Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.

Check for updates

Cite this: *Org. Biomol. Chem.*, 2018, **16**, 3151

The control of stereochemistry by the pentafluorosulfanyl group†

Paul R. Savoie, Cortney N. von Hahmann, Alexander Penger, Zheng Wei and John T. Welch *

Received 20th December 2017,
Accepted 3rd April 2018

DOI: 10.1039/c7ob03146g

rsc.li/obc

The influence of pentafluorosulfanylation on biological activity has been revealed in numerous comparative studies of biologically active compounds, but considerably less is known about the influence of pentafluorosulfanylation on reactivity. Among the distinctive properties of the pentafluorosulfanyl group is the profound dipole moment that results from introduction of this substituent. It has been shown that dipolar effects coupled with the steric demand of the SF_5 group may be employed to influence the stereochemistry of reactions, especially those processes with significant charge separation in the transition state. The Staudinger ketene-imine cycloaddition reaction is an ideal platform for investigation of dipolar control of diastereoselectivity by the pentafluorosulfanyl group.

Introduction

Numerous pentafluorosulfanyl(SF_5)-containing organic compounds[1–10] have been prepared that have potential utility in drug discovery, agrochemical synthesis and materials science. The surge of interest in this area is a consequence of the increasing availability of building blocks, or reagents, that were previously very difficult to access.[7] Much of what is known about the effect of pentafluorosulfanylation is derived from comparative studies of biologically active trifluoromethylated compounds, where the trifluoromethyl (CF_3) group was replaced by an SF_5 group.[11–17] Reports of the physical chemical influences of pentafluorosulfanylation on aliphatic systems are especially fragmented and tentative.

Conformational control

The SF_5 group has been variously described as a "super" CF_3 group[18] or a *tert*-butyl isostere.[19] The volume of the SF_5 group (55.4 Å^3) is less than that of a *tert*-butyl group (76.9 Å^3),[1,20] but greater than that of a CF_3 group (34.6 Å^3). The octahedral geometry around sulfur results in a dramatic reduction of the barrier to rotation of a carbon–SF_5 bond relative to carbon–carbon bonds. The longer carbon–sulfur and sulfur–fluorine bonds have other surprising conformational effects as a consequence of the octahedral geometry around sulfur. On incorporation into a hydrocarbon chain, the restricted rotation about the carbon–sulfur bond that results from interactions with nearby methylene groups, can lead to localized conformational rigidity of the alkyl chain.[21,22]

Pentafluorosulfanyl substituents adjacent to hydroxyl groups also influence conformation. The constraint of the S–C–C–OH dihedral angle to ±85° by the SF_5 group[22] cannot be rationalized by the stereoelectronic influences[23] shown to constrain the dihedral $C_{(CF3)}$–C–C–OH angle in the analogous trifluoromethylated molecules. Stereoelectronic control of conformation by the SF_5 group involves very different orbital interactions, a consequence of the hypervalent sulfur of the SF_5 group.[22]

Electronic effects

The magnitude of the electron withdrawing effects of SF_5 (electronegativity, 3.65)[24] and CF_3 (electronegativity, 3.36)[24] are similar.[25,26] When Hammett σ_p values are compared, the value of SF_5 (0.68) is greater than that of CF_3 (0.54).[27] The greater σ_I value of SF_5 (0.55) relative to the value for CF_3 (0.39) is indicative of a greater bond polarization, and is consistent with the electronic effects observed in the estimation of electronegativity.[25,26] In contrast, σ_R values of 0.11 for SF_5 [27] and 0.12 for CF_3 [28,29] indicate comparable resonance contributions from both functional groups to the respective σ_p values.

Dipolar effects of the SF_5 group on reactivity

The profound dipole of the hydrolytically and chemically stable[7,30–33] SF_5 group may be used to influence the stereo-

Department of Chemistry, University at Albany, SUNY, 1400 Washington Ave., Albany, NY 12222, USA. E-mail: jwelch@albany.edu

†Electronic supplementary information (ESI) available. CCDC 1552163. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob03146g

Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.

selectivity of reactions, especially those processes where there is significant charge separation in the transition state. The computationally determined dipole moment of pentafluorosulfanylmethane (2.78 D) (B3LYP/6-31G**) is significantly greater than that of 1,1,1-trifluoroethane (2.06 D) (B3LYP/6-31G**) and nearly as large as that of nitromethane (3.48 D) (B3LYP/6-31G**).

Steric demand, torsional strain, and electronic effects are well known to influence stereoselectivity.[34,35] The staggered transition state of the Felkin–Anh model[36–38] for carbonyl additions (Fig. 1, structures **A** and **B**) can be supplanted by a modified Cornforth rationale (Fig. 1, structures **C** and **D**),[39] when a significant dipole is induced by a substituent.[40–42] The Cornforth model is characterized by the antiperiplanar conformational preference of the dipole-inducing functional group (Fig. 1).

TS **B** and **C** both are consistent with formation of the *ul* product, with **C** having the most accessibility to the *Re* face of the aldehyde. The Cornforth model hence affords a rationale for the very diastereoselective addition of even non-sterically demanding nucleophiles to SF_5-containing aldehydes as shown in Fig. 2.[43]

Enolate selectivity

Benzyl,[44,45] methyl[46] and octyl[44] esters of pentafluorosulfanyl acetic acid have been employed in directed aldol condensations. The selective addition of boryl enolates of the benzyl and octyl esters to carbonyl groups formed *anti*-aldol products.[44,45] The specificity was the consequence of (*Z*)-enolate formation (n.b., the stereochemistry of the enolate is a result of the pentafluorosulfanyl group being (*Z*) to the higher priority of carbon of the benzyloxy group relative to boron of the enolate). Selective enolization apparently is a result of simple steric interactions.

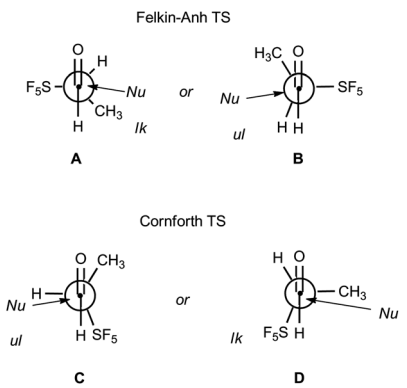


Fig. 1 Predicted influence of SF_5 group on additions to an aldehyde according to the Felkin–Anh TS (top row; **A**, (*lk*-attack) favored); or the Cornforth TS (bottom row; **C**, (*ul*-attack) favored).

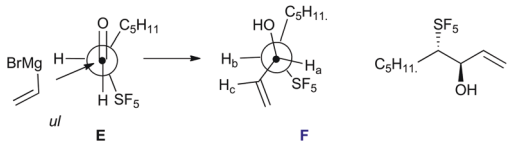


Fig. 2 The diastereoselectivity of Grignard addition to an α-SF_5-aldehyde is consistent with the Cornforth TS model (ref. 45).

Stereoselectivity in pericyclic reactions

[3,3]-Sigmatropic rearrangements

The SF_5 group may control the stereochemistry of sigmatropic rearrangements by electronic or steric effects. Analogously, 7 : 1 *ul* to *lk* diastereoselectivity[47] was found in a [3,3]-sigmatropic rearrangement of an allylic trifluoromethyl ester.[48] In that stereoelectronically driven example, cyclization occurred opposite to the more electron-rich face of the double bond as would be predicted by Cieplak analysis.[49] Enol silyl ketene acetals prepared from the cinnamyl α-CF_3- and α-SF_5-acetates failed to demonstrate diastereoselectivity[50] in the Ireland–Claisen rearrangement as a consequence of SF_5-induced steric effects. However, [3,3]-sigmatropic rearrangement of SF_5-acetates of aliphatic allylic esters proceed diastereoselectively due to the differential reactivity of the intermediate (*E*/*Z*) silyl ketene acetals.[51] The potential diastereoselectivity of the rearrangement was degraded by the steric-induced accessibility of both chair- and boat-like transition states.

[2 + 2]-Cycloaddition reactions

The highly diastereoselective formation of SF_5-containing β-lactams has been previously reported.[52] A SF_5 group at a stereogenic center of the aldimine induced formation of the *u*,*l*-β-lactam ***rac*-1** very selectively by *lk*,*lk*-1,2 (*Si*,*Si-S* or *Re*,*Re-R*) cyclization, albeit in only modest yield (Fig. 3).[52] A more thorough investigation of the effect of pentafluorosulfanylation is necessary to assess the generality of dipolar stereocontrol by pentafluorosulfanylation. To that end a mechanistic study of the ketene-pentafluorosulfanylaldimine cycloaddition reaction was required.

Results and discussion

The influence of the *N*-alkyl substituent on pentafluorosulfanyl aldimine reactivity

The pronounced electron withdrawing effect of pentafluorosulfanylation on the acidity of an adjacent proton may adversely affect pentafluorosulfanyl aldimine formation. Even though the ketene-imine cycloaddition process is very well studied,[53–62] systematic comparative studies of the influence of

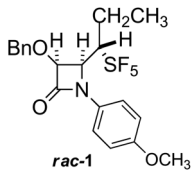


Fig. 3 Stereogenic SF_5-substituted carbon directed *u*,*l*-β-lactam ***rac*-1** by *lk*,*lk*-1,2 cyclization (ref. 52).

 This journal is © The Royal Society of Chemistry 2018

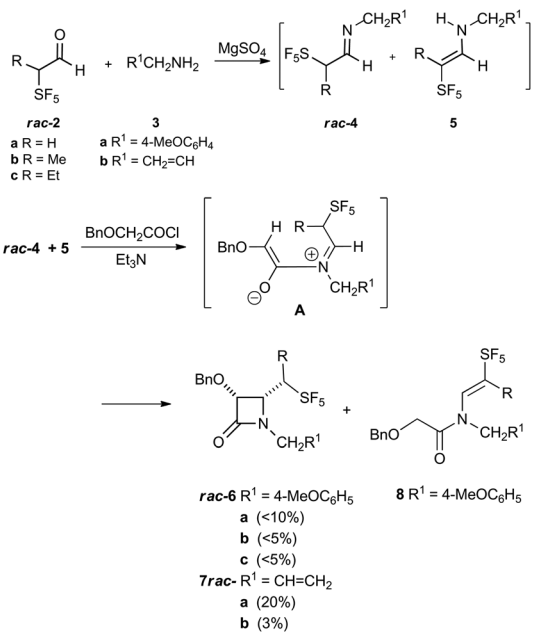
Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.

simple *N*-protection are far less abundant.[62] Our hypothesis was that the 4-methoxybenzyl (PMB) group of pentafluorosulfanyl aldimine ***rac*-4** (R^1 = 4-$MeOC_6H_5$ in Scheme 1) could render the imine nitrogen of ***rac*-4** more basic, stabilizing the intermediate iminium ion of **A**. However, the amine should not be so basic as to promote formation of enamine **5** or acyl enamine **8**. Precedence for the formation of pentafluorosulfanyl enamine **5** can be found in comparison with the published reactivity of the trifluoromethylated aldimine, *N*-ethyl 3,3,3-trifluoro-propanaldimine.[63]

Replacement of the *para*-methoxyphenyl (PMP) protecting group[52] previously employed in the synthesis of ***rac*-1** by the PMB group resulted in a modest reduction in the already limited β-lactam yield. Whereas introduction of an allyl moiety had a very modest effect on increasing the overall yield of ***rac*-7** from the published values for PMP protected imines.[52] By ^{19}F NMR, there was no detectable reduction in the 3,4-diastereoselectivity (see Fig. 4) or the influence of the asymmetric SF_5-bearing carbon on diastereoselectivity during formation of reaction product ***rac*-7** relative that previously observed with the PMP protected β-lactams.[52]

Azidoketene in the Staudinger reaction

Consideration of the charge distribution (Fig. 5), geometry, and reactivity of azidoketene[64] suggested that azidoketene may increase the rate of ring closure in the ketene-imine addition reaction[65,66] relative to the rate of SF_5-facilitated acyl enamine formation. From computational studies at the MP4 level of theory,[67] the C–C–N–N torsional angle of 120° of azidoketene, a consequence of the repulsive interactions of the N-lone pair



Scheme 1 Staudinger reaction of benzyloxyketene and pentafluorosulfanyl aldimines ot form *l,l*-β-lactams ***rac*-6** and ***rac*-7**. Trace amounts of enamine **8** were detected spectroscopically in the reaction mixture but were not quantitatively characterized.

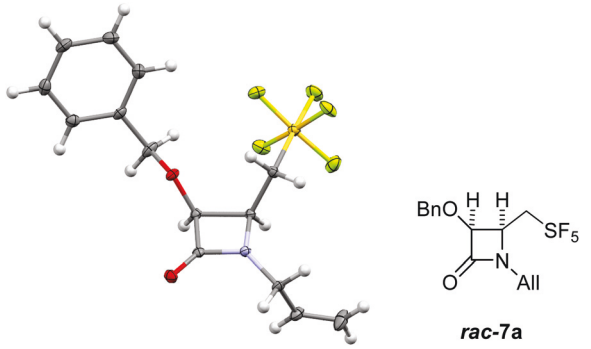


Fig. 4 The 3,4-*lk* stereochemistry of ***rac*-7a** as determined by single crystal X-ray diffraction. Thermal ellipsoids are set at 50% probability.

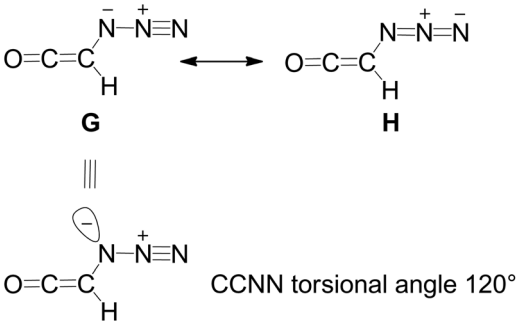


Fig. 5 Azidoketene resonance forms and geometry.

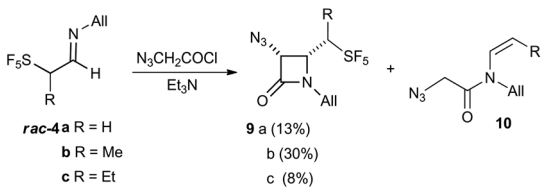
with the adjacent π-system, may increase the propensity of the intermediate zwitterionic adduct **I** (Scheme 3) to rapidly cyclize.

The reactions of **4a–c** (Scheme 2) with azidoketene retained the characteristic stereoselectivity of pentafluorosulfanyl aldimines, and formed **9** somewhat more efficiently albeit still in modest overall yield.

Due to the susceptibility of **4** to hydrolysis, the reactive imines were used in the cycloaddition reaction without purification. Unfortunately unreacted amine **3** or enamine **5** quickly consume the azidoketene or the acid chloride precursor in side reactions, reducing the formation of **9** and forming complex side products.

Stereochemistry of β-lactam formation

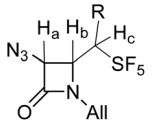
Previously, the Staudinger reaction was shown to proceed through the *E*-imine.[52] In this work, the *lk* ring closure



Scheme 2 Staudinger reaction of azidoketene and pentafluorosulfanyl aldimines. Enamine **10** was not isolated and was only tentatively identified spectroscopically.

Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.

product of conrotatory ring closure was confirmed for **6c** by single crystal X-ray diffraction studies (see ESI, Fig S1†). The *lk* ring closure that formed **9** was established by interpretation of the ^{1}H coupling constants utilizing the Haasnoot equation[68–70] that employs electronegativity data in concert with spectroscopic results (see ESI,† p. S6–S11).



9

a R = H_d
b R = Me
c R = Et

For **9a–c**, the coupling constants $J_{a,b}$ = 4.6 Hz, 4.9 Hz, and 4.8 Hz, respectively, correspond to H_a–C–C–H_b dihedral angles of 19–21°, angles that can only be consistent with *lk* ring closures. These values were in addition consistent with those found for **7a** and **7b**, 4.9 Hz and 4.7 Hz respectively. In addition there was excellent agreement with the coupling constants determined in our previous work, 4.7–4.9 Hz.[52] Validation of the stereochemical assignment was possible in the case of **9a** where R = H_d. From the $J_{b,c}$ and $J_{b,d}$ values, a model for **9** could be constructed that had an S–C–C–N dihedral angle (θ SCCN) of +165°, a dihedral angle consistent with that determined from SF_5-substituted β-lactam crystal structures.[52]

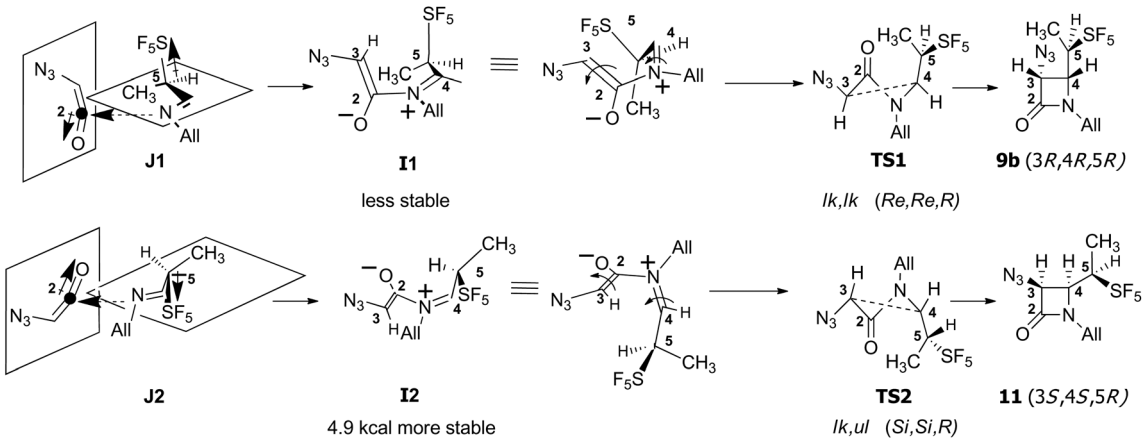
Control of ring closure stereochemistry by the SF_5 group

Diastereomeric excess. The reactive aldimines **4b** or **4c** would be predicted to react equally by the *lk*,*lk* or *lk*,*ul* reaction topicity,[47] however the stereogenic SF_5-bearing carbon profoundly affected the ring closure.[52] The descriptor 1,2-*lk*,*lk* describes the ring closure step of the ketene-imine addition process (see **I1** or **I2**, Scheme 3) where the *Re*-face of the ketene reacts with the *Re*-face of the imine and the stereochemistry of pentafluorosulfanylated imine is (*R*) as possible with **4b** or **4c**. Similarly when the imine **4** has the (*S*) configuration and the *Si*-faces of the ketene and the imine react, the reaction topicity could be described as 1,2-*lk*,*lk*. When the *Si* face of the (*R*)-imine **4** reacts with the *Si* face of ketene the reaction topicity can be described as 1,2-*lk*,*ul*. As described below, the 3,4-stereochemistry of the β-lactam, products **7** and **9** reported in this work and the earlier described β-lactams[52] requires *Re*,*Re* or *Si*,*Si* ring closure. The influence of the asymmetry of pentafluorosulfanylated carbon will be discussed subsequently (Scheme 3).

Required conrotatory ring closure for control of 3,4-stereochemistry. The zwitterionic intermediates **I1** or **I2** formed by reaction at the *Re* and *Si* faces, respectively, of azidoketene, can undergo conrotatory ring closure to form the β-lactam ring by either counterclockwise or clockwise rotation. The direction of rotation for closure is dependent upon the conformation of **I1** or **I2**, and thus the geometry of approach to the ketene (Scheme 3). Diastereoselective *lk* ring closure[47] occurs on the bonding of the two reactive carbons (C3 and C4) of intermediate **I** by rotation through the smaller of the two possible dihedral angles.[59]

In Fig. 6, the ^{19}F NMR spectra of **9b** prior to workup is consistent with the formation of a significant excess of a single diastereomeric *l*,*l* pair[47] in a very diastereofacially selective reaction. The principal pair of ^{19}F resonances was favored by more than 20 : 1 over those of the minor *l*,*u* diastereomers. The *l*,*l* pair would correspond to the products shown in Fig. 6 when R = Me. The minor *l*,*u* pair would be derived from the product where *Re*,*Re*-product is formed from (*S*)-**4b** and the *Si*,*Si*-product is formed from (*R*)-**4b**.

The role of the pentafluorosulfanylated stereogenic center on diastereoselectivity. Racemic **4b** was found to form only a single racemic diastereomer **9b** by ^{19}F NMR. The addition of azidoketene to a single enantiomer, (*R*)-**4b** in dichloromethane was modelled at the (SM8)M06-2X/6-31+G(d,p) level of theory (Fig. 7). Consistent with the recognized stepwise mechanism



Scheme 3 Effect of intermediate conformation on reaction topicity. For simplicity only the reactivity of (*R*)-**4b** is shown however the reaction will follow a similar path for (*S*)-**4b**. From Fig. 3 it is apparent that only a single pair of diastereomers of **9b** is favored. In all cases the *Re*,*Re* or *Si*,*Si* ring closure step is consistent with conrotatory ring closure[59] and our single crystal X-ray diffraction studies.[52]

 This journal is © The Royal Society of Chemistry 2018

Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.

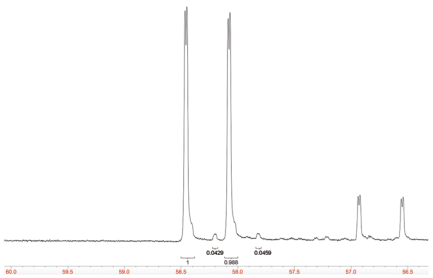


Fig. 6 Approximately 20 : 1 diastereoselectivity for a single pair of β-lactam ***rac*-9b** *l,l*-diastereomers. The fluorine NMR spectrum of the reaction mixture prior to workup. The resonances near δ 58 ppm are from the equatorial fluorines of the SF_5-bearing β-lactams. Integration of the pentets from the axial fluorine resonances (*ca.* δ 85 ppm) of the SF_5-group is confounded by both the diminished intensity and complex coupling.

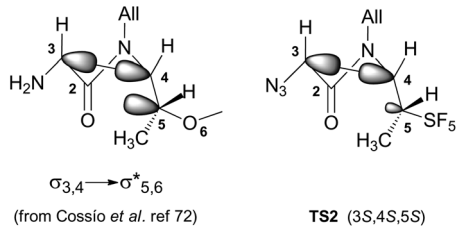


Fig. 8 A comparison of the stereoelectronic interactions from the published example of Cossío (ref. 72) and a comparable model related to **TS2** with (*S*) stereochemistry for the pentafluorosulfanylated carbon analogous to the published example.

of the process,[71–73] energies for the intermediate zwitterions **I1** and **I2** as well as those of the rate determining transition states **TS1** and **TS2** have been computed.

Irrespective of the *endo* or *exo* reaction[71] of azidoketene (see Scheme 3) with (*R*)-**4b**, the energy barrier to formation of transition states **J1** or **J2** was negligible, with less than a 1 kcal energy difference between the two states.[74] The apparent absence of a barrier to reaction is consistent with reaction of a highly reactive ketene and an electron deficient imine. Torquoelectronic or torquoselective control[75] of the diastereoselectivity of the ring closure process of the Staudinger reaction has been widely invoked[72–74]

The stable conformations computed for intermediates **I1** and **I2** (Scheme 3) are very similar to the transition state structures reported by Cossío.[72] Torquoselectivity resulted from steric encumbrance by an inward turned methyl group (similar to the conformation found for **I1**) that disrupted stabilizing stereoelectronic interactions (Fig. 8).

The stabilizing effects minimized repulsive filled–filled orbital interactions between a donor orbital and the σ orbital of the partially formed σ-bond that closes the β-lactam ring.[72] In Cossío's system the ~5 kcal lower energy transition state occurred when stabilizing interactions between the newly formed bond and the σ* orbital of the C–O σ-bond were possible. In the ring closure of **I1** or **I2** such electronic effects are not likely to be as influential as carbon–sulfur NBO analysis confirms C–S bond interactions with adjacent σ bonds are significantly less effective than the C–O interactions of the Cossío example.[76]

The concept of torquoselectivity can be extended to the reactions of **4b** in the ketene-imine cycloaddition process, if the "inward" methyl group of **I1** is recognized to destabilize the intermediate effectively reducing the barrier to ring closure. The antiperiplanar alignment of the C2–O bond and C5–SF_5 bonds in either intermediate zwitterions **I1** and **I2** (Scheme 3) is consistent with the profound dipolar influence

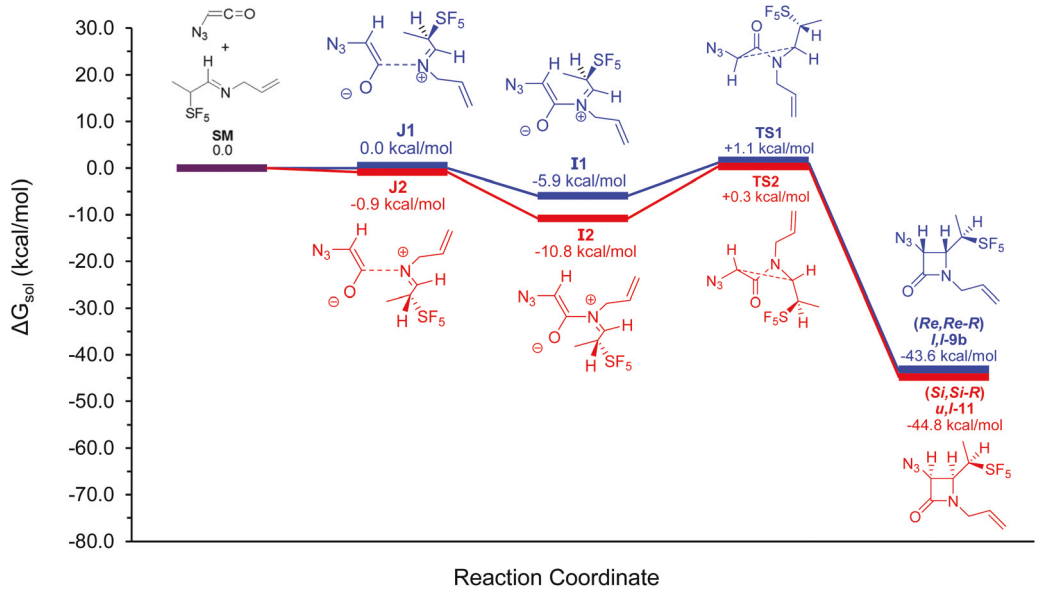
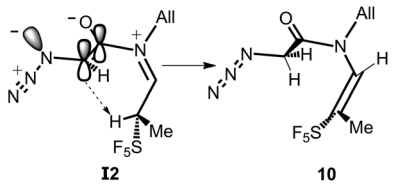


Fig. 7 Computed reaction profile for the [2 + 2] cycloaddition reaction of (*R*)-**4b** with azidoketene in dichloromethane at the (SM8)M06-2X/6-31+G(d,p) level of theory.

Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.



I2 10

Scheme 4 Intramolecular proton transfer to form **10** from **I2**.

of the SF_5 group. The greater congestion of **I1** that results from the aforementioned inward turned methyl group is reflected by the 4.9 kcal mol^{-1} greater stability of **I2** relative to **I1** (Fig. 7). Even though the **TS1** and **TS2** energies differ by only 800 cal, the barrier to the cyclization of **I1** is 7.0 kcal mol^{-1} while the barrier for **I2** to cyclize is 11.1 kcal mol^{-1} (see Fig. 6, **TS1** and **TS2**).

It is hypothesized that competing with the slower cyclization of the more stable **I2** is formation of the enamine **10** by intramolecular proton transfer. The conformation of **I2** places the reactive nucleophilic carbon in relatively close proximity to the acidic α-proton attached to the pentafluorosulfanylated carbon (Scheme 4). The depletion of **I2** would result in a further reduction in the yield of *l*,*u*-**11**.

Experimental

General methods

All reactions were carried out under an argon atmosphere. Reagents were purchased from commercial sources and used without further purification. All solvents were purified by standard methods and freshly distilled under argon. A Bruker 400 MHz spectrometer was used to record the ^{1}H (400 MHz), ^{13}C (100 MHz), and ^{19}F (376 MHz) spectra for all prepared compounds. All chemical shifts are reported relative to the residual signal of $CDCl_3$ (^{1}H, δ = 7.24; ^{13}C, δ = 77.00) or C_6D_6 (^{1}H, δ = 7.15; ^{13}C, δ = 128.00). All ^{13}C NMR spectra were acquired in proton-decoupled mode. Chemical shifts in ^{19}F NMR spectra are reported relative to the resonance assigned to $CFCl_3$ (δ = 0.0). Thin layer chromatography was performed with silica gel F_{254} adsorbent on 0.2 mm thick plastic-backed plates. The chromatograms were visualized under ultraviolet light at 254 nm, followed by staining with an aqueous solution of $KMnO_4$ followed by heating. Flash column chromatography was performed by the method of Still[77] using 70–230 mesh silica gel 60. High-resolution mass spectra were acquired using a JEOL Accu-TOF DART mass spectrometer in negative ion mode.

Reaction profile calculations for the Staudinger reaction of azidoketene and (*R*)-**4e** were performed at the M06-2X/6-31+G (d,p) level of theory using Q-Chem version 4.32. All calculations included solvent effects using the SM8 solvent model and parameters for dichloromethane. All optimized structures were verified by vibrational frequency analyses at the same level of theory to ensure the optimized structures were either minima (with no negative vibrational frequencies), or in the case of transition states, maxima (with one negative vibrational frequency).

Preparation of 2-pentafluorosulfanyl aldimines

To a 25 mL round-bottom flask with a male 14/20 joint equipped with a magnetic stirring bar was added approximately 0.6 g of magnesium sulfate. The flask, Schlenk filter, and 25 mL two-neck round bottom flask equipped with a second magnetic stirring bar were dried in an oven at 150 °C for 2 hours and then allowed to cool to room temperature in a desiccator. Once cooled, the aldehyde (*ca.* 1.0 mmol) was added as a dichloromethane solution followed by allylamine (2 mL, 0.5 M, 1.0 mmol) in dichloromethane. The reaction mixture was stirred at room temperature for about 6 hours, after which time another 2 mL aliquot of allylamine in dichloromethane was added to the mixture. The mixture was then stirred overnight at room temperature to afford a dichloromethane solution containing the imine.

***N*-(2-Pentafluorosulfanylethylidene)-3-aminoprop-1-ene (*rac*-4a).** Orange-colored solution; 82% conversion by ^{19}F NMR. ^{19}F NMR ($CDCl_3$) δ 82.0 (qn; J = 146.5 Hz; 1F), 69.1 (dt; J = 146.5 Hz, 7.7 Hz; 4F).

***N*-(2-Pentafluorosulfanylpropylidene)-3-aminoprop-1-ene (*rac*-4b) and *N*-(2-pentafluorosulfanylprop-1-enyl)-3-aminoprop-1-ene (5b).** Orange-colored solution; 70% conversion to imine ***rac*-4b** and 19% conversion to enamine **5b** by ^{19}F NMR. ^{19}F NMR (CDCl3) δ 93.7 (qn; J = 148.8 Hz; 1F; **5b**), 83.7 (qn; J = 143.3 Hz; 1F; **4b**), 65.5 (d; J = 148.8 Hz; 4F; **5b**), 58.8 (dd; J = 143.4 Hz, 4.4 Hz; 4F; **4b**).

***N*-(2-Pentafluorosulfanylbutylidene)-3-aminoprop-1-ene (*rac*-4c) and *N*-(2-pentafluorosulfanylbut-1-enyl)-3-aminoprop-1-ene (5c).** Orange-colored solution; 91% conversion to imine **4c** and 9% conversion to enamine **5c** by ^{19}F NMR. ^{19}F NMR ($CDCl_3$) δ 94.6 (qn; J = 148.8 Hz; 1F; **5c**), 84.2 (qn; J = 143.4 Hz; 1F; **4c**), 66.8 (d; J = 148.2 Hz; 4F; **5c**), 59.9 (dd; J = 143.2 Hz, 5.9 Hz; 4F; **4c**).

Preparation of pentafluorosulfanylated 3-benzyloxy β-lactams

On completion of the imine synthesis, the reaction mixture was added to a valved Schlenk filter that was connected to empty two-neck round bottom flask cooled to −78 °C. Triethylamine (1 g, 10 mmol) dissolved in 2 mL of dichloromethane was added to the warm round bottom flask under argon. After cooling to 0 °C, benzyloxyacetyl chloride (1.9 g, 10 mmol) was added dropwise to the amine solution, the imine was transferred dropwise by direct filtration into the reaction. After two days, a saturated $NaHCO_3$ solution was added. Extraction with dichloromethane was followed by washing with water. The dried solution ($MgSO_4$) was filtered then silica gel (1 g) was added and slurry concentrated *in vacuo*. Purification by silica gel (60 g) chromatography with 20% ethyl acetate and 80% hexanes yielded the purified products.

(3*RS*,4*RS*)-3-(Benzyloxy)-4-(1-pentafluorosulfanylmethyl)-1-(prop-2-enyl)azetidin-2-one (*rac*-7a). The product was visible under both UV light and potassium permanganate with an R_f value of 0.2; 0.058 g, 20% yield. ^{1}H-NMR ($CDCl_3$) δ 7.41–7.30

 This journal is © The Royal Society of Chemistry 2018

Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.

(m, 5H), 5.73 (dddd, 1H, $^3J_{trans}$ = 16.0 Hz, $^3J_{cis}$ = 10.5 Hz, ^3J = 6.7 Hz, ^3J = 5.7 Hz), 5.25 (dm, ^3J = 10.5 Hz), 5.24 (dm, ^3J = 16.0 Hz), 4.82 (AB, 2H, ^2J = 11.7 Hz), 4.78 (d, 1H, ^3J = 4.9 Hz), 4.37–4.32 (m, 1H), 4.14–4.04 (m, 1H), 4.09–4.02 (m, 1H), 3.81 (dpd, 1H, $^2J_{(H-H)}$ = 14.0 Hz, $^3J_{(H-H)}$ = 5.7 Hz, $^3J_{(H-F)}$ = 8.4 Hz, Hα), 3.68 (dd, 1H, $^2J_{(H-H)}$ = 15.7 Hz, $^3J_{(H-H)}$ = 6.8 Hz). ^{13}C-NMR ($CDCl_3$) δ 166.9, 136.4, 131.0, 128.6, 128.3, 128.0, 119.4, 81.8, 73.4, 69.0 (p, $^2J_{(C-F)}$ = 13.0–13.2 Hz), 54.5 (p, $^3J_{(C-F)}$ = 4.8–5.0 Hz), 43.0. ^{19}F-NMR ($CDCl_3$) δ 83.3 (9 signals, 1F), 67.0 (dt, 4F, $^2J_{(F-F)}$ = 146.1 Hz, $^3J_{(F-H)}$ = 8.2 Hz). HRMS (ESI, positive) *m*/*z*: $[M]^+$ calcd for $C_{14}H_{16}F_5NO_2S$ 357.0822; found 357.0808.

(3*RS*,4*RS*)-3-(Benzyloxy)-4-[(1′*RS*)-1-pentafluorosulfanyl-ethyl]-1-(prop-2-enyl)azetidin-2-one (*rac*-7b). 0.01 g, 3% yield. ^{1}H-NMR ($CDCl_3$) δ 7.40–7.29 (m, 5H), 5.73 (dddd, 1H, $^3J_{trans}$ = 16.8 Hz, $^3J_{cis}$ = 10.4 Hz, ^3J = 7.2 Hz, ^3J = 5.7 Hz), 5.26 (dm, ^3J = 10.5 Hz), 5.25 (dm, ^3J = 16.8 Hz), 4.83 (AB, 2H, ^2J = 11.7 Hz), 4.77 (d, 1H, ^3J = 4.7 Hz), 4.31–4.27 (m, 1H), 4.28–4.20 (m, 1H), 4.14 (dd, 1H, ^2J = 15.4 Hz, ^3J = 5.7 Hz), 3.60 (dd, 1H, ^2J = 15.4 Hz, ^3J = 7.2 Hz), 1.66 (d, 3H, ^3J = 6.8 Hz). ^{13}C-NMR ($CDCl_3$) δ 167.7, 136.7, 130.7, 128.5, 128.1, 127.9, 119.9, 82.8, 81.0 (p, $^2J_{(C-F)}$ = 10.0 Hz), 73.6, 58.2 (p, $^3J_{(C-F)}$ = 4.4 Hz), 43.1 (s), 13.9 (p, $^3J_{(C-F)}$ = 3.8–4.3 Hz). ^{19}F-NMR ($CDCl_3$) δ 84.8 (9 signals, 1F), 57.8 (dd, 4F, $^2J_{(F-F)}$ = 143.4 Hz, $^3J_{(F-H)}$ = 6.0 Hz). HRMS (ESI, positive) *m*/*z*: $[M]^+$ calcd for $C_{15}H_{18}F_5NO_2S$ 371.0978; found 371.0978.

Preparation of pentafluorosulfanylated 3-azido-β-lactams

A solution of azidoacetyl chloride (*ca.* 0.72 g, 6 mmol, 5 eq.) in dichloromethane (5 mL) was introduced to the round-bottom flask containing apparatus described above followed by a solution of triethylamine (*ca.* 0.61 g, 6 mmol, 5 eq.). On completion of triethylamine addition, the resultant mixture was allowed to stir 5 minutes at −78 °C at which time the filtered imine solution was directly introduced to the round bottom flask. The reaction mixture was then allowed to warm to room temperature with stirring overnight.

The reaction was quenched with 10 mL saturated sodium bicarbonate solution, and the organic phase was separated from the aqueous phase. The aqueous phase was extracted with three 10 mL portions of dichloromethane. The organic fractions were combined and then washed with brine (3 × 10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to afford the crude product. Purification of the product was accomplished by flash column chromatography using silica gel and 12 : 6 : 1 dichloromethane/hexane/ethyl acetate as the eluent.

(3*RS*,4*RS*)-3-Azido-4-(pentafluorosulfanylmethyl)-1-(prop-2-enyl) azetidin-2-one (*rac*-9a). Yellow oil; 0.039 g, 13% yield. ^{1}H NMR ($CDCl_3$) δ 5.76 (dddd; *J* = 17.0 Hz, 10.2 Hz, 6.8 Hz, 5.8 Hz; 1H), 5.34–5.27 (m; 2H), 4.93 (d; *J* = 4.8 Hz; 1H), 4.43 (dt; *J* = 7.7 Hz, 4.7 Hz), 4.13–4.00 (m; 2H), 3.90–3.78 (m; 1H), 3.72 (ddt; *J* = 15.7 Hz, 6.7 Hz, 1.3 Hz; 1H). ^{13}C NMR ($CDCl_3$) δ 163.4, 130.5, 119.7 (t; *J* = 3.2 Hz), 67.9 (qn; *J* = 13.5 Hz), 67.0, 53.9 (qn; *J* = 5.3 Hz), 43.4. ^{19}F NMR ($CDCl_3$) δ 82.9 (qn; *J* = 146.7 Hz; 1F), 67.5 (dtd; *J* = 146.7 Hz, 8.0 Hz, 1.2 Hz; 4F). IR (film) 2114 (m), 1767 (str), 820 (str) cm^{-1}. HRMS (DART, negative) *m*/*z*: $[M - H]^-$ calcd for $C_7H_8F_5N_4OS$ 291.0339; found, 291.0333.

(3*RS*,4*RS*)-3-Azido-4-[(1′*RS*)-1-(pentafluorosulfanylethyl]-1-(prop-2-enyl))azetidin-2-one (*rac*-9b). Yellow oil; 0.093 g, 30% yield. ^{1}H NMR ($CDCl_3$) δ 5.76 (dddd; *J* = 17.1 Hz, 10.1 Hz, 7.2 Hz, 5.8 Hz; 1H), 5.34–5.28 (m; 2H), 4.91 (d; *J* = 4.9 Hz; 1H), 4.41 (t; *J* = 5.0 Hz; 1H), 4.22 (m; 1H), 4.13 (ddt; *J* = 15.4 Hz, 5.8 Hz, 1.4 Hz; 1H), 3.60 (ddt; *J* = 15.3 Hz, 7.2 Hz, 1.0 Hz; 1H), 1.70 (dt; *J* = 7.2 Hz, 1.8 Hz; 3H). ^{13}C NMR ($CDCl_3$) δ 163.9, 130.1, 120.6, 80.2 (t; *J* = 10.2 Hz), 67.5, 57.3 (qn; *J* = 4.8 Hz), 43.7, 13.2 (qn; *J* = 4.0 Hz). ^{19}F NMR ($CDCl_3$) δ 84.6 (qn; *J* = 143.3 Hz; 1F), 58.4 (dd; *J* = 143.3 Hz, 6.3 Hz; 4F). IR (film) 2118 (m), 1766 (m), 819 (str) cm^{-1}. HRMS (DART, negative) *m*/*z*: $[M - Allyl]^-$ calcd for $C_5H_6F_5N_4OS$ 265.0182; found, 265.0184.

(3*RS*,4*RS*)-3-Azido-4-[(1′*RS*)-1-(pentafluorosulfanylpropyl]-1-(prop-2-enyl))azetidin-2-one (*rac*-9c). Yellow oil; 0.027 g, 8% yield. ^{1}H NMR ($CDCl_3$) δ 5.76 (ddt; *J* = 16.8 Hz, 10.2 Hz, 6.6 Hz; 1H), 5.35–5.29 (m; 2H), 4.89 (d; *J* = 4.8 Hz; 1H), 4.46 (t; *J* = 4.8 Hz; 1H), 4.06 (dd; *J* = 15.4 Hz, 6.1 Hz; 2H), 3.64 (dd; *J* = 15.3 Hz, 7.1 Hz; 1H), 2.49–2.37 (m; 1H), 1.98–1.87 (m; 1H), 1.18 (t; *J* = 7.3 Hz; 3H). ^{13}C NMR ($CDCl_3$) δ 163.9, 130.2, 120.6, 87.5 (qn; *J* = 7.7 Hz), 67.5, 57.9 (qn; *J* = 5.4 Hz), 43.9, 21.0 (t; *J* = 3.1 Hz), 13.0. ^{19}F NMR ($CDCl_3$) δ 85.9 (qn; *J* = 143.0 Hz; 1F), 62.0 (d; *J* = 143.0 Hz; 4F). IR (film) 2115 (m), 1766 (str), 820 (str) cm^{-1}. HRMS (DART, negative) *m*/*z*: $[M - Allyl]^-$ calcd for $C_6H_8F_5N_4OS$ 279.0339; found, 279.0335.

Conclusions

The introduction of the SF_5 group into aliphatic molecules influences reactivity by electronic, steric and dipolar effects. The electron withdrawing effects of the SF_5 group inhibit formation of pentafluorosulfanylated aldimines by promoting enamine formation. The profound dipole moment that results on introduction of the pentafluorosulfanyl group and the steric demand of the SF_5 group can very effectively control the diastereoselectivity of additions to α-pentafluorosulfanylated aldehydes and aldimines. The highly polar intermediate in the Staudinger-ketene imine cycloaddition reaction is an ideal test for the potency of SF_5-induced dipolar effects to control conformation. As found from computational modelling, regulation of the conformation of the initial zwitterionic adducts formed on reaction of a reactive ketene with an α-SF_5-substituted aldimine defines the energetic landscape for the cycloaddition process. The anti-periplanar alignment of the C2–O and C5–S bonds that was determined suggests a rationale for the differences in intermediate stabilities. Those differences influence the barrier to ring closure and hence lead to the remarkable diastereoselectivity of β-lactam formation. The more stable intermediate conformation is another illustration of the electronic effects of pentafluorosulfanylation. In the more stable intermediate conformation, the acidic proton adjacent to the SF_5 group is especially susceptible to intramolecular proton transfer to form an undesired enamine side product. Combination of the influences of the SF_5 group may be employed to dramatically affect both the stereoselectivity and regiochemistry of pentafluoro-sulfanylated reactants.

Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the support of this by National Science Foundation grants CHE-0957544 and CHE-1337594.

Notes and references

1 D. Lentz, K. Seppelt and K.-y. Akiba, in *Chemistry of Hypervalent Compounds*, ed. K.-y. Akiba, Wiley-VCH, New York, 1999.
2 R. W. Winter, R. A. Dodean, G. L. Gard and V. A. Soloshonok, in *Fluorine Containing Synthons*, ed. V. A. Soloshonok, American Chemical Society, Washington D.C., 2005, vol. 911, pp. 87–118.
3 G. S. Lal and R. G. Syvret, *Chim. Oggi*, 2008, **26**, 26–27.
4 G. L. Gard, *Chim. Oggi*, 2009, **27**, 10–13.
5 S. Altomonte and M. Zanda, *J. Fluorine Chem.*, 2012, **143**, 57–93.
6 P. Kirsch and G.-V. Röschenthaler, in *Current Fluoroorganic Chemistry*, American Chemical Society, Washington, D.C., 2007, vol. 949, pp. 221–243.
7 P. Kirsch, *Modern Fluoroorganic Chemistry; Synthesiis, Reactivity and Applications*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2nd edn, 2013.
8 P. R. Savoie and J. T. Welch, *Chem. Rev.*, 2015, **115**, 1130–1190.
9 J. T. Welch, *Mol. Med. Med. Chem.*, 2012, **6**, 175–207.
10 C. N. von Hahmann, P. R. Savoie and J. T. Welch, *Curr. Org. Chem.*, 2015, **19**, 1592–1618.
11 J. T. Welch and D. S. Lim, *Bioorg. Med. Chem.*, 2007, **15**, 6659–6666.
12 B. Stump, C. Eberle, W. B. Schweizer, M. Kaiser, R. Brun, R. L. Krauth-Siegel, D. Lentz and F. Diederich, *ChemBioChem*, 2009, **10**, 79–83.
13 P. Wipf, T. Mo, S. J. Geib, D. Caridha, G. S. Dow, L. Gerena, N. Roncal and E. E. Milner, *Org. Biomol. Chem.*, 2009, **7**, 4163–4165.
14 P. W. Chia, S. C. Brennan, A. M. Z. Slawin, D. Riccardi and D. O'Hagan, *Org. Biomol. Chem.*, 2012, **10**, 7922–7927.
15 R. Gujjar, F. El Mazouni, K. L. White, J. White, S. Creason, D. M. Shackleford, X. Deng, W. N. Charman, I. Bathurst, J. Burrows, D. M. Floyd, D. Matthews, F. S. Buckner, S. A. Charman, M. A. Phillips and P. K. Rathod, *J. Med. Chem.*, 2011, **54**, 3935–3949.
16 J. M. Coteron, M. Marco, J. Esquivias, X. Deng, K. L. White, J. White, M. Koltun, F. El Mazouni, S. Kokkonda, K. Katneni, R. Bhamidipati, D. M. Shackleford, I. Angulo-Barturen, S. B. Ferrer, M. B. Jimenez-Diaz, F.-J. Gamo, E. J. Goldsmith, W. N. Charman, I. Bathurst, D. Floyd, D. Matthews, J. N. Burrows, P. K. Rathod, S. A. Charman and M. A. Phillips, *J. Med. Chem.*, 2011, **54**, 5540–5561.
17 S. Altomonte, G. L. Baillie, R. A. Ross, J. Riley and M. Zanda, *RSC Adv.*, 2014, **4**, 20164–20176.
18 T. Umemoto, L. M. Garrick and N. Saito, *Beilstein J. Org. Chem.*, 2012, **8**, 461–471.
19 M. V. Westphal, B. T. Wolfstädter, J.-M. Plancher, J. Gatfield and E. M. Carreira, *ChemMedChem*, 2015, **10**, 461–469.
20 M. Anthony, *Aust. N. Z. J. Med.*, 1984, **14**, 888–895.
21 P. R. Savoie, S. Higashiya, J.-H. Lin, D. V. Wagle and J. T. Welch, *J. Fluorine Chem.*, 2012, **143**, 281–286.
22 P. R. Savoie, J. M. Welch, S. Higashiya and J. T. Welch, *J. Fluorine Chem.*, 2013, **148**, 1–5.
23 I. Ojima and F. A. Jameison, *Bioorg. Med. Chem. Lett.*, 1991, **1**, 581–584.
24 L. J. Saethre, N. Berrah, J. D. Bozek, K. J. Børve, T. X. Carroll, E. Kukk, G. L. Gard, R. Winter and T. D. Thomas, *J. Am. Chem. Soc.*, 2001, **123**, 10729–10737.
25 P. Brant, A. D. Berry, R. A. DeMarco, F. L. Carter, W. B. Fox and J. A. Hashmall, *J. Electron Spectrosc. Relat. Phenom.*, 1981, **22**, 119–129.
26 J. E. True, T. D. Thomas, R. W. Winter and G. L. Gard, *Inorg. Chem.*, 2003, **42**, 4437–4441.
27 W. A. Sheppard, *J. Am. Chem. Soc.*, 1962, **84**, 3072–3076.
28 R. W. Taft Jr. and I. C. Lewis, *J. Am. Chem. Soc.*, 1959, **81**, 5343–5352.
29 R. W. Taft Jr., *J. Phys. Chem.*, 1960, **64**, 1805–1815.
30 P. Kirsch, M. Bremer, M. Heckmeier and K. Tarumi, *Angew. Chem., Int. Ed.*, 1999, **38**, 1989–1992.
31 R. D. Bowden, P. J. Comina, M. P. Greenhall, B. M. Kariuki, A. Loveday and D. Philp, *Tetrahedron*, 2000, **56**, 3399–3408.
32 P. Kirsch and M. Bremer, *Angew. Chem., Int. Ed.*, 2000, **39**, 4216–4235.
33 P. Kirsch, M. Bremer, A. Taugerbeck and T. Wallmichrath, *Angew. Chem., Int. Ed.*, 2001, **40**, 1480–1484.
34 R. E. Rosenberg and W. J. Kelly, *J. Phys. Org. Chem.*, 2015, **28**, 47–56.
35 A. G. O'Brien, *Tetrahedron*, 2011, **67**, 9639–9667.
36 M. Chérest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, **9**, 2199–2204.
37 R. J. Smith, M. Trzoss, M. Bühl and S. Bienz, *Eur. J. Org. Chem.*, 2002, 2770–2775.
38 N. T. Anh, in *Organic Chemistry Syntheses and Reactivity*, Springer Berlin Heidelberg, Berlin, Heidelberg, 1980.
39 J. W. Cornforth, R. H. Cornforth and K. K. Mathew, *J. Chem. Soc.*, 1959, 112–127.
40 D. A. Evans, V. J. Cee and S. J. Siska, *J. Am. Chem. Soc.*, 2006, **128**, 9433–9441.
41 D. A. Evans, S. J. Siska and V. J. Cee, *Angew. Chem., Int. Ed.*, 2003, **42**, 1761–1765.
42 V. J. Cee, C. J. Cramer and D. A. Evans, *J. Am. Chem. Soc.*, 2006, **128**, 2920–2930.
43 S. C. Ngo, J.-H. Lin, P. R. Savoie, E. M. Hines, K. M. Pugliese and J. T. Welch, *Eur. J. Org. Chem.*, 2012, 4902–4905.

 This journal is © The Royal Society of Chemistry 2018

Published on 07 April 2018. Downloaded by State University of New York at Albany on 11/28/2020 1:56:02 AM.

44 F. W. Friese, A.-L. Dreier, A. V. Matsnev, C. G. Daniliuc, J. S. Thrasher and G. Haufe, *Org. Lett.*, 2016, **18**, 1012–1015.
45 A. Joliton, J.-M. Plancher and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2016, **55**, 2113–2117.
46 M. V. Ponomarenko, S. Grabowsky, R. Pal, G.-V. Röschenthaler and A. A. Fokin, *J. Org. Chem.*, 2016, **81**, 6783–6791.
47 D. Seebach and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 654–660.
48 T. Yamazaki, N. Shinohara, T. Kitazume and S. Sato, *J. Org. Chem.*, 1995, **60**, 8140–8141.
49 A. S. Cieplak, *Chem. Rev.*, 1999, **99**, 1265–1336.
50 A.-L. Dreier, B. Beutel, C. Mueck-Lichtenfeld, A. V. Matsnev, J. S. Thrasher and G. Haufe, *J. Org. Chem.*, 2017, **82**, 1638–1648.
51 A.-L. Dreier, A. V. Matsnev, J. S. Thrasher and G. Haufe, *J. Fluorine Chem.*, 2014, **167**, 84–90.
52 A. Penger, C. N. von Hahmann, A. S. Filatov and J. T. Welch, *Beilstein J. Org. Chem.*, 2013, **9**, 2675–2680.
53 M. T. Aranda, P. Perez-Faginas and R. Gonzalez-Muniz, *Curr. Org. Synth.*, 2009, **6**, 325–341.
54 M. I. Konaklieva and B. J. Plotkin, in *Amino Acids, Peptides and Proteins in Organic Chemistry*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2011, vol. 4.
55 C. Palomo, J. M. Aizpurua, I. Ganboa and M. Oiarbide, *Eur. J. Org. Chem.*, 1999, 3223–3235.
56 G. S. Singh, *Tetrahedron*, 2003, **59**, 7631–7649.
57 C. Palomo, J. M. Aizpurua, I. Ganboa and M. Oiarbide, *Curr. Med. Chem.*, 2004, **11**, 1837–1872.
58 B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Rev.*, 2007, **107**, 4437–4492.
59 F. P. Cossío, A. Arrieta and M. A. Sierra, *Acc. Chem. Res.*, 2008, **41**, 925–936.
60 A. Brandi, S. Cicchi and F. M. Cordero, *Chem. Rev.*, 2008, **108**, 3988–4035.
61 N. Fu and T. T. Tidwell, *Tetrahedron*, 2008, **64**, 10465–10496.
62 G. I. Georg and V. T. Ravikumar, in *The Organic Chemistry of β-Lactams*, ed. G. I. Georg, VCH Publishers, New York, 1993.
63 N. P. Stepanova, V. B. Lebedev, N. A. Orlova, E. S. Turbanova and A. A. Petrov, *Zh. Org. Khim.*, 1988, **24**, 692–699.
64 A. D. Allen and T. T. Tidwell, *Chem. Rev.*, 2013, **113**, 7287–7342.
65 N. Hatanaka and I. Ojima, *J. Chem. Soc., Chem. Commun.*, 1981, 344–346.
66 I. Ojima, K. Nakahashi, S. M. Brandstadter and N. Hatanaka, *J. Am. Chem. Soc.*, 1987, **109**, 1798–1805.
67 H. M. Badawi, W. Förner and A. A. Al-Saadi, *J. Mol. Struct.: THEOCHEM*, 2004, **712**, 131–138.
68 C. A. G. Haasnoot, F. A. A. M. de Leeuw and C. Altona, *Tetrahedron*, 1980, **36**, 2783–2792.
69 C. A. G. Haasnoot, F. A. A. M. de Leeuw, H. P. M. de Leeuw and C. Altona, *Org. Magn. Reson.*, 1981, **15**, 43–52.
70 G. Schrumpf and A.-W. Klein, *Chem. Ber.*, 1973, **106**, 266–279.
71 F. P. Cossío, A. Arrieta and M. A. Sierra, *Acc. Chem. Res.*, 2008, **41**, 925–936.
72 A. Arrieta, F. P. Cossío and B. Lecea, *J. Org. Chem.*, 2000, **65**, 8458–8464.
73 D. Marx and M. I. Menéndez, *J. Org. Chem.*, 2018, **83**, 2438–2441.
74 Y. Liang, L. Jiao, S. Zhang, Z.-X. Yu and J. Xu, *J. Am. Chem. Soc.*, 2009, **131**, 1542–1549.
75 S. Niwayama, E. A. Kallel, D. C. Spellmeyer, C. Sheu and K. N. Houk, *J. Org. Chem.*, 1996, **61**, 2813–2825.
76 I. V. Alabugin, *J. Org. Chem.*, 2000, **65**, 3910–3919.
77 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923–2925.