Fluorine-Induced Diastereodivergence Discovered in an Equally Rare Enantioselective *syn*-aza-Henry Reaction

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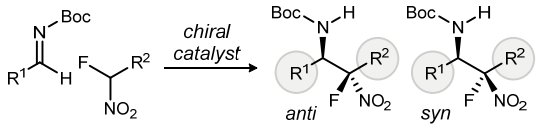
Additional Notes Regarding Protocol Selection for Enantioselective Type I-IV aza-Henry Reactions

A goal of this study was to identify, if not understand the factors that determined diastereoselection using standard protocols that required little deviation to quantify selectivity (dr, ee). These standard protocols may not be optimal for individual cases, and further optimization could lead to higher yield and selectivity. These caveats notwithstanding, the tables below provide different representations, with cross-reference to the related experiment in Table 1.

The crystallinity that is typical of the products not only allowed the use of X-ray diffractometry to directly assign configuration for the adducts, but it also provided a means to enrich products further. For example, adduct **6e** could be recrystallized (ethyl acetate/hexanes) from 15:1 dr, 87/51% ee to >20:1 dr, 96% ee material.

Figure S1. Catalyst selection charts for Type I-IV aza-Henry reactions.



superior catalyst (these optimized conditions)

Type I - H	**1**	**Type III - H**	**1**•$HNTf_2$
Type I - F	**1**•$HNTf_2$	**Type III - F**	**1**•$HNTf_2$
Type II - H	**2**	**Type IV - H**	**2**
Type II - F	**1**•$HNTf_2$	**Type IV - F**	**2**

Superior Protocol	Type I		Type II		Type III		Type IV	
	H	F	H	F	H	F	H	F
catalyst	**1**	**1**·$HNTf_2$	**2**	**1**·$HNTf_2$	**1**·$HNTf_2$	**1**·$HNTf_2$	**2**	**2**
selectivity	*anti*	*anti*	*anti*	*anti*	*anti*	***syn***	*anti*	***syn***
entry (manuscript Table 1)	1	3	6	7	9	11	14	16

Stereochemical Assignment Maps Across Substrates and Publications

To simplify the comparison of stereochemical outcomes, based on assignments by numerous investigators, the following figures are organized by Type (I-IV) and reference the original publications. “Analogy” is the practice of extrapolating the assignment for one compound in a series to the remaining examples.

Figure S2. Stereochemical assignment of Type II aza-Henry adducts by comparison to Type I adducts.[1,2,3]

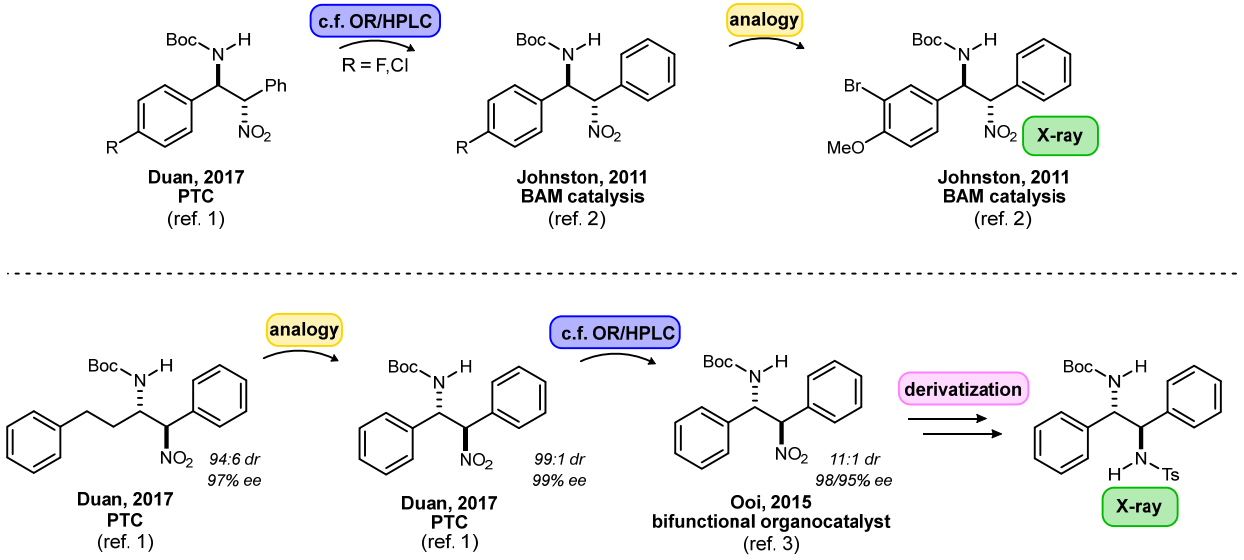
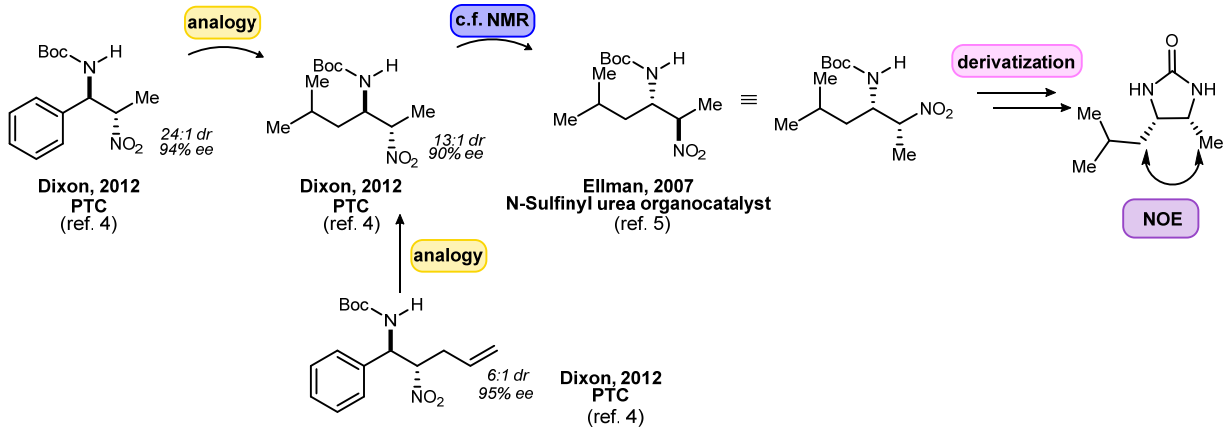
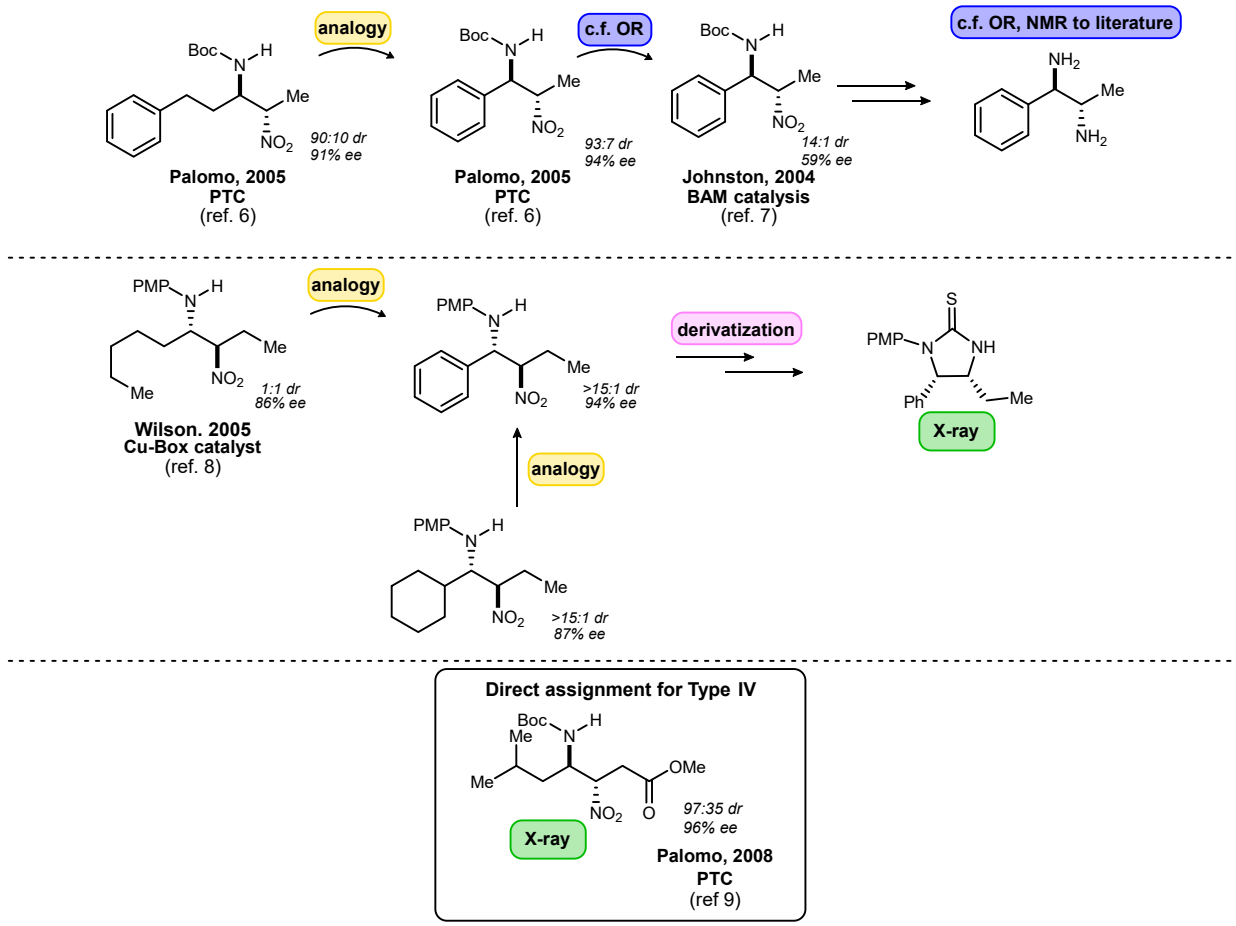


Figure S3. Stereochemical assignment of Type II aza-Henry adducts by comparison to Type I adducts.[4,5]



[1] Lu, N.; Li, R.; Wei, Z.; Cao, J.; Liang, D.; Lin, Y.; Duan, H. *J. Org. Chem.* **2017**, *82*, 4668.
[2] Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076.
[3] Uraguchi, D.; Oyaizu, K.; Noguchi, H.; Ooi, T. *Chem. - Asian J.* **2015**, *10*, 334.
[4] Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nunez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492.
[5] Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110.

Figure S4. Stereochemical assignment of Type II aza-Henry adducts by comparison to Type I adducts.[6,7,8,9]



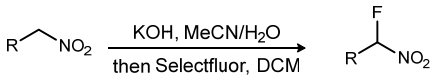
General Experimental Section

All reagents and solvents were commercial grade and purified prior to use when necessary. Acetonitrile (MeCN), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene were dried by passage through a column of activated alumina as described by Grubbs[10] for microscale reactions. Flame-dried (under vacuum) glassware was used for all reactions. Stainless steel syringe needles or cannulae attached to a glass syringe barrel were used to transfer air- and moisture-sensitive liquids. Anhydrous magnesium sulfate ($MgSO_4$) was used as a drying agent after extractions unless otherwise indicated. Compound **6b** was prepared as previously reported.[11]

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μm) plates and flash chromatography utilized 230–400 mesh silica gel from Sorbent Technologies. UV light, and/or the use of ceric ammonium molybdate, *p*-anisaldehyde, potassium permanganate or phosphomolybdic acid solutions were used to visualize products.

[6] Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622.
[7] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.
[8] Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665.
[9] Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Mugica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955.
[10] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
[11] Vara, B. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2016**, *138*, 13794.

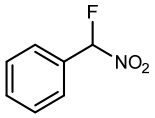
IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm $^{-1}$) analyzed as neat films on NaCl plates (transmission). Nuclear magnetic resonance spectra (NMR) were obtained on a Bruker DRX-500 (500 MHz), Bruker AV-400 (400 MHz), or Bruker AV II-600 (600 MHz). Chemical shifts are measured to residual non-deuterated solvent peaks as an internal standard. Mass spectra were recorded by use of chemical ionization (CI), electron impact ionization (EI), or electro-spray ionization (ESI) on a high resolution Thermo Electron Corporation MAT 95XP-Trap by the Indiana University Mass Spectrometry Facility or on a TQ-Orbitrap 3 XL Penn or Orbitrap 2 Classic FPG in the Vanderbilt Mass Spectrometry Core Laboratory. Optical rotations were measured on a Perkin Elmer-341 polarimeter or a Jasco P-2000 polarimeter. Chiral HPLC analysis was conducted on an Agilent 1100 series or an Agilent 1260 Infinity instrument using the designated ChiralPak column. Absolute configuration was determined by X-ray (see X-Ray Crystallographic Data).



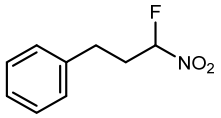
In cases where diastereoselection is high, the ee determined for the minor diastereomer is often based on two very small peaks. Therefore, ee values calculated for the minor diastereomer may contain more error since they are based on the observance of only one small peak. However, the observed (major) peak is consistent between the two catalysts.

General Procedure for the Preparation of α-Fluoro Nitroalkanes[12]

A round bottom flask was charged with the nitroalkane (6.05 mmol) and MeCN/H_2O (4.7 mL/9.0 mL). The solution was cooled to 0 °C, solid KOH (97%) (390 mg, 6.05 mmol) was added, and the reaction was vigorously stirred for 1 h at 0 °C. The reaction mixture was chilled to -20 °C to partially precipitate the nitronate salt, and Selectfluor (9.68 mol) was added followed immediately by CH_2Cl_2 (21 mL) which was pre-cooled to -78 °C. This mixture was gradually warmed to 10 °C and monitored by TLC. Upon completion, the resulting biphasic mixture was diluted with diethyl ether and stirred for an additional 10 min before being passed through a pad of Celite (Et_2O). The water layer was extracted with diethyl ether, and the combined organics were dried ($MgSO_4$), filtered, and concentrated.



(Fluoro(nitro)methyl)benzene (4b). This compound was prepared according to the General Procedure using 1.50 g (10.9 mmol) of the nitroalkane. The crude mixture was purified by flash column chromatography (0-2-4% EtOAc/hexanes) to afford the product as a pale-yellow oil (1.27 g, 75%). All spectral data matched the literature values.[12]

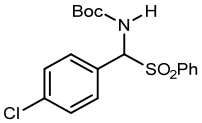


(3-Fluoro-3-nitropropyl)benzene (4d). This compound was prepared according to the General Procedure using 1.00 g (6.05 mmol) of the nitroalkane. The resulting pale-yellow oil was used without further purification. R_f = 0.69 (20% Et_2O/hexanes); IR (film) 3028, 2932, 1570, 1453, 1124, 747, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, J = 7.5, 7.5 Hz, 2H), 7.27-7.24 (m, 1H), 7.20 (d, J = 7.4 Hz, 2H), 5.75 (ddd, $^2J_{HF}$ = 50.6, $^3J_{HH}$ = 7.0, 4.0 Hz, 1H), 2.87-2.77 (m, 2H), 2.56-2.39 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 138.4, 129.0, 128.5, 127.0, 110.4 (d, $^1J_{CF}$ = 239 Hz), 34.9 (d, $^2J_{CF}$ = 19.8 Hz), 29.2 (d, $^3J_{CF}$ = 3.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -147.8; HRMS (-ESI): Exact mass calcd for $C_9H_9FNO_2$ [M-H]$^-$ 182.0623, found 182.0618.

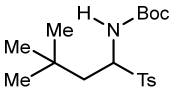
[12] Hu, H.; Huang, Y.; Guo, Y. *J. Fluorine Chem.* **2012**, *133*, 108.

General Procedure for the Preparation of *N*-Boc α-Amidosulfones[13,14,15]

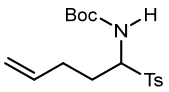
To a round-bottomed flask equipped with a stir bar was added *tert*-butyl carbamate (1 equiv.), *para*-toluenesulfinic acid sodium salt (2 equiv.), MeOH and water. The corresponding aldehyde (1.5 equiv.) was then added, followed by formic acid (2 equiv.). The mixture was stirred for 96 h at room temperature. The resulting precipitate was filtered and washed with water and hexanes to afford the desired α-amidosulfone without further purification.



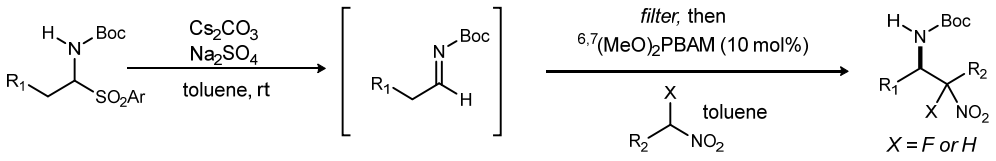
***tert*-Butyl ((4-chlorophenyl)(phenylsulfonyl)methyl)carbamate (S1).** The title compound was prepared according to the general procedure from *tert*-butyl carbamate (8.3 g, 71 mmol) and 4-chlorobenzaldehyde (15.0 g, 107 mmol) and isolated as a white solid (20.8 g, 77%). All spectral data matched that in the literature.[16]



***tert*-Butyl (3,3-dimethyl-1-tosylbutyl)carbamate (S2).** The title compound was prepared according to the general procedure from *tert*-butyl carbamate (1.17 g, 10.0 mmol) and 3,3-dimethylbutanal (1.89 mL, 15.0 mmol) and isolated as a white solid (3.35 g, 94%). All spectral data matched that in the literature.[17]



***tert*-Butyl (1-tosylpent-4-en-1-yl)carbamate (S3).** Pent-4-enal (8.90 g, 106 mmol) was dissolved in a mixture of MeOH/H_2O (1:2, 235 mL) in a round-bottomed flask. To the solution was added *tert*-butyl carbamate (8.26 g, 70.5 mmol), *para*-toluene sulfinic acid sodium salt (25.14 g, 141.1 mmol) and formic acid (5.32 mL, 141 mmol). The mixture was stirred at room temperature and the resulting precipitate was filtered and washed with water and hexanes to afford the α-amidosulfone, which was used without further purification, as a white solid (14.9 g, 62%). Mp 95.2-96.0 °C, 113.2°C (Boc thermolysis); R_f = 0.36 (20% EtOAc/hexanes); IR (film) 3334, 2977, 1720, 1518, 1316, 1165, 1141 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.82-5.72 (m, 1H), 5.07-5.02 (m, 2H), 4.96 (d, *J* = 10.8 Hz, 1H), 4.81 (ddd, *J* = 10.8, 10.8, 3.0 Hz, 1H), 2.40 (s, 3H), 2.38-2.27 (m, 2H), 2.18-2.12 (m, 1H), 1.86-1.78 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 153.8, 145.0, 136.1, 133.9, 129.8, 129.5, 116.7, 80.8, 70.3, 29.5, 28.0, 25.9, 21.7; HRMS (ESI): Exact mass calcd for $C_{17}H_{25}NNaO_4S$ $[M+Na]^+$ 362.1402, found 362.1401.

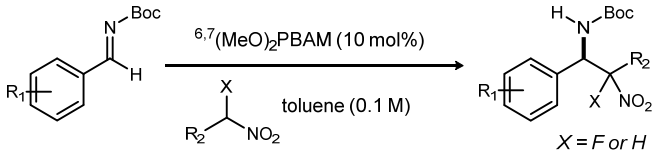


General Procedure A: BAM-Catalyzed aza-Henry Reaction with Alkyl Electrophiles[13]

To a flame-dried vial equipped with a stir bar was added *N*-Boc α-amidosulfone (100 μmol), Na_2SO_4 (500 μmol), Cs_2CO_3 (500 μmol) and toluene (500 μL). The reaction stirred for 3 hours at room temperature. The

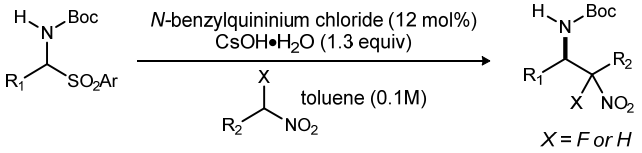
[13] Schwieter, K. E.; Johnston, J. N. *ACS Catalysis* **2015**, *5*, 6559.
[14] Gomez-Bengoa, E.; Linden, A.; Lopez, R.; Mugica-Mendiola, I.; Oiarbide, M.; Palomo, C. *J. Am. Chem. Soc.* **2008**, *130*, 7955.
[15] Pettersen, D.; Marcolini, M.; Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzani, V.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 6269.
[16] Davis, T. A.; Vilgelm, A. E.; Richmond, A.; Johnston, J. N. *J. Org. Chem.* **2013**, *78*, 10605.
[17] Schwieter, K. E.; Johnston, J. N. *Chem. Sci.* **2015**, *6*, 2590.

mixture was filtered through a short pad of Celite into a flame dried vial containing the nitroalkane (1.1 equiv). The Celite was rinsed with an additional 500 µL of toluene into the reaction vial. The reaction mixture was cooled to the indicated temperature and the catalyst (10 mol%) was added. Upon completion, the reaction was filtered through a short plug of silica gel, concentrated, and purified by flash column chromatography if necessary.



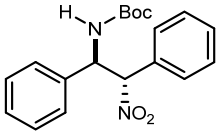
General Procedure B: BAM Catalyzed aza-Henry Reaction with Aryl Aldimines[11]

To a flame dried vial equipped with a stir bar was added the nitroalkane (120 µmol), toluene (500 µL), and $^{6,7}(MeO)_2$PBAM or $^{6,7}(MeO)_2$PBAM•$HNTf_2$ (10 µmol) at room temperature. The mixture was stirred until homogeneous and then cooled to the indicated temperature before the imine (100 µmol) was added. Upon completion of the reaction, the mixture was quickly flushed through a pad of silica gel and concentrated. The resultant residue was purified by column chromatography to afford the title compound.

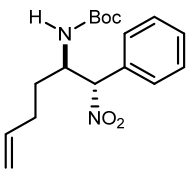


General Procedure C: Phase Transfer Catalyzed aza-Henry Reaction[14]

To a flame dried vial equipped with a stir bar was added the *N*-Boc α-amidosulfone (100 µmol), nitroalkane (450 µmol), *N*-benzylquininium chloride (12 µmol) and toluene (1 mL). The reaction mixture was cooled to the indicated temperature and CsOH•H_2O (130 µmol) was added. The reaction was stirred vigorously at the indicated temperature for 72 hours. Upon completion the reaction mixture was quenched with 1 M aq HCl while still cold, and extracted with dichloromethane. The combined organic layers were washed with 1 M aq HCl, dried, and concentrated. The resultant mixture was purified by column chromatography to afford the desired β-amino nitroalkane.



***tert*-Butyl ((1*R*,2*S*)-2-nitro-1,2-diphenylethyl)carbamate (6a).** This compound was prepared according to General Procedure B using *tert*-butyl benzylidenecarbamate (20.5 mg, 100 µmol), phenylnitromethane (16.5 mg, 120 µmol) and $^{6,7}(MeO)_2$PBAM (6.3 mg, 10 µmol) at -55 °C. The reaction mixture was passed through a short pad of silica gel and concentrated to afford the desired product in 78% yield (^{1}H-NMR, mesitylene internal standard). The product was determined to be 20:1 dr and 78% ee by chiral HPLC analysis (Chiralpak AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, 25 °C, t_r(*d*$_1$*e*$_1$, minor/major) = 13.8 min, t_r(*d*$_1$*e*$_2$, minor/minor) = 27.6 min, t_r(*d*$_2$*e*$_1$, major/major) = 18.3 min, t_r(*d*$_2$*e*$_2$, minor/major) = 20.2 min). All spectral data matched that in the literature.[3]

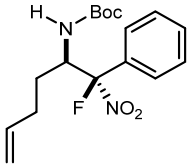


***tert*-Butyl ((1*S*,2*R*)-1-nitro-1-phenylhex-5-en-2-yl)carbamate (6c).** This compound was prepared according to General Procedure A using *tert*-butyl (1-tosylpent-4-en-1-yl)carbamate (33.9 mg, 100 µmol), phenylnitromethane (15.1 mg, 110 µmol) and $^{6,7}(MeO)_2$PBAM (6.3 mg, 10 µmol). Flash column chromatography (10-20-40% diethyl

ether in hexanes) afforded the product as a white solid (11.2 mg, 35% yield), which was determined the be >20:1 dr and 60% ee by chiral HPLC analysis.

Phase transfer catalysis: Prepared according to General Procedure C at -35 °C from *tert*-butyl (1-tosylpent-4-en-1-yl)carbamate (33.9 mg, 100 µmol), phenylnitromethane (61.7 mg, 450 µmol) and *N*-benzylquininium chloride (5.4 mg, 12 µmol). Flash column chromatography (10-20-40% diethyl ether in hexanes) afforded the product as a white solid (10 mg, 31% yield), which was determined to be >11:1 dr and 90/>99% ee by chiral HPLC analysis.

White solid, mp = 122-125 °C[18]; $[\alpha]_D^{20}$ + 12.4 (*c* 0.24, $CHCl_3$)[19]; (Chiralpak AD, 3% ^{i}PrOH/hexanes, 1.0 mL/min: $t_r(d_1e_1$, major/minor) = 18.6 min, $t_r(d_1e_2$, major/major) = 20.0 min, $t_r(d_2e_1$, minor/minor) = 21.7 min, $t_r(d_2e_2$, minor/major) = 24.7 min). R_f = 0.23 (10% EtOAc/hexanes); IR (film) 3374, 2978, 2918, 1683, 1542, 1522, 1367, 1165 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.39-7.38 (m, 3H), 5.76 (dddd, *J* =17.0, 10.3, 6.8, 6.5 Hz, 1H), 5.65 (d, *J* = 7.1 Hz, 1H), 5.05-5.00 (br m, 2H), 4.42-4.39 (m, 2H), 2.25-2.21 (m, 1H), 2.14-2.07 (m, 1H), 1.74-1.66 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.0, 137.0, 132.3, 129.9, 128.9, 128.4, 116.0, 93.8, 801, 53.0, 30.36, 30.2, 28.3; HRMS (ESI): Exact mass calcd for $C_{17}H_{23}N_2O_4$ [M-H]$^-$, 319.1663, found 319.1654.

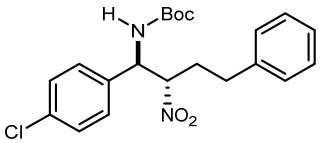


***tert*-Butyl ((1*R*,2*R*)-1-fluoro-1-nitro-1-phenylhex-5-en-2-yl) (6d).** This compound was prepared according to General Procedure A using *tert*-butyl (1-tosylpent-4-en-1-yl)carbamate (500 mg, 1.47 mmol), (fluoro(nitro)methyl)benzene (274 mg, 1.77 µmol) and [6,7](OMe)$_2$PBAM·HNTf$_2$ (267 mg, 295 µmol). ^{19}F-NMR analysis of the crude mixture showed a 5.2:1 dr. Flash column chromatography (2-4-6% EtOAc/hexanes) afforded the product as a white solid (263 mg, 53% yield), which was determined by chiral HPLC analysis to be 83% ee for the major *anti* diastereomer and >99% ee for the minor *syn* diastereomer. Absolute and relative stereochemistry was determined by X-Ray analysis of a single crystal of the major diastereomer grown by slow evaporation of dichloromethane. See **X-Ray Crystallographic Data** for more details.

When 10 mol% catalyst was used the product was isolated in 43% yield as a 5.8:1 mixture of diastereomers with 87/<99% ee.

White solid, mp = 77-81 °C[20]; $[\alpha]_D^{20}$ + 4.0 (*c* 0.45, $CHCl_3$)[21]; Agilent 1100 Series, Chiralpak AD-H, 4% EtOH/hexanes, 1.0 mL/min, 25 °C: $t_r(d_1e_1$, major/major) = 5.6 min, $t_r(d_1e_2$, major/minor) = 6.7 min, $t_r(d_2e_1$, minor/major) = 11.7 min, $t_r(d_2e_2$, minor/minor) = 16.7 min). R_f = 0.57 (20% EtOAc/hexanes); IR (film) 3334, 2980, 2934, 1705, 1571, 1515, 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.45-7.38 (m, 3H), 5.84-5.74 (m, 1H), 5.15 (dddd, *J* = 10.9, 10.9, 2.6 Hz, $^3J_{HF}$ = 27.1 Hz, 1H), 5.10-5.04 (m, 2H), 4.41 (d, *J* = 10.8 Hz, 1H), 2.28-2.21 (m, 1H), 2.16 (ddd, *J* = 22.4, 14.8, 7.5 Hz, 1H), 1.71-1.62 (m, 1H), 1.58-1.51 (m, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.9, 136.6, 131.6 (d, $^2J_{CF}$ = 23.3 Hz), 131.0, 128.6 (d, $^4J_{CF}$ = 1.1 Hz), 126.0 (d, $^3J_{CF}$ = 8.7 Hz), 120.3 (d, $^1J_{CF}$ = 242.9), 116.4, 80.4, 54.1 (d, $^2J_{CF}$ = 20.8 Hz), 29.7, 28.3 (d, $^3J_{CF}$ = 3.9 Hz), 28.1 ppm; ^{19}F-NMR (376 MHz) -141.4, HRMS (-ESI): Exact mass calcd for $C_{17}H_{23}FN_2NaO_4$ [M+Na]$^+$ 361.1540, found 361.1539.

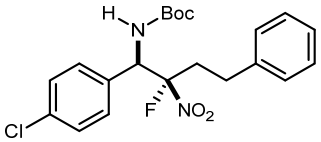
[18] The melting point was measured on >20:1 dr material.
[19] The optical rotation measured on >11:1 dr, 86/99% ee material.
[20] The melting point was measured on 16:1 dr material.
[21] The optical rotation was measured on 16:1 dr, 83/99% ee material.



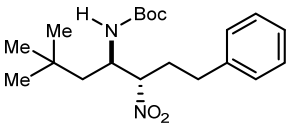
***tert*-Butyl ((1*R*,2*S*)-1-(4-chlorophenyl)-2-nitro-4-phenylbutyl)carbamate (6e).** This compound was prepared according to General Procedure B using *tert*-butyl (*E*)-(4-chlorobenzylidene)carbamate (24.0 mg, 100 μmol), 3-(nitropropyl)benzene (19.8 mg, 120 μmol) and [6,7](OMe)$_2$PBAM·HNTf$_2$ (9.1 mg, 10 μmol). Flash column chromatography (10-20% EtOAc/hexanes) afforded the product as a white solid (20 mg, 49% yield), which was determined to be >20:1 dr and 87/51% ee by chiral HPLC analysis. Recrystallization from ethyl acetate provided >20:1 dr and 96% ee material.

Phase transfer catalysis: Prepared according to General Procedure C at -55 ℃ from *tert*-butyl ((4-chlorophenyl)(phenylsulfonyl)methyl)carbamate (38.2 mg, 100 μmol), 3-(nitropropyl)benzene (74.3 mg, 450 μmol) and *N*-benzylquininium chloride (5.4 mg, 12 μmol). Analysis of the crude ^{1}H-NMR spectrum showed a 94% yield. Chiral HPLC analysis of the crude mixture showed the product was 3:1 dr with 30/8% ee.

White solid, mp = 159-161 °C; $[\alpha]_D^{20}$ -36 (*c* 0.43, $CHCl_3$); Chiralpak AD-H, 10% ^{i}PrOH/hexanes, 1.0 mL/min, 25 °C: t_r(*d*$_1$*e*$_1$, major/minor) = 9.2 min, t_r(*d*$_2$*e*$_1$, minor/minor) = 11.7 min, t_r(*d*$_2$*e*$_2$, minor/major) = 13.0 min, t_r(*d*$_1$*e*$_2$, major/major) = 25.5 min; R_f = 0.26 (10% EtOAc/hexanes); IR (film) 3386, 2977, 1683, 1547, 1519, 1494, 1367, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 4H), 7.24-7.20 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 4H), 5.12 (br s, 2H), 4.74 (br s, 1H), 2.74 (ddd, *J* = 13.9, 9.1, 4.8 Hz, 1H), 2.54 (ddd, *J* = 13.9, 8.1, 8.1 Hz, 1H), 2.40-2.30 (m, 1H), 2.10-2.01 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 154.7, 139.4, 135.0, 134.7, 129.2, 128.7, 128.5, 128.2, 126.6, 90.1, 80.9, 56.3, 31.9, 31.5, 28.2; HRMS (-ESI): Exact mass calcd for $C_{21}H_{24}ClN_2O_4$ [M-H]$^-$ 403.1430, found 403.1422.



***tert*-Butyl ((1*R*,2*S*)-1-(4-chlorophenyl)-2-fluoro-2-nitro-4- phenylbutyl)carbamate (6f).** This compound was prepared according to General Procedure C at -35 ℃ from *tert*-butyl ((4-chlorophenyl)(phenylsulfonyl)methyl)carbamate (38.2 mg, 100 μmol), (3-fluoro-3-nitropropyl)benzene (82.4 mg, 450 μmol) and *N*-benzylquininium chloride (5.4 mg, 12 μmol). The crude reaction mixture was purified by flash column chromatography (SiO_2, 10-20% diethyl ether in hexanes) to provide the product (33 mg, 79%) as a 2.8:1 mixture of diastereomers. The major diastereomer (*syn*) was found to be 60% ee and the minor (*anti*) was found to be 24% ee by chiral HPLC analysis (Chiralpak IA, 5% EtOH/hexanes, 1.0 mL/min, 30 °C: t_r(*d*$_1$*e*$_1$, minor/major) = 6.6 min, t_r(*d*$_2$*e*$_1$, major/minor) = 7.1 min, t_r(*d*$_2$*e*$_2$, major/major) = 9.8 min, t_r(*d*$_1$*e*$_2$, minor/minor) = 14.3 min). All other spectral data matched the literature.[11] Absolute and relative stereochemistry was determined by X-Ray analysis of a single crystal of the major diastereomer grown by slow liquid/liquid diffusion with ethyl acetate/hexanes.[22] See **X-Ray Crystallographic Data** for more details.



***tert*-Butyl ((3*S*,4*R*)-6,6-dimethyl-3-nitro-1-phenylheptan-4-yl)carbamate (6g).** This compound was prepared according to the General Procedure A using *tert*-butyl (3,3-dimethyl-1-tosylbutyl)carbamate (35.5 mg, 100 μmol), (3-nitropropyl)benzene (18.2 mg, 110 μmol) and [6,7](MeO)$_2$PBAM (6.3 mg, 10 μmol) at -55 °C for 48 hours. ^{1}H

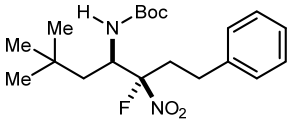
[22] This diastereomer was assigned by analogy in ref. 11, but that assignment is now corrected here by X-ray crystallography.

NMR analysis of the crude reaction mixture showed a 1:1 mixture of diastereomers which were separated and purified by flash column chromatography (5-10-20% Et_2O in hexanes) to afford the major diastereomer (4.3 mg, 12%) and the minor diastereomer (3.5 mg, 10%), both as white solids with 20% and 11% ee respectively as determined by chiral HPLC analysis. Absolute and relative stereochemistry was determined by X-Ray analysis of a single crystal of the major diastereomer grown by slow evaporation of benzene. See **X-Ray Crystallographic Data** for more details.

Phase transfer catalysis: Prepared according to General Procedure C at -55 °C using *tert*-butyl (3,3-dimethyl-1-tosylbutyl)carbamate (35.5 mg, 100 µmol), (3-nitropropyl)benzene (74.3 mg, 450 µmol) and *N*-benzylquininium chloride (5.4 mg, 12 µmol). Analysis of the crude ^{1}H NMR showed >20:1 dr with a 94% yield (^{1}H NMR). The reaction mixture was purified by column chromatography (5-10-20% diethyl ether in hexanes) to provide the product as a white solid (33 mg, 90% yield), which was determined to be >20:1 dr and >99% ee by chiral HPLC analysis.

Major diastereomer (*anti*): White solid, mp = 115-119 °C; $[\alpha]_D^{20}$ +20.4 (*c* 0.67, $CHCl_3$)[23]; Chiralpak AD-H, 5% ^{i}PrOH/hexanes, 1.0 mL/min, 30 °C: $t_r(e_1$, major) = 6.6 min, $t_r(e_2$, minor) = 7.4 min; R_f = 0.17 (10% Et_2O/hexanes); IR (film) 3344, 2956, 1703, 1548, 1366, 1167 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.21 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 4.55-4.51 (m, 2H), 4.06 (ddd, *J* = 13.8, 4.9, 4.9 Hz, 1H), 2.71 (dddd, *J* = 14.7, 9.7, 4.9, 4.9 Hz, 1H), 2.64-2.59 (m, 1H), 2.40-2.34 (m, 1H), 1.43 (s, 9H), 1.15 (dd, *J* = 14.8, 10.1 Hz, 1H), 0.97-0.93 (m, 1H), 0.91 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.0, 140.0, 128.8, 128.6, 126.6, 91.6, 80.3, 50.4, 43.5, 32.3, 31.9, 30.4, 29.7, 28.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{33}N_2O_4$ $[M+H]^+$ 365.2435, found 365.2423.

Minor diastereomer (*syn*): White solid, mp = 117-119 °C; $[\alpha]_D^{20}$ +8.7 (*c* 0.09, $CHCl_3$)[24]; Chiralpak IC, 10% ^{i}PrOH/hexanes, 1.0 mL/min, 25 °C: $t_r(e_1$, major) = 3.9 min, $t_r(e_2$, minor) = 4.4 min; R_f = 0.33 (10% Et_2O/hexanes); IR (film) 3449, 3355, 1957, 2867, 1714, 1554, 1504, 1366, 1168 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.22 (dd, = 7.4, 7.4 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 4.95 (d, *J* = 10.0 Hz, 1H), 4.44 (ddd, *J* = 8.9, 5.1, 3.9 Hz, 1H), 4.11 (tdd, *J* = 9.9, 3.5, 2.2 Hz, 1H), 2.74-2.63 (m, 2H), 2.37-2.31 (m, 1H), 2.16-2.10 (m, 1H), 1.45 (s, 9H), 1.39 (dd, *J* = 14.4, 2.1 Hz, 1H), 1.28 (dd, *J* = 14.8, 9.7 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.4, 139.8, 128.8, 128.7, 126.6, 91.3, 80.1, 48.7, 46.1, 32.5, 31.8, 30.5, 29.7, 28.5; HRMS (ESI): Exact mass calcd for $C_{20}H_{32}N_2NaO_4$ $[M+Na]^+$ 387.2254, found 387.2237.



***tert*-Butyl ((3*S*,4*R*)-3-fluoro-6,6-dimethyl-3-nitro-1-phenylheptan-4-yl)carbamate (6h).** This compound was prepared according to the General Procedure C at -35 °C using *tert*-butyl (3,3-dimethyl-1-tosylbutyl)carbamate (35.5 mg, 100 µmol), (3-fluoro-3-nitropropyl)benzene (82.4 mg, 450 µmol), and *N*-benzylquininium chloride (5.4 mg, 12 µmol). Analysis of the crude ^{19}F NMR showed 7.2:1 dr. The diastereomers were separated by column chromatography (5-10-20% diethyl ether in hexanes) to provide a combined 84% yield (31.9 mg). The major *syn* diastereomer was isolated as a white solid in >20:1 dr with 91% ee and the minor *anti* diastereomer was isolated in >20:1 dr with 76% ee as determined by chiral HPLC analysis. Absolute and relative stereochemistry was determined by X-Ray analysis of a single crystal of both the major and minor diastereomers. A single crystal of the major *syn* diastereomer was grown by slow evaporation of toluene at 0 °C. A single crystal of the minor *anti* diastereomer was grown by slow evaporation of benzene. See **X-Ray Crystallographic Data** for more details.

Major diastereomer (*syn*): White solid, mp = 91-93 °C; $[\alpha]_D^{20}$ +24.7 (*c* 0.92, $CHCl_3$); Chiralpak OD-H, 2% ^{i}PrOH/hexanes, 1.0 mL/min, 25 °C: $t_r(e_1$, major) = 3.6 min, $t_r(e_2$, minor) = 4.0 min; R_f = 0.53 (10% Et_2O/hexanes); IR (film) 3352, 2958, 2869, 1716, 1564, 1502, 1368, 1163 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29-7.27 (br m,

[23] Optical rotation measured on >99% ee material.
[24] Optical rotation measured on 11% ee material.

2H), 7.22-7.20 (br m, 1H), 7.15 (d, *J* = 7.2 Hz, 2H), 4.94 (d, *J* = 10.3 Hz, 1H), 4.35 (apparent dd, $^3J_{HH}$ = 10.2 Hz, $^3J_{HF}$ = 20.2 Hz, 1H), 2.95-2.90 (m, 1H), 2.59-2.46 (series of m, 3H), 1.59 (br d, *J* = 13.5 Hz, 1H), 1.44 (s, 9H), 1.07 (dd, *J* = 14.4, 10.2 Hz, 1H), 0.95 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) 155.1, 139.3, 128.8, 128.5, 126.7, 122.6 (d, $^1J_{CF}$ = 244.7 Hz), 80.7, 51.6 (d, $^2J_{CF}$ = 29.4 Hz), 42.7, 36.3 (d, $^2J_{CF}$ = 20.8 Hz), 29.5, 28.4, 28.4 (d, $^3J_{CF}$ = 3.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -131.3; HRMS (ESI): Exact mass calcd for $C_{20}H_{31}FN_2NaO_4$ $[M+Na]^+$ 405.2160, found 405.2160.

Minor diastereomer (*anti*): White solid, mp = 98-103 °C; $[\alpha]_D^{20}$ -25.9 (*c* 0.21, $CHCl_3$); Chiralpak AD-H, 3% EtOH/hexanes, 0.8 mL/min, 25 °C: t_r(*e*$_1$, major) = 5.2 min, t_r(*e*$_2$, minor) = 6.0 min. R_f = 0.33 (10% Et_2O/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (br dd, *J* = 7.3, 6.8 Hz, 2H), 7.21 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 2H), 4.58 (dddd, $^3J_{HF}$ = 24.5 Hz, $^3J_{HH}$ = 9.8, 9.8, 1.4 Hz, 1H), 4.45 (d, *J* = 9.6 Hz, 1H), 2.74 (ddd, *J* = 12.7, 12.7, 4.5 Hz, 1H), 2.68-2.58 (m, 1H), 2.52 (ddd, *J* = 12.6, 12.6, 4.5 Hz, 1H), 2.39-2.33 (m, 1H), 1.43 (s, 9H), 1.33-1.29 (m, 2H), 0.92 (s, 9H) ; ^{13}C NMR (150 MHz, $CDCl_3$) ppm 155.2, 139.3, 128.7, 128.4, 126.6, 123.4 ($^1J_{CF}$ = 246 Hz), 80.8, 52.6 ($^2J_{CF}$ = 22 Hz), 42.8, 35.7 ($^2J_{CF}$ = 21 Hz), 30.2, 29.5, 28.5, 28.3 ($^3J_{CF}$ = 4 Hz); ^{19}F NMR (376 Hz, $CDCl_3$) δ −140.1; HRMS (ESI): Exact mass calcd for $C_{20}H_{31}FN_2NaO_4$ $[M+Na]^+$ 405.2166, found 405.2158.

X-Ray Crystallographic Data

Details of crystallographic refinement for compounds *anti*-**6d**, *syn*-**6f**, *anti*-**6g**, *syn*-**6h**, and *anti*-**6h**.

General Methods. A suitable crystal of each sample was selected for analysis and mounted in a polyimide loop. All measurements were made on a Rigaku Oxford Diffraction Supernova Eos CCD with filtered Cu-Kα radiation at a temperature of 100 K. Using Olex2,[25] the structure was solved with the ShelXT structure solution program using Direct Methods and refined with the ShelXL refinement package[26] using Least Squares minimization.

Compound *anti*-**6d**
A disordered vinyl group was modeled over two positions without restraint. The absolute configuration was determined on the basis of the Flack parameter.

Compounds *syn*-**6f**, *anti*-**6g**, *syn*-**6h**, and *anti*-**6h**
Structures were refined without restraint. The absolute configuration was determined on the basis of the Flack parameter in each case.

[25] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339.
[26] Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112.

Table 1. Crystal data and structure refinement for *anti*-**6d**.

Identification code	**6d**
Empirical formula	$C_{17}H_{23}FN_2O_4$
Formula weight	338.37
Temperature	99.98(10) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 1 21 1
Unit cell dimensions	a = 10.32624(13) Å α = 90°
	b = 15.5828(2) Å β = 106.1130(14)°
	c = 11.74267(16) Å γ = 90°
Volume	1815.30(4) $Å^3$
Z	4
Density (calculated)	1.238 Mg/m^3
Absorption coefficient	0.794 mm^{-1}
F(000)	720
Crystal size	0.189 x 0.158 x 0.101 mm^3
Theta range for data collection	3.918 to 72.965°.
Index ranges	-9<=h<=12, -19<=k<=19, -14<=l<=14
Reflections collected	24691
Independent reflections	6879 [R(int) = 0.0290]
Completeness to theta = 67.684°	99.8 %
Absorption correction	Gaussian
Max. and min. transmission	1.000 and 0.811
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6879 / 1 / 458
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0273, wR2 = 0.0640
R indices (all data)	R1 = 0.0307, wR2 = 0.0687
Absolute structure parameter	0.02(5)
Largest diff. peak and hole	0.187 and -0.207 $e/Å^{-3}$

Table 2. Crystal data and structure refinement for *syn*-**6f**.

Identification code	**6f**	
Empirical formula	$C_{21}H_{24}ClFN_2O_4$	
Formula weight	422.87	
Temperature	100.01(10) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 12.8885(3) Å	α = 90°
	b = 5.3127(2) Å	β = 95.058(2)°
	c = 15.1705(4) Å	γ = 90°
Volume	1034.72(5) $Å^3$	
Z	2	
Density (calculated)	1.357 Mg/m^3	
Absorption coefficient	1.972 mm^{-1}	
F(000)	444	
Crystal size	0.249 x 0.034 x 0.017 mm^3	
Theta range for data collection	2.924 to 72.299°.	
Index ranges	-15<=h<=15, -5<=k<=6, -18<=l<=15	
Reflections collected	13856	
Independent reflections	3635 [R(int) = 0.0387]	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.000 and 0.731	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3635 / 1 / 265	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0361, wR2 = 0.0916	
R indices (all data)	R1 = 0.0372, wR2 = 0.0927	
Absolute structure parameter	-0.010(13)	
Largest diff. peak and hole	0.537 and -0.220 $e/Å^{-3}$	

Table 3. Crystal data and structure refinement for *syn*-**6h**.

Identification code	*syn*-**6h**
Empirical formula	$C_{20}H_{31}FN_2O_4$
Formula weight	382.47
Temperature	100.00(10) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 11.50004(6) Å α = 90°
	b = 18.45454(10) Å β = 90°
	c = 30.36728(18) Å γ = 90°
Volume	6444.79(6) Å^3
Z	12
Density (calculated)	1.183 Mg/m^3
Absorption coefficient	0.722 mm^{-1}
F(000)	2472
Crystal size	0.465 x 0.375 x 0.246 mm^3
Theta range for data collection	2.802 to 72.268°.
Index ranges	-14<=h<=13, -22<=k<=22, -27<=l<=37
Reflections collected	35099
Independent reflections	12498 [R(int) = 0.0245]
Completeness to theta = 67.684°	100.0 %
Absorption correction	Gaussian
Max. and min. transmission	1.000 and 0.340
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12498 / 0 / 748
Goodness-of-fit on F^2	1.046
Final R indices [I>2sigma(I)]	R1 = 0.0306, wR2 = 0.0764
R indices (all data)	R1 = 0.0315, wR2 = 0.0771
Absolute structure parameter	-0.01(3)
Largest diff. peak and hole	0.165 and -0.265 e/Å^{-3}

Table 4. Crystal data and structure refinement for *anti*-**6h**.

Identification code	*anti*-**6h**
Empirical formula	$C_{20}H_{31}FN_2O_4$
Formula weight	382.47
Temperature	100.01(10) K
Wavelength	1.54184 Å
Crystal system	Hexagonal
Space group	$P6_1$
Unit cell dimensions	a = 11.84190(10) Å α = 90°
	b = 11.84190(10) Å β = 90°
	c = 27.22040(10) Å γ = 120°
Volume	3305.73(6) Å^3
Z	6
Density (calculated)	1.153 Mg/m^3
Absorption coefficient	0.704 mm^{-1}
F(000)	1236
Crystal size	0.415 x 0.077 x 0.065 mm^3
Theta range for data collection	4.311 to 72.268°.
Index ranges	-14<=h<=14, -14<=k<=14, -33<=l<=33
Reflections collected	50607
Independent reflections	4353 [R(int) = 0.0349]
Completeness to theta = 67.684°	100.0 %
Absorption correction	Gaussian
Max. and min. transmission	1.000 and 0.580
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4353 / 1 / 250
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0232, wR2 = 0.0584
R indices (all data)	R1 = 0.0235, wR2 = 0.0586
Absolute structure parameter	0.04(3)
Largest diff. peak and hole	0.140 and -0.148 e/Å^{-3}

Table 5. Crystal data and structure refinement for *anti*-**6g.**

Identification code	**6g**
Empirical formula	$C_{20}H_{32}N_2O_4$
Formula weight	364.47
Temperature	100.01(10) K
Wavelength	1.54184 Å
Crystal system	Hexagonal
Space group	$P6_1$
Unit cell dimensions	a = 11.84105(5) Å α = 90°
	b = 11.84105(5) Å β = 90°
	c = 27.02804(15) Å γ = 120°
Volume	3281.90(3) $Å^3$
Z	6
Density (calculated)	1.106 Mg/m^3
Absorption coefficient	0.618 mm^{-1}
F(000)	1188
Crystal size	0.346 x 0.152 x 0.107 mm^3
Theta range for data collection	4.311 to 72.350°.
Index ranges	-14<=h<=14, -14<=k<=14, -31<=l<=33
Reflections collected	62164
Independent reflections	4242 [R(int) = 0.0423]
Completeness to theta = 67.684°	100.0 %
Absorption correction	Gaussian
Max. and min. transmission	1.000 and 0.474
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4242 / 1 / 241
Goodness-of-fit on F^2	1.083
Final R indices [I>2sigma(I)]	R1 = 0.0276, wR2 = 0.0742
R indices (all data)	R1 = 0.0278, wR2 = 0.0744
Absolute structure parameter	0.00(6)
Largest diff. peak and hole	0.160 and -0.140 $e/Å^{-3}$