloride in THF for 2 h. The resulting solution was allowed to cool to room temperature.



Scheme 1. Kinetic resolution of 1-phenylethanol (*rac*)-**1** using pyridinium chloride (*R*)-**2**.



Scheme 2. Kinetic resolution of 1-phenylethanol (*rac*)-**1** using oxazolidin-2-one (*S*)-**4**.

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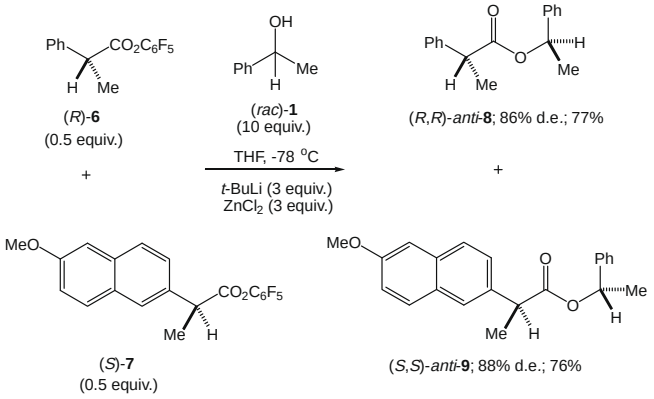
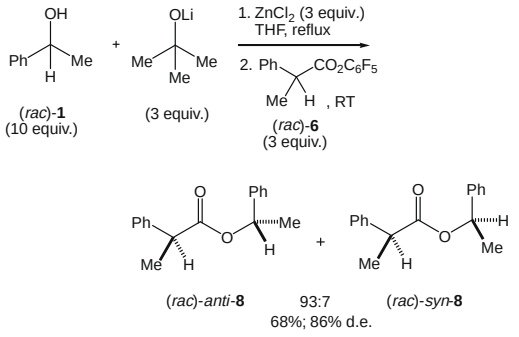


Scheme 3. Parallel resolution of 1-phenylethanol (*rac*)-**1** using *quasi*-enantiomeric esters (*R*)-**6** and (*S*)-**7**.

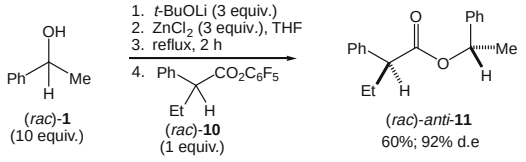
We first chose to investigate the use of this nucleophilic source of zinc 1-phenylethoxide for the mutual kinetic resolution of pentafluorophenyl 2-phenylpropionate (*rac*)-**6** at room temperature (Scheme 4). Treatment of this zinc 1-phenylethoxide solution with the active ester (*rac*)-**6** in THF at room temperature, gave after 12 h, an inseparable diastereoisomeric mixture of esters (*rac*)-*anti*- and (*rac*)-*syn*-**8** in 68% yield with excellent levels of diastereoselectivity (*anti*/*syn*, 93:7) (Scheme 4). Without pre-heating this zinc 1-phenylethoxide solution, the ester (*rac*)-*anti*-**8** was formed in a reduced yield (27%) over 12 h with comparable diastereoselectivity (84% de). Over a longer reaction time (36 h), the yield of (*rac*)-*anti*-**8** was improved to 34% (84% de), whereas heating this solution under reflux for 12 h gave the required ester (*rac*)-*anti*-**8** with an improved yield (68%) but with reduced diastereoselectivity (68% de).

In an attempt to improve the levels of mutual recognition, we next probed the use of a more sterically demanding active ester, pentafluorophenyl 2-phenylbutanoate (*rac*)-**10** (Scheme 5). Under our standard reaction conditions, this active ester proved to be more stereoselective favoring the formation of the ester (*rac*)-*anti*-**11** in 60% yield with 92% de (Scheme 5).

With this information in hand, we next investigated the resolution of 1-phenylethanol (*rac*)-**1** using the enantiomerically pure active ester (*S*)-**10** (Scheme 6). This resolution proved to be highly enantiomer selective for the (*S*)-enantiomer of 1-phenylethanol **1**, leading to the formation of the corresponding ester (*S*,*S*)-*anti*-**11** in 52% yield with 91% de (Scheme 6).



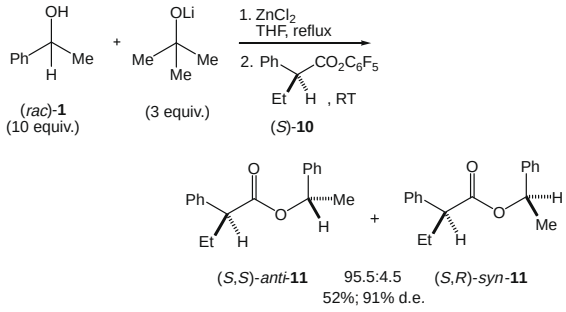
Scheme 4. Mutual resolution of 1-phenylethanol (*rac*)-**1** using pentafluorophenyl 2-phenylpropionate (*rac*)-**6**.



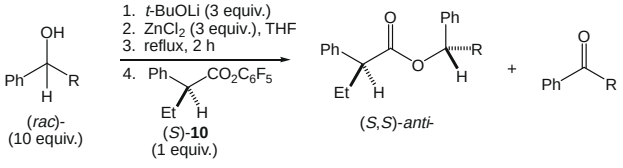
Scheme 5. Mutual resolution of 1-phenylethanol (*rac*)-**1** using pentafluorophenyl 2-phenylbutanoate (*rac*)-**10**.

The active zinc 1-phenylethoxide was shown to be configurationally stable as its isotopomer, zinc 1-deuterio-1-phenylethoxide [derived from 1-deuterio-1-phenylethanol (*rac*)-[D_1]-**1**], as this gave the corresponding ester (*S*,*S*)-*anti*-[D_1]-**11** with no loss of deuterium content (>99%) in 47% yield with 90% de (Scheme 7, entry 2 vs entry 1).[16]

We next attempted to improve the levels of diastereocontrol by using more sterically demanding alkylaryl secondary alcohols (Schemes 7 and 8). Increasing the steric demand of the alkyl substituent [e.g., 1-phenylpropanol (*rac*)-**12**] had little effect on the levels of enantiomer selection giving the ester (*S*,*S*)-*anti*-**13** in 57% yield with 90% de (Scheme 7, entry 3). However, unwanted in situ oxidation of 1-phenylpropanol (*rac*)-**12** to give phenylpropanone **14** (in 20% yield) was found to be a competitive side reaction. By increasing the steric demand of this alkyl group, as in the case of 1-phenyl-2-methylpropanol (*rac*)-**15**, gave exclusive oxidation to form 2-methyl-1-phenylpropanone **17** in 40% yield (Scheme 7,



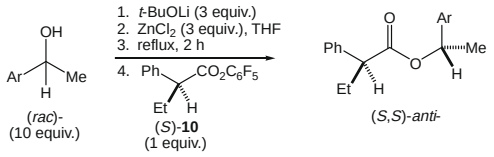
Scheme 6. Resolution of 1-phenylethanol (*rac*)-**1** using pentafluorophenyl 2-phenylbutanoate (*S*)-**10**.

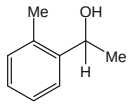
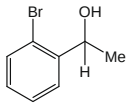
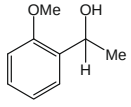
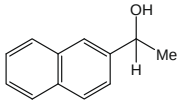


Entry	Secondary alcohol	Ester	d.e.	Yield	Ketone
1	(*rac*)-**1**	(*S*,*S*)-*anti*-**11**	91%	52%	—
2	(*rac*)-[D_1]-**1**	(*S*,*S*)-*anti*-[D_1]-**11**	90%	47%[a]	—
3	(*rac*)-**12**	(*S*,*S*)-*anti*-**13**	90%	57%	**14**; 20%[b]
4	(*rac*)-**15**	(*S*,*S*)-*anti*-**16**	—	—	**17**; 40%[b]

[a] >99% D incorporation; [b] Yield based on active ester (*S*)-**10**

Scheme 7. Resolution of secondary alcohols (*rac*)-**1**, (*rac*)-[D_2]-**1**, (*rac*)-**12**, and (*rac*)-**15** using pentafluorophenyl 2-phenylbutanoate (*S*)-**10**.



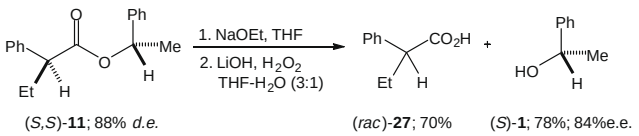
Entry	Secondary alcohol		Ester	d.e.	Yield
1		(*rac*)-**18**	(*S*,*S*)-*anti*-**23**	94%	15%
2		(*rac*)-**19**	(*S*,*S*)-*anti*-**24**	91%	40%
3		(*rac*)-**20**	(*S*,*S*)-*anti*-**25**	88%	62%
4		(*rac*)-**21**	(*S*,*S*)-*anti*-**26**	88%	38%

Scheme 8. Resolution of secondary alcohols (*rac*)-**18**–**21** using pentafluorophenyl 2-phenylbutanoate (*S*)-**10**.

entry 4). From this study, it appeared that competitive oxidation occurs for the less nucleophilic alcohols (*rac*)-**12** and (*rac*)-**15**. This oxidation presumably occurs via an Oppenauer-type process involving the active ester (*S*)-**10** as the hydride acceptor.[17] In comparison, increasing the steric demand of the phenyl ring in (*rac*)-**1** increased the levels of diastereocontrol without promoting oxidation to the corresponding ketone. Using a series of 1-(2-substituted-phenyl)ethanols (*rac*)-**18**–**20** under our standard conditions, gave the esters (*S*,*S*)-*anti*-**23**–**25** in 15%, 40%, and 62% yields, respectively, with 94%, 91%, and 88% diastereoisomeric excesses, respectively (Scheme 8, entries 1–3). The less sterically demanding 1-arylethanol (*rac*)-**21** gave the corresponding ester (*S*,*S*)-*anti*-**26** in 38% yield with 88% diastereoisomeric excess (Scheme 8, entry 4).

Access to enantiomerically enriched 1-phenylethanol (*S*)-**1** in good yield (78%) with 84% ee[18] was achieved by transesterification of the ester (*S*,*S*)-**11** with sodium ethoxide followed by hydrolysis with lithium hydroxide. The resulting 2-phenylbutanoic acid **27** was found to be racemic (Scheme 9).[19]

In conclusion, we have reported an enantiomer selective resolution of 1-phenylethanol (*rac*)-**1** using pentafluorophenyl 2-phenylbutanoate (*S*)-**10** (derived from a commercially available 2-phenylbutanoic acid **27**) as our resolving component. The levels of diastereocontrol were found to be excellent favoring the formation of the corresponding (*S*,*S*)-*anti*-esters in moderate to good yields. We are currently exploring the scope and limitation of this diastereoselective coupling procedure, and the results will be reported in due course.



Scheme 9. Formation of 1-phenylethanol (*S*)-**1**.

Acknowledgements

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References and notes

1. For representative reviews, see: (a) Fu, G. *Acc. Chem. Res.* **2000**, *33*, 412–420; (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601–610; (c) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985–3012; (d) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436–5441; (e) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974–4001; (f) Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247–3261; (g) Robinson, E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446; (h) Eames, J. *Sci. Synth.* **2008**, *36*, 341–421.
2. For comprehensive examples, see: (a) Morgan, B.; Oehlschlager, A. O.; Stokes, T. M. *J. Org. Chem.* **1992**, *57*, 3231–3236; (b) Brown, S. M.; Davies, S. G.; de Sousa, J. A. A. *Tetrahedron: Asymmetry* **1993**, *4*, 813–822; (c) Naemura, K.; Murata, M.; Tanake, R.; Yano, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 1581–1584; (d) Naemura, K.; Murata, M.; Tanake, R.; Yano, M.; Hirose, K.; Tobe, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 3285–3294; (e) Cordova, A.; Tremblay, M. R.; Clapham, B.; Janda, K. D. *J. Org. Chem.* **2001**, *66*, 5645–5648; (f) Swaleh, S. M.; Hungerhoff, B.; Sonnenschein, H.; Theil, F. *Tetrahedron* **2002**, *58*, 4085–4089; (g) Hungerhoff, B.; Sonnenschein, H.; Theil, F. *J. Org. Chem.* **2002**, *67*, 1781–1785.
3. Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809–1810.
4. Evans, D. A.; Anderson, J. C.; Taylor, M. K. *Tetrahedron Lett.* **1993**, *34*, 5563–5566.
5. Bull, S. D.; Davies, S. G.; Garner, A. C.; Kruchinin, D.; Key, M. S.; Roberts, P. M.; Savory, A. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *4*, 2945–2964.
6. Coulbeck, E.; Eames, J. *Tetrahedron: Asymmetry* **2007**, *18*, 2313–2325.
7. Al-Shaye, N.; Boa, A. N.; Coulbeck, E.; Eames, J. *Tetrahedron Lett.* **2008**, *49*, 4661–4665.
8. Coulbeck, E.; Eames, J. *Synlett* **2008**, 333–338.
9. For a comprehensive review into quasi-enantiomers, see: Zhang, Q.; Curran, D. P. *Chem. Eur. J.* **2005**, *11*, 4866–4880.
10. *n*-BuLi (in hexanes) and PhLi (in dibutyl ether) have been shown to contain trace amounts of lithium butoxide which can lead to the formation of an inseparable by-product, butyl 2-phenylpropionate (in ~16% and ~5% yields for *n*-BuLi and PhLi, respectively). For additional information see Ref. 8.
11. Separation is generally achieved by column chromatography {ΔR_F 0.18 [light petroleum (bp 40–60 °C):diethyl ether (1:1)]}.
12. Competitive formation of *t*-butyl 2-phenylpropanoate does not occur.
13. Fu has reported the use of a tertiary alcohol [e.g., 2-methyl-2-butanol (*t*-amyl alcohol)] as a solvent within the resolution of 1-phenylethanol using a chiral DMAP equivalent. For additional information, see: Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794–2795.
14. *Representative experimental procedure*: 1-phenylethyl 2-phenylbutanoate (*S*,*S*)-*anti*-**11** derived from the resolution of 1-phenylethanol (*rac*)-**1** using pentafluorophenyl 2-phenylbutanoate (*S*)-**10**: Lithium *tert*-butoxide (73 mg, 0.91 mmol), anhydrous zinc chloride (0.124 g, 0.91 mmol), and THF (5 mL) were sequentially added to a round-bottomed flask containing 1-phenylethanol (*rac*)-**1** (0.37 g, 3.03 mmol) under a nitrogen atmosphere. The resulting solution was refluxed for 2 h and then allowed to cool to room temperature over 1 h. Pentafluorophenyl 2-phenylbutanoate (*S*)-**10** (0.10 g, 0.30 mmol) in THF (5 mL) was added and the resulting solution was stirred for 12 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The organic layer was extracted with dichloromethane (3 × 25 mL), washed with water (50 mL), 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 (40–60 °C): diethyl ether (9:1) to give a pair of inseparable diastereoisomers (ratio: *anti*-:*syn*- 95.5:4.5; 91% de) of 1-phenylethyl 2-phenylbutanoates (*S*,*S*)-*anti*- and (*S*,*R*)-*syn*-**11** (42 mg, 52%) as colorless oils {R_F 0.82 [light petroleum (bp 40–60 °C):diethyl ether (1:1)]}. For characterisation data, see Ref. 6. All compounds synthesized have satisfactory ^1H and ^{13}C NMR, IR, and HRMS spectra with >95% purity.
15. The use of 10 equiv[4–8] of racemic alcohol has also been reported by Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629–1630. For our study, an excess of 1-phenylethanol (*rac*)-**1** was used to minimize the kinetic resolution concentration effect, epimerization of the product, potential racemization of the active ester(s), and as a competitive Lewis base.
16. The major diastereoisomeric ester (*S*,*S*)-*anti*-**8** can be formed stereospecifically in 82% yield with 99.4% de by using 1-phenylethanol (*S*)-**1** (>99% ee) and pentafluorophenyl 2-phenylpropanoate (*S*)-**6**.
17. (a) Cao, H. Y.; Grée, R. *Tetrahedron Lett.* **2009**, *50*, 1493–1494; (b) Linghu, X.; Satterfield, A. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 9302–9303; (c) Hodge, P.; Sung, D. W. L.; Stratford, P. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2335–2342.
18. The enantiomeric excess was determined by derivatisation with (*S*)-Ibuprofen using a DMAP-mediated DCC coupling procedure.
19. The enantiomeric excess was determined through statistical anhydride formation by treatment with DCC. For further information, see: Coulbeck, E.; Eames, J. *Tetrahedron: Asymmetry* **2009**, *20*, 635–640.