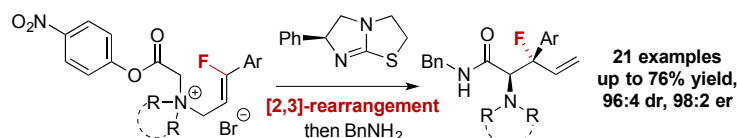


Enantioselective synthesis of β -fluoro- β -aryl- α -amino pentenamides by organocatalytic [2,3]-sigmatropic rearrangement

Kevin Kasten, Alexandra M. Z. Slawin and Andrew D. Smith*

EaStCHEM, University of St Andrews, School of Chemistry, North Haugh, St Andrews, Fife, KY16 9ST, Scotland, UK.

Supporting Information Placeholder



ABSTRACT: The tetramisole promoted catalytic enantioselective [2,3]-sigmatropic rearrangement of quaternary ammonium salts bearing a (*Z*)-3-fluoro-3-arylprop-2-ene group generates, after addition of benzylamine, a range of β -fluoro- β -aryl- α -amino pentenamides containing a stereogenic tertiary fluorine substituent. Cyclic and acyclic nitrogen substituents, as well as various aromatic substituents are tolerated, giving the β -fluoro- β -aryl- α -amino pentenamide products in up to 76% yield, 96:4 dr and 98:2 er.

The development of methods for the selective incorporation of fluorine into amino acid derivatives has grown extensively in recent years. These targets are of interest as probes in PET¹ and NMR² for studying the behavior of enzymes,³ and for incorporation into peptide structures and drug candidates.^{3,4} The most common strategies to incorporate a fluorine-containing stereogenic carbon involve either C-F or C-C bond formation, exploiting chiral fluorine sources, chiral starting materials, or prochiral fluorine-containing substrates.⁵ Despite advances in these areas, the preparation of α -amino acid derivatives containing a stereogenic tertiary fluorocarbon still represents a significant challenge in synthetic chemistry.⁶ Typical methods to prepare these structures use cyclic constraints and enantioenriched starting materials to achieve high selectivity.⁷ The current state-of-the-art in this area has been developed independently by the groups of Jacobsen and Zhou, who demonstrated the organocatalytic construction of this motif. Jacobsen *et al.* (Figure 1a) used the thiourea **3**-catalyzed asymmetric Mannich reaction of fluorinated 1,3-diketones **1** and α -chloro amino esters, such as **2**, to give **4**.⁸ This approach gave **4** in good yield and excellent enantioselectivity, although with poor diastereoselectivity (67%, 98:2 er, 54:46 dr). Zhou investigated the organocatalyzed Mukaiyama-Mannich reaction of cyclic fluorinated silyl enol ethers **5** and cyclic *N*-sulfonyl ketimines **6** (Figure 1b).⁹ Benzosultam products **8** were isolated in excellent yield and stereocontrol ($\geq 78\%$, $\geq 95:5$ er, and $>20:1$ dr), but only 3 examples were demonstrated and prolonged reaction times were required.

Building on previous work using isothiureas as Lewis bases in enantioselective catalysis,^{10,11} we envisaged an alternative approach for the synthesis of β -fluoro- β -aryl- α -amino acid derivatives through an organocatalyzed [2,3]-sigmatropic rearrangement of allylic ammonium salts.¹² In this manuscript we demonstrate that rearrangement of ammonium salts bear-

ing a (*Z*)-3-fluoro-3-arylprop-2-ene substituent allows the enantioselective construction of functionalized β -fluoro- β -aryl- α -amino acid derivatives containing a stereogenic tertiary fluorine-substituted β -carbon in up to 96:4 dr and 98:2 er.

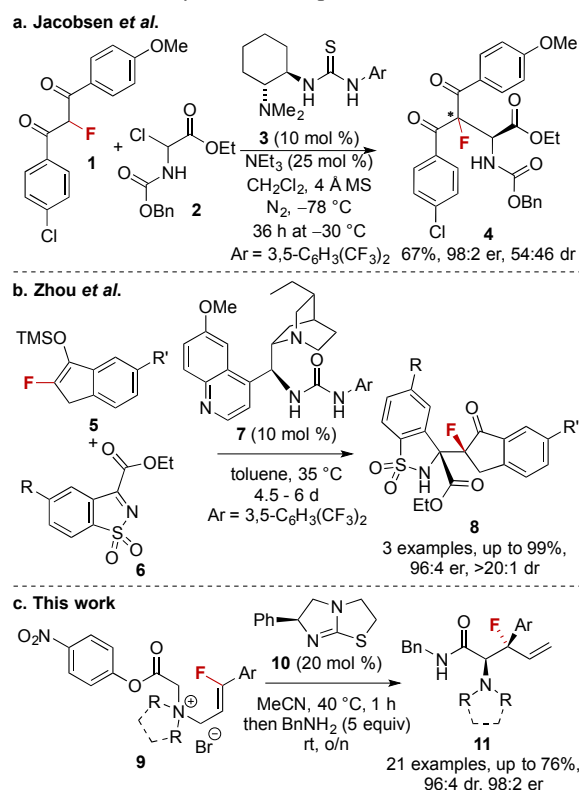
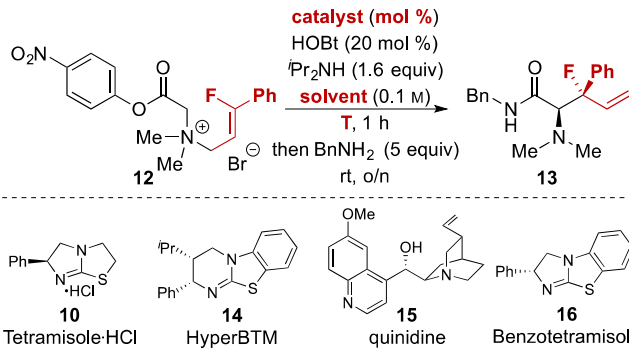


Figure 1. Context of this work.

The (*Z*)-3-fluoro-3-phenylprop-2-ene substituted ammonium salt **12** was chosen as a model compound for optimization studies. Treatment of **12** with catalysts **10**, **14–16**, cocatalytic HOBT (20 mol %), and $^i\text{Pr}_2\text{NH}$ was initially trialed using a 1 hour reaction time as standard (Table 1).¹² HyperBTM **14** and quinidine **15** gave the rearrangement product **13** in poor yield (23%) and in essentially racemic form in each case (entries 1 and 2). The use of benzotetramisole **16** and tetramisole hydrochloride **10** returned the product in high diastereo- and enantioselectivity (entries 3 and 4), with higher yield using **10** (62% vs 40%). Employing **10** as the optimal catalyst, the influence of temperature was investigated. Decreasing the temperature to $-20\text{ }^\circ\text{C}$ resulted in decreased yield and enantioselectivity (entry 5, 23%, 84:16 er), while increasing the temperature to $40\text{ }^\circ\text{C}$ or $80\text{ }^\circ\text{C}$ led to increased enantioselectivity (entries 6 and 7, up to 95:5 er). Alternative polar solvents were trialed at $40\text{ }^\circ\text{C}$, with ethylene carbonate (EC) showing high enantioselectivity (entry 8), while DMSO and DMF gave diminished stereoselectivity (entries 9 and 10, up to 87:13 er). Reducing the catalyst loading to either 10 or 5 mol % gave reduced yield and stereocontrol (entries 11 and 12).

Table 1. Optimization of reaction conditions.^a



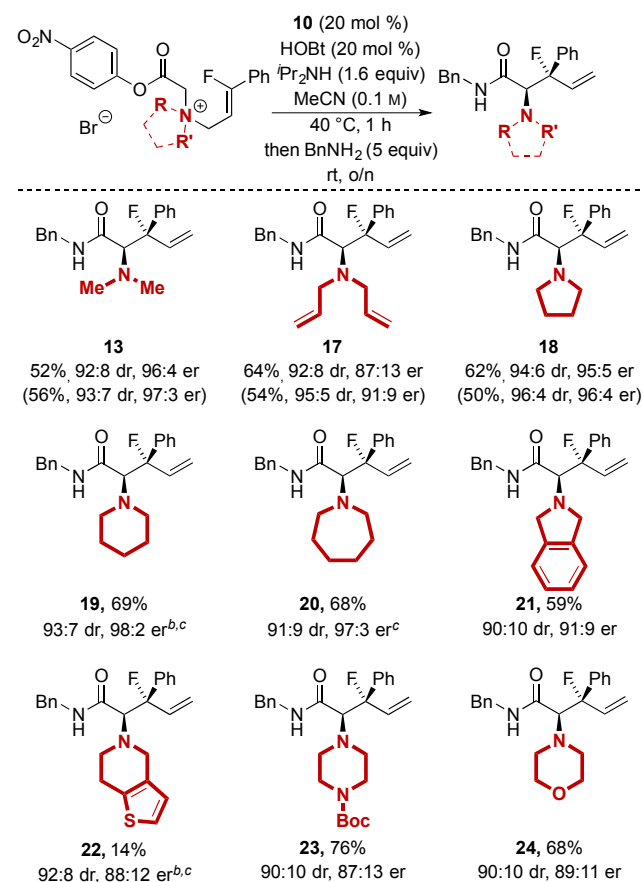
entry	catalyst	solvent	T [$^\circ\text{C}$]	yield [%]	dr ^b	er ^{c,d}
1 ^e	14	MeCN	20	23	90:10	55:45
2 ^e	15	MeCN	20	23	92: 8	51:49
3 ^e	16	MeCN	20	40	93: 7	10:90
4 ^e	10	MeCN	20	62	93: 7	89:11
5 ^e	10	MeCN	-20	23	96: 4	84:16
6	10	MeCN	40	52	92: 8	95: 5
7	10	MeCN	80	54	91: 9	93: 7
8	10	EC	40	56	93: 7	97: 3
9	10	DMSO	40	58	88:12	87:13
10	10	DMF	40	74	88:12	85:15
11 ^f	10	MeCN	40	28	89:11	86:14
12 ^g	10	MeCN	40	33	88:12	81:19

^a 0.20 mmol of substrate, ^b determined by $^{19}\text{F}\{^1\text{H}\}$ -NMR analysis of the crude reaction mixture, ^c determined by chiral HPLC analysis after purification, ^d ratio of (*2S,3S*)-**13**:(*2R,3R*)-**13**, ^e reaction time overnight, ^f 10 mol % of **10**, ^g 5 mol % of **10**.

With optimum conditions for the model substrate identified, the influence of nitrogen substitution upon the [2,3]-rearrangement was investigated. Due to operational simplicity MeCN was chosen as the optimal solvent, although a number

of compounds were prepared in both EC and MeCN for comparison (Figure 2). All starting materials were prepared using Sonogashira coupling and AgF-promoted hydrofluorination as key steps.¹³ Rearrangement of an *N,N*-diallyl ammonium salt gave selective [2,3]-rearrangement at the (*Z*)-3-fluoro-3-phenylprop-2-ene group, giving **17** with good stereocontrol (64%, 92:8 dr, 87:13 er). Higher diastereo- and enantioselectivity, but reduced yield, was observed in EC (54%, 95:5 dr, 91:9 er). Further investigation showed that a wide range of cyclic nitrogen substituents are tolerated in this process, with pyrrolidinyl, piperidinyl and azepanyl derivatives **18–20** being prepared in good yields and with high diastereo- and enantiocontrol (62 – 69%, 91:9 – 94:6 dr, 95:5 – 98:2 er). Alternative nitrogen heterocycles (isoindolyl, 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridinyl, *N*-Boc piperazinyl and morpholinyl) were also successfully incorporated giving products **21–24** with generally good yields and stereoselectivity (up to 92:8 dr and 91:9 er). However, attempted chromatographic purification of **22** led to extensive decomposition, while trituration allowed its isolation but in a poor 14% yield.

Figure 2. Substrate Scope – variation of N-substitution.^a



^a Results in parentheses performed in EC. dr determined by $^{19}\text{F}\{^1\text{H}\}$ -NMR analysis of the crude reaction mixture. er determined by chiral HPLC analysis after purification. ^b Product purified using basified silica. ^c Product precipitated from $\text{CH}_2\text{Cl}_2/\text{hexanes}$.

The relative and absolute configuration within product **20** was determined using X-ray crystallography, with the expected gauche relationship between the C-F and C-N bond of the secondary amine observed (Figure 3).¹⁴ All other examples were assigned by analogy.¹⁵

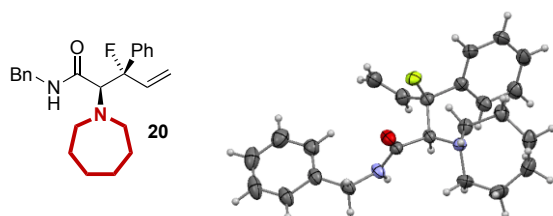


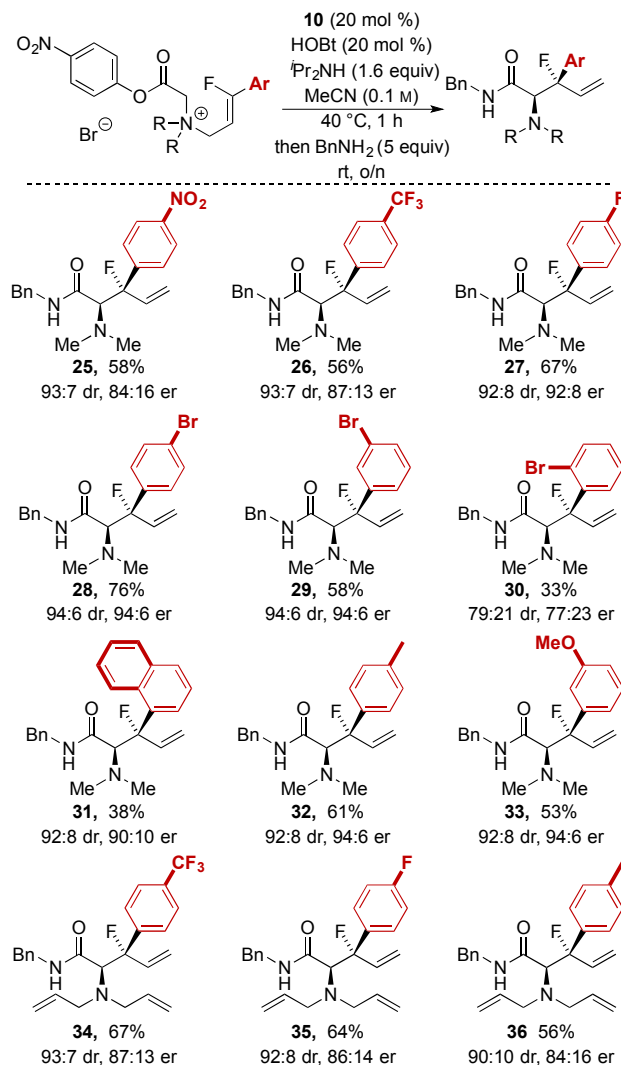
Figure 3. Molecular representation of the X-ray crystal structure of (2*S*,3*S*)-**20**.

The influence of varying aryl substitution within the (*Z*)-3-fluoro-3-arylprop-2-ene unit was also investigated (Figure 4). Incorporating electron-deficient *p*-nitro and *p*-trifluoromethyl substituents gave rearrangement products **25** and **26** in good yields with marginally reduced enantioselectivity (58% and 56% respectively, 84:16 and 87:13 er). A range of *m*- and *p*-halogenated aryl groups was tolerated, giving **27–29** in good yields and enantioselectivity (58 – 76%, 92:8 – 94:6 er). Sterically challenging *o*-substituents were also tested, with *o*-bromo substitution giving **30** in reduced yield and moderate stereoselectivity, while α -naphthyl substitution gave **31** with good stereocontrol (92:8 dr, 90:10 er). Both *p*-tolyl and *m*-anisyl substituents were tolerated, giving rearrangement products **32** and **33** with excellent stereocontrol (92:8 dr, 94:6 er). In addition, rearrangement of a number of *N,N*-diallyl substituted substrates was probed, giving products **34–36** in acceptable yield and stereocontrol (56 – 67%, up to 93:7 dr and 87:13 er) arising from selective [2,3]-rearrangement of the cinnamyl group. Notably the observed enantiocontrol was consistently lower in comparison to that of the corresponding *N,N*-dimethylamino analogues. Unfortunately the effect of incorporating an electron rich *p*-anisyl substituent could not be evaluated as this substrate proved impossible to prepare due to fluoride elimination.¹³

The mechanism of this rearrangement process (Scheme 1, illustrated for the formation of **13** from **12**) is believed to proceed *via* initial acylation of isothioureia **10** with ammonium salt **12** to give dicationic species **37**. Subsequent deprotonation gives the ylide **38**, with [2,3]-sigmatropic rearrangement leading to acyl isothiuronium derivative **39**. The catalyst is regenerated either through the addition of 1-hydroxybenzotriazole (HOBt) to **39** to form HOBt ester **40**, with subsequent addition of *p*-nitrophenoxide giving **41**, or

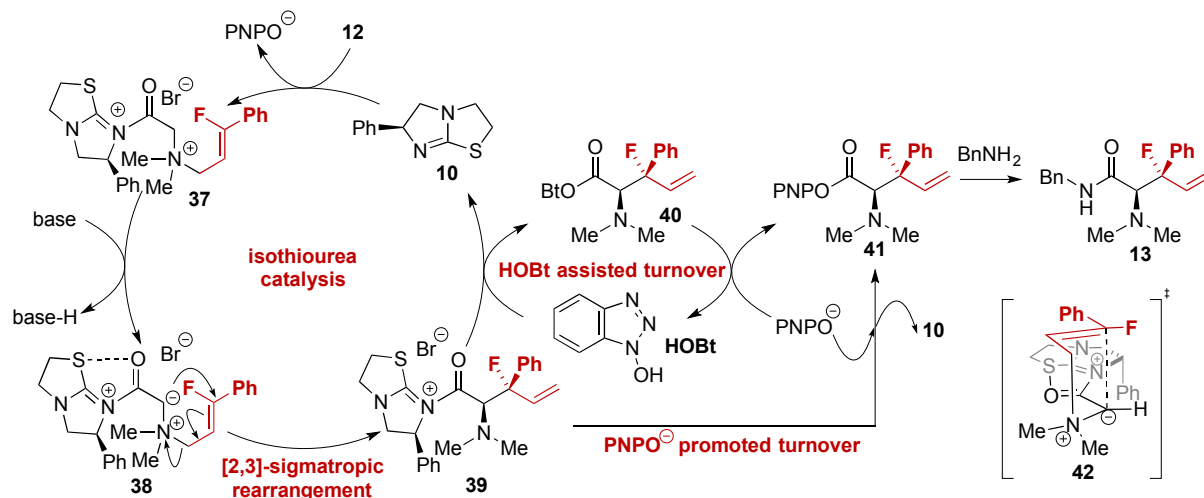
direct acylation of *p*-nitrophenoxide with **39** to give **41**. Addition of BnNH_2 gives the isolable product **13**.^{12b}

Figure 4. Substrate Scope – variation of aryl substitution.^a



^a dr determined by ¹⁹F{¹H}-NMR analysis of the crude reaction mixture. er determined by chiral HPLC analysis after purification.

Scheme 1: Mechanistic and Stereochemical Proposal



The observed stereocontrol is consistent with the [2,3]-sigmatropic rearrangement proceeding through the *endo* pre-transition state assembly **42**. In this arrangement, a 1,5-S•••O interaction^{16,17} serves to limit conformational flexibility, with the stereodirecting phenyl substituent adopting a pseudoaxial position to minimize 1,2-strain. [2,3]-Rearrangement proceeds *anti*- to the phenyl substituent with the cinnamyl unit participating in a stabilizing cation / π -interaction with the isothiouronium cation, giving rise to the observed stereocontrol.

To conclude, a range of enantioenriched tertiary β -fluoro- β -aryl- α -amino amides has been successfully synthesized using an organocatalytic [2,3]-sigmatropic rearrangement strategy. In general, highest yields and stereoselectivity were obtained for substrates with *N,N*-dimethyl, pyrrolidinyl, piperidinyl or azepanyl *N*-substituents. Halogen substituents in the *p*- and *m*-position of the aryl group were well tolerated, whereas electron-withdrawing (*p*-trifluoromethyl and *p*-nitro) and *o*-substituted aryl groups lead to reduced enantioselectivity. Further application of this methodology, and of isothiouroniums in enantioselective catalysis, is currently underway.

ASSOCIATED CONTENT

REFERENCES

- (a) Laverman, P.; Boerman, O. C.; Corstens, F. H. M.; Oyen, W. J. G. *Eur. J. Nucl. Med.* **2002**, *29*, 681-690. (b) Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 3216-3221.
- (a) Berkowitz, D. B.; Karukurichi, K. R.; de la Salud-Bea, R.; Nelson, D. L.; McCune, C. D. *J. Fluorine Chem.* **2008**, *129*, 731-742. (b) Yoder, N. C.; Kumar, K. *Chem. Soc. Rev.* **2002**, *31*, 335-341.
- (a) Odar, C.; Winkler, M.; Wiltshi, B. *Biotechnol. J.* **2015**, *10*, 427-446. (b) Marsh, E. N. G. *Acc. Chem. Res.* **2014**, *47*, 2878-2886. (c) Gerling, U. I. M.; Salwiczek, M.; Cadicamo, C. D.; Erdbrink, H.; Czekelius, C.; Grage, S. L.; Wadhvani, P.; Ulrich, A. S.; Behrends, M.; Haufe, G.; Kokschi, B. *Chem. Sci.* **2014**, *5*, 819-830. (d) Biava, H.; Budisa, N. *Eng. Life Sci.* **2014**, *14*, 340-351. (e) Smart, B. E., *J. Fluorine Chem.* **2001**, *109*, 3-11. (f) O'Hagan, D.; B. Harper, D. *J. Fluorine Chem.* **1999**, *100*, 127-133. (g) Pace, C. J.; Zheng, H.; Mylvaganam, R.; Kim, D.; Gao, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 103-107. (h) Buer, B. C.; Marsh, E. N. G. *Protein Sci.* **2012**, *21*, 453-462.
- (a) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359-4369. (b) Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Kokschi, B. *Chem. Soc. Rev.* **2012**, *41*, 2135-2171. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320-330. (d) Meng, H.; Kumar, K. *J. Am. Chem. Soc.* **2007**, *129*, 15615-15622.
- (a) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 8214-8264; (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308-319.
- Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 4690-4693.
- (a) Baldwin, J. E.; Cobb, J. E.; Sheppard, L. N. *Tetrahedron* **1987**, *43*, 1003-1012. (b) Abouabdellah, A.; Boros, L.; Gyenes, F.; Welch, J. T. *J. Fluorine Chem.* **1995**, *72*, 255-259. (c) Genêt, J.-P.; Durand, J.-O.; Roland, S.; Savignac, M.; Jung, F. *Tetrahedron Lett.* **1997**, *38*, 69-72. (d) Ferrary, T.; David, E.; Milanole, G.; Besset, T.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 5598-5601. (e) Pons, A.; Beucher, H.; Ivashkin, P.; Lemonnier, G.; Poisson, T.; Charette, A. B.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2015**, *17*, 1790-1793. (f) Chan, J. Z.; Yao, W.; Hastings, B. T.; Lok, C. K.; Wasa, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 13877-13881. (g) Leroy, J.; Cantacuzene, D.; Wakselman, C. *Synthesis* **1982**, *14*, 313-315. (h) Leroy, J.; Wakselman, C. *Can. J. Chem.* **1976**, *54*, 218-225. (i) Jakowiecki, J.; Loska, R.; Makosza, M. *J. Org. Chem.* **2008**, *73*, 5436-5441. (j) Patrick, T. B.; Shadmehr, M.; Khan, A. H.; Singh, R. K.; Asmelash, B. *J. Fluorine Chem.* **2012**, *143*, 109-111.
- Wasa, M.; Liu, R. Y.; Roche, S. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 12872-12875.
- Yu, J.-S.; Zhou, J. *Org. Chem. Front.* **2016**, *3*, 298-303.
- For seminal reports, see: (a) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859-4861. (b) Jiang, H.; Li, X.; Guo, L.; Uffman, E. W.; Birman, V. B. *J.*

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. This contains the synthesis and characterization data of the rearrangement products, ammonium salts and precursors; copies of the ¹H-NMR, ¹³C-NMR, ¹⁹F-NMR and HPLC chromatograms are provided for novel compounds. Crystallographic data for compound **20** (CIF) is provided.¹⁸

AUTHOR INFORMATION

Corresponding Author

* ads10@st-andrews.ac.uk

Author Contributions

All authors have given approval to the final manuscript version.

ACKNOWLEDGMENT

The research leading to these results (K.K.) has received funding from the ERC under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC grant agreement n° 279850. A.D.S. thanks the Royal Society for a Wolfson Research Merit Award. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

- Am. Chem. Soc.* **2006**, *128*, 6536-6537. (c) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347-4350. (d) Li, X.; Birman, V. B. *Org. Lett.* **2008**, *10*, 1115-1118. (e) Joannesse, C.; Johnston, C. P.; Concellón, C.; Simal, C.; Philp, D.; Smith, A. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 8914-8918. (f) Belmessieri, D.; Morrill, L. C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714-2720.
- For reviews see: (a) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109-2121. (b) Morrill, L. C.; Smith, A. D. *Chem. Soc. Rev.* **2014**, *43*, 6214-6226. (c) Merad, J.; Pons, J.-M.; Chuzel, O.; Bressy, C. *Eur. J. Org. Chem.* **2016**, *2016*, 5589-5610.
 - (a) West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, *136*, 4476-4479. (b) West, T. H.; Walden, D. M.; Taylor, J. E.; Brueckner, A. C.; Johnston, R. C.; Cheong, P. H. Y.; Lloyd-Jones, G. C.; Smith, A. D. *J. Am. Chem. Soc.* **2017**, *139*, 4366-4375. (c) West, T. H.; Spoehrle, S. S. M.; Smith, A. D. *Tetrahedron* **2017**, *73*, 4138-4149. For a review of stereoselective [2,3]-rearrangements see West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446-7479.
 - The SI contains detailed information of starting material synthesis. Attempted synthesis of the *p*-anisyl substrate was unsuccessful due to degradation of the corresponding (*Z*)-3-fluoro-3-arylprop-2-ene-1-ol.
 - For a review see Thiehoff, C.; Rey, Y. P.; Gilmour, R. *Isr. J. Chem.* **2017**, *51*, 92-100.
 - Crystallographic data obtained for **20** has been deposited with the Cambridge Crystallographic Data Centre and the supplementary data can be found via CCDC 1531810.
 - For S•••O interactions as control elements in isothiouronia catalysis, see: (a) Robinson, E. R. T.; Walden, D. M.; Fallan, C.; Greenhalgh, M. D.; Cheong, P. H.-Y.; Smith, A. D. *Chem. Sci.* **2016**, *7*, 6919-6927. (b) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2014**, *136*, 4492-4495. (c) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3288-3291. (d) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37-40. For the use of S•••O interactions in asymmetric synthesis see (e) Nagao, Y.; Miyamoto, S.; Miyamoto, M.; Takeshige, H.; Hayashi, K.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9722-9729.
 - For discussions on the origin of S•••O interactions, see: (a) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 4383-4438. (b) Zhang, X.; Gong, Z.; Li, J.; Lu, T. *J. Chem. Inf. Model.* **2015**, *55*, 2138-2153. (c) Reid, R. C.; Yau, M.-K.; Singh, R.; Lim, J.; Fairlie, D. P. *J. Am. Chem. Soc.* **2014**, *136*, 11914-11919.
 - The data underpinning this research can be found at <http://dx.doi.org/10.17630/af3745e3-c727-4668-b871-c8dec2>

