Strain-Release Pentafluorosulfanylation of [1.1.0]Bicyclobutanes: An Entryway to Achiral SF_5-Cyclobutanes

Yannick Kraemer, Jón Atiba Buldt, Alexander M. Stephens, Wang-Yeuk Kong, Abbey N. Ragan, Zane C. Haidar, Ansh Hiten Patel, James C. Fettinger, Dean J. Tantillo,* and Cody Ross Pitts*[a]

[a] Y. Kraemer, J. A. Buldt, A. M. Stephens, W.-Y. Kong, A. N. Ragan, Z. C. Haidar, A. H. Patel, Dr. J. C. Fettinger, Prof. Dr. D. J. Tantillo, Prof. Dr. C. R. Pitts
Department of Chemistry
University of California, Davis
1 Shields Avenue, Davis, CA 95616, U.S.A.
E-mail: djtantillo@ucdavis.edu, crpitts@ucdavis.edu

Abstract: The first assortment of achiral pentafluorosulfanylated cyclobutanes (SF_5-CBs) are now synthetically accessible through strain-release functionalization of [1.1.0]bicyclobutanes (BCBs) using SF_5Cl. Methods for both chloropentafluorosulfanylation and hydropentafluorosulfanylation of BCBs are detailed herein, as well as proof-of-concept that the logic extends to tetrafluoro(aryl)sulfanylation, tetrafluoro(trifluoromethyl)sulfanylation, and iodopentafluorosulfanyl-ation. Considering the SF_5 group and CBs have been employed as nonclassical bioisosteres, structural aspects of these unique SF_5-CB "hybrid isosteres" were also studied using SC-XRD. Ostensibly, the reaction proceeds through a curious *polarity mismatch* addition of SF_5 radicals to the electrophilic sites of the BCBs. The nature of the C(sp^3)–SF_5 bond formation step was studied and contextualized using DFT calculations.

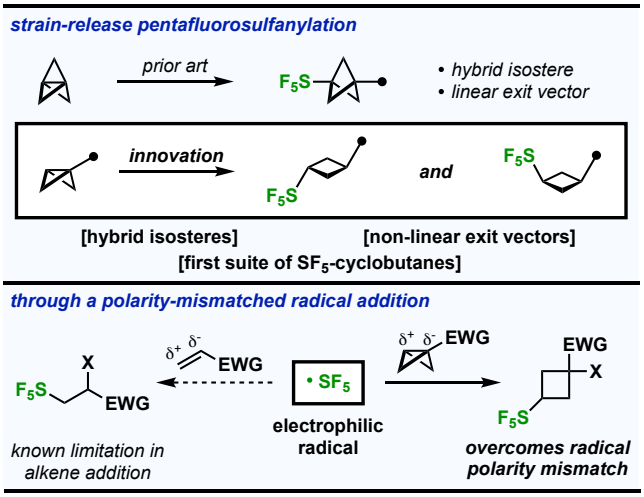
The pursuit of new methods to install the pentafluorosulfanyl (SF_5) group on organic molecules is no longer reserved for connoisseurs. Traditionally, synthesizing or working with SF_5Cl – one of the few known SF_5-transfer reagents – has mandated handling toxic and corrosive gases (arguably stifling growth in this research area).[1] However, using a contemporary mild oxidative fluorination strategy,[2,3] a stock solution of SF_5Cl can now be prepared easily in house without the need to handle it as a gas.[4] This timely advance in reagent accessibility empowers the broader chemical community to address a lag in the development of tactics to make C–SF_5 bonds.

Notably distinct from *bottom-up* aryl-SF_5 synthesis,[2,5] methods for *direct* C–SF_5 bond formation have been largely limited to SF_5 radical addition across π-bonds for decades (i.e., alkenes and alkynes,[6] as well as α-diazo carbonyls[4b]).[1b] This topic remains a lively focus of several research programs and has served as a prominent strategy to access SF_5-containing building blocks.[7] These efforts have, for instance, enabled the evaluation of the SF_5 group as a promising bioisosteric replacement for a CF_3 or *t*-Bu group in medicinal and agrochemistry settings.[8]

Recently, our group has begun to explore an alternative approach to C–SF_5 bond formation by merging SF_5 radical chemistry with strain-release functionalization of σ-bonds. In collaboration with the Cornella group in 2022, we reported the first strategy for pentafluorosulfanylation of [1.1.1]propellane (Scheme 1, *top panel*).[9] Remarkably, the resultant SF_5-bicyclopentane (SF_5-BCP) core structure comprises two distinct elements of bioisosterism, as BCPs are established bioisosteric replacements for arenes.[10] We proposed that access to SF_5-BCP and similar "hybrid isosteres" could create new opportunities for mix-and-match molecular design strategies in drug discovery.[9,11] Note that additional validation for the concept was provided earlier this year in a study on the role of CF_2-BCPs in such a capacity.[12]

Herein, we disclose two synthetic methods that grant access to complementary types of SF_5-containing hybrid isosteres – SF_5-cyclobutanes (SF_5-CBs) – through SF_5 radical addition across [1.1.0]bicyclobutanes (BCBs).[13] Similar to BCPs, cyclobutane (CB) rings are being employed more frequently in medicinal chemistry,[14] e.g., as bioisosteric replacements for arenes or alkenes.[15] In contrast to SF_5-BCPs, the non-linear exit vectors of SF_5-CBs afford an added degree of flexibility in the three-dimensional organization of the SF_5 group (Scheme 1, *top panel*).

To our knowledge, no SF_5-containing cyclobutanes with 1,3-substitution patterns have been reported in the literature to date,[16] prompting further investigation into structural features, chemical stability, and downstream functionalization of SF_5-CBs. Interestingly, this study also demonstrates that addition of "electrophilic" SF_5 radicals across BCBs substituted with electron-withdrawing groups (EWGs) can overcome an apparent radical polarity mismatch[17] that has notoriously inhibited analogous reactions with alkenes (Scheme 1, *bottom panel*).[6]



Scheme 1. (*Top*) Strain-release pentafluorosulfanylation of [1.1.1]propellane (previous work) and [1.1.0]bicyclobutane (this work) to access hybrid isosteres. (*Bottom*) Highlighting how strain-release SF_5-functionalization overrides a radical polarity mismatch that has hindered related transformations.

We began screening for pentafluorosulfanylation conditions using 1-(phenylsulfonyl)bicyclo[1.1.0]butane, due to the relative synthetic accessibility of sulfone-substituted BCBs.[18] During reaction optimization (see SI), we determined that overnight irradiation of the substrate and SF_5Cl with white LEDs in an *n*-pentane:EtOAc solvent mixture provided the anticipated chloropentafluorosulfanylated products (**1**) in 71% yield by ^{19}F NMR analysis (Table 1). The *anti* and *syn* isomers of **1** formed in a 1.1:1 ratio and proved completely separable by chromatography on silica gel without need for HPLC purification. Isomers were assigned based on distinct shifts in the ^1H NMR spectra and confirmed by single-crystal X-ray diffraction (SC-XRD).

Using these conditions, we explored the scope of the reaction on a variety of substituted BCBs (Method A, Table 1). For one, chloropentafluorosulfanylated CBs bearing arylsulfonyl substituents with a range of electron-withdrawing and electron-donating substituents in the *para* (**2**-**8**), *meta* (**9**-**10**), and *ortho* (**11**-**12**) positions are accessible in 52-85% yield by ^{19}F NMR. Products containing alkylsulfonyl substituents, such as *i*-Pr (**13**) or *t*-Bu (**14**), were also formed in good yields (92% and 63%, respectively). Additionally, we found that both unsaturated and saturated heterocycles may be tolerated to varying degrees. For instance, thiophene-containing **15** formed in 76% yield, while the piperidine-based sulfonamide **16** only formed in 25% yield (isolation also proved particularly challenging for **16**). Note that indole-containing substrates and sterically hindered substrates (e.g., with a 1-phenylsulfonyl-2,2-dimethyl or a 1-phenylsulfonyl-3-trimethylsilyl substitution pattern) were less compatible under these conditions. See the SI for details.

Regarding selectivity, the *anti*:*syn* ratios range from 1:1 to 2.5:1, which is typical for radical addition reactions to BCBs.[19] It is important to stress that the difference in retention factors (R_f values) of both isomers is enough to permit complete chromatographic separation in nearly all cases.

Over the course of this study, we discovered that hydropentafluorosulfanylated cyclobutanes often accounted for a portion of the material balance. Initial attempts to re-optimize reaction conditions for hydropentafluorosulfanylation (inspired by recent work from Paquin and co-workers[20]) indicated that chloropentafluorosulfanylation often still competes. To circumvent this problem, we pursued an alternative approach to access hydropentafluorosulfanylated cyclobutanes from their chlorinated congeners via C–Cl bond reduction.

Upon screening for C–Cl bond functionalization conditions, we found that **1** can be converted to **17** using inexpensive transition metal salts and $NaBH_4$, i.e., via a metal boride-type reduction.[21] Originally, we observed that $Co(acac)_2$, $NiCl_2$, $FeCl_2$, and $CuCl_2$ were all competent in transforming purified **1** to **17** (see SI). We later discovered that $Co(acac)_2$ provided reliably higher conversions when telescoping the crude reaction mixture from Method A to reductive conditions without intermediate purification. This convenient one-pot formal hydropentafluorosulfanylation sequence is defined as Method B in Table 1.

The substrate scope and functional group tolerance of Method B to access compounds **17**-**32** largely reflect that of Method A, with some exceptions. For instance, upon submitting a crude reaction mixture containing **3** to reduction conditions, conversion to **17** in 52% yield by ^{19}F NMR was observed in lieu of **19**. This is consistent with the known propensity of metal borides and aluminides to reduce aryl bromides to their corresponding benzene rings.[22] Regarding selectivity, the *cis*:*trans* ratios range from 1:1 to 1.6:1 and often differ from ratios observed using Method A, also indicating that C–Cl bond reduction is not stereoretentive. Lastly, note that both *cis* and *trans* isomers were separable by chromatography in nearly all cases.

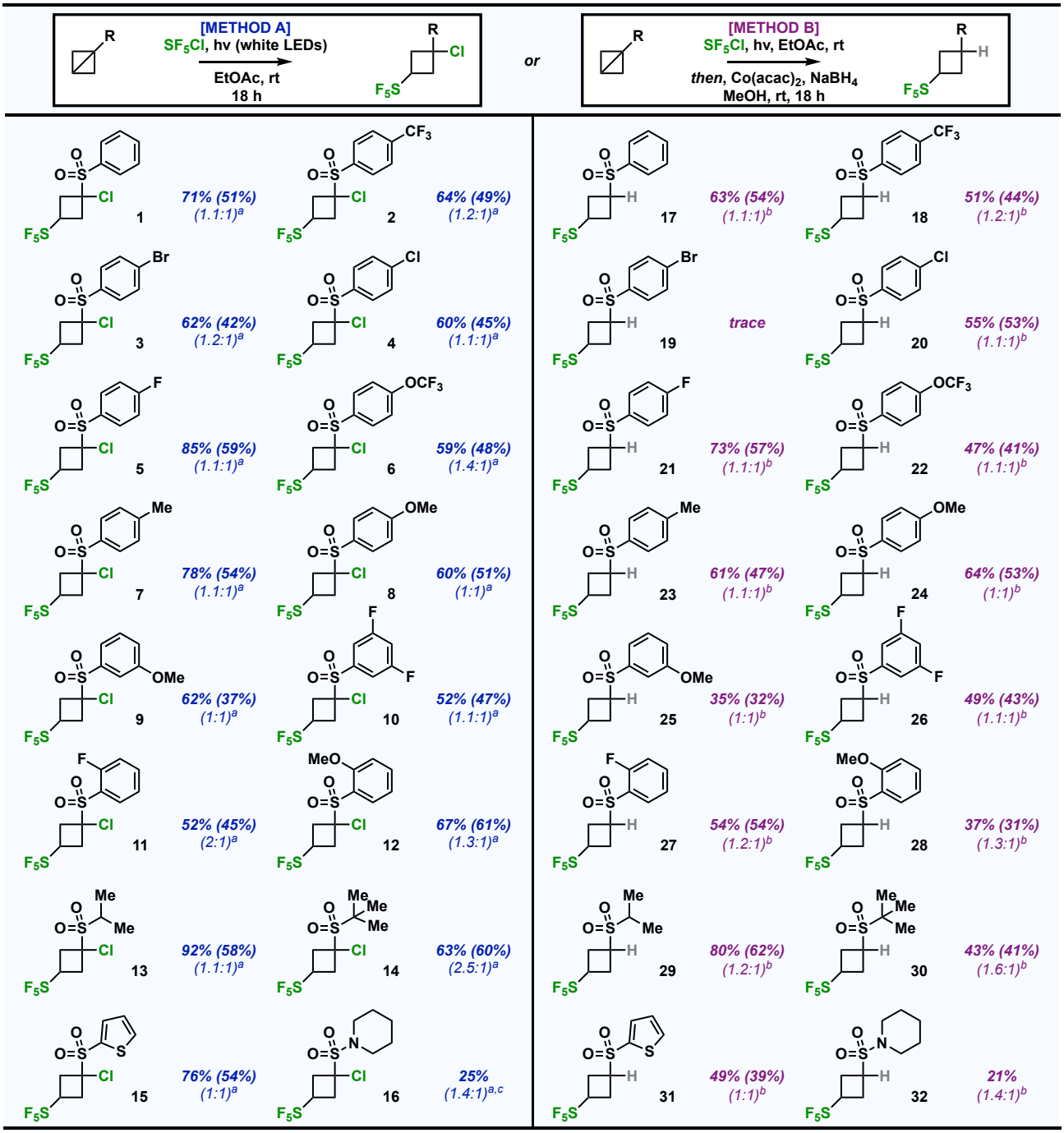
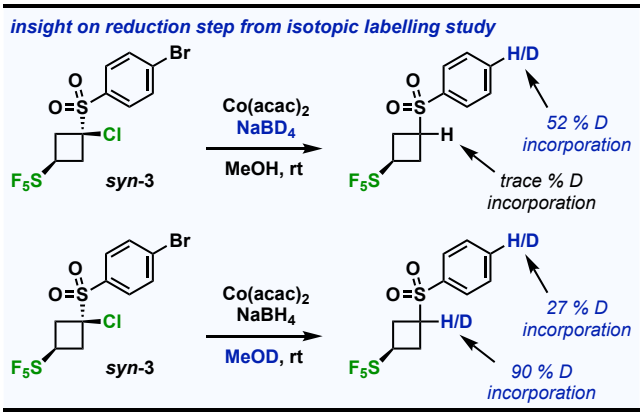


Table 1. Substrate scope for chloropentafluorosulfanylation (Method A) and hydropentafluorosulfanylation (Method B) of [1.1.0]bicyclobutanes. ^{19}F NMR yields are reported with isolated yields in parentheses. [a]Observed *anti*:*syn* product ratio. [b]Observed *cis*:*trans* product ratio. [c]Only the *syn* isomer was isolated.

Although a complete mechanistic study on the metal boride reduction step in Method B is beyond the scope of this work, we conducted a brief isotopic labelling study of the hydride and proton sources using ***syn*-3**, which undergoes both α-chloro and aryl bromide reduction (Scheme 2). Our observations of % D incorporation under these reaction conditions are consistent with previous metal boride and aluminide literature on aryl halide reduction and also suggest that α-chloro reduction likely occurs via a radical or anionic intermediate.[23]

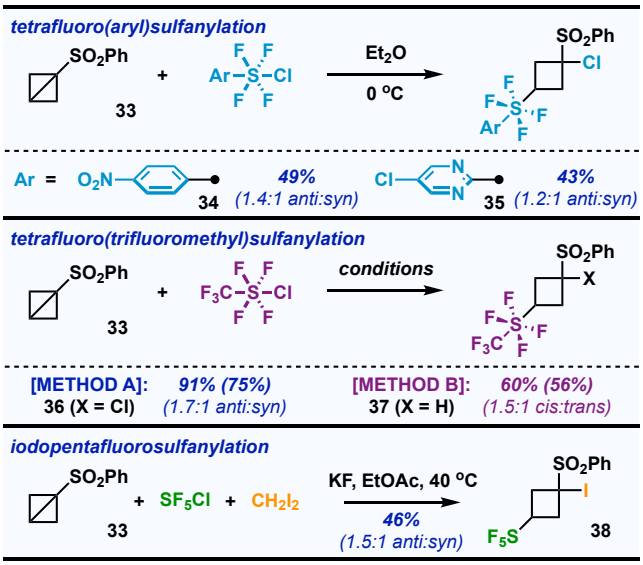


Scheme 2. Probing reductive dechlorination with deuterium-labelled reagents.

While reductive dechlorination of α-chloro-EWG-containing substrates using metal borides has been reported,[21,24] to our knowledge, this approach has not been investigated extensively on α-chloro-sulfones prior to this work. Moreover, it is remarkable that the SF_5 group remains unscathed under such conditions.

Subsequently, we examined whether Methods A & B translate from pentafluorosulfanylation to tetrafluoro(aryl)sulfanylation and tetrafluoro(trifluoromethyl)sulfanylation of BCBs (Scheme 3, *top and middle panels*). Both aryl-SF_4Cl compounds and CF_3SF_4Cl are known to participate in radical chain propagation reactions a la SF_5Cl[2a,9,25,26] and have recently become more accessible through corrosive gas reagent-free syntheses.[2,4a,27]

Although tetrafluoro(aryl)sulfanylation of **33** required additional optimization (see SI), we were able to access phenyl- and pyrimidyl-based compounds **34** and **35** in modest yields by ^{19}F NMR. Note that the -SF_4- moiety in each case was prone to hydrolysis during workup/isolation; thus, we did not further pursue this avenue. Conversely, tetrafluoro(trifluoromethyl)sulfanylation proceeded smoothly under Method A conditions to provide **36** in 75% isolated yield. Furthermore, the CF_3SF_4 group tolerated Method B conditions and afforded **37** in 56% isolated yield. To our knowledge, **36** and **37** are the first CF_3SF_4-CBs disclosed.

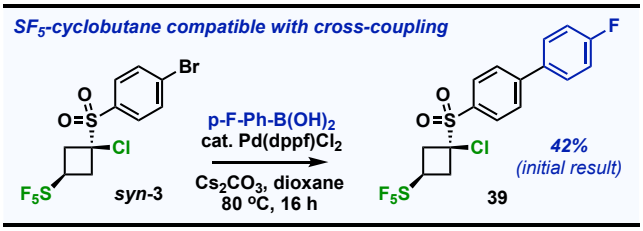


Scheme 3. (*Top*) Extension to tetrafluoro(aryl)sulfanylation. (*Middle*) Extension to tetrafluoro(trifluoromethyl)sulfanylation. (*Bottom*) Proof-of-concept for a three-component reaction, i.e., iodopentafluorosulfanylation. ^{19}F NMR yields are reported with isolated yields in parentheses.

Additionally, we were inspired by the recent work of Qing and co-workers[28] to attempt iodopentafluorosulfanylation of BCBs. To our satisfaction, we were able to obtain proof-of-concept that **33** can be converted to **38** using a similar type of three-component reaction (3CR) strategy (Scheme 3, *bottom panel*).

Furthermore, we have begun to examine downstream synthetic modifications of select SF_5-CBs reported in Table 1. Although we intend to explore this facet in greater detail in a follow-up study, we wish to disclose herein that SF_5-CBs are

compatible with palladium-catalyzed arylation conditions[29] (commonly employed in the medicinal chemistry setting[30]). Specifically, we converted ***syn*-3** to **39** in 42% isolated yield on the first attempt; the SF_5 group survived heating in the presence of base (Scheme 4). We have also included data on initial unsuccessful attempts at C–Cl and C–H bond functionalization in the SI.



Scheme 4. Proof-of-concept that SF_5-CBs are compatible with Pd-catalyzed cross-coupling conditions. Isolated yield reported.

Considering cyclobutane rings have been employed as bioisosteric replacements for arenes,[15a] we proceeded to compare structural features of SF_5-CBs with a similarly-substituted SF_5-arene using SC-XRD (Figure 1). Compound **40** was synthesized according to literature,[31] and single crystals were grown that proved suitable for X-ray diffraction. This SF_5-arene structure – already containing one element of bioisosterism (i.e., the SF_5 group[8]) – was compared to "hybrid isostere" (SF_5-CB) structures of ***trans*-17**, ***syn*-1**, and ***cis*-17**.

A condensed view of pronounced differences in our SC-XRD analyses is provided in Figure 1. In general, the replacement of the phenyl ring with a cyclobutane effectively results in a 21-24% reduction in distance between terminal carbon atoms. The virtue, however, of the Ph → CB replacement is the added flexibility in spatial reorganization of the SF_5 group that SF_5-arenes cannot offer. In **40**, the S–C1–C4–S array, with the axis defined by C1 and C4, is virtually linear. In ***trans*-17**, the SF_5 group is situated well below the axis defined by C1 and C3 ($\theta \approx 42°$), while the SO_2Ph substituent hovers above it ($\phi \approx 63°$). Interestingly, the introduction of a Cl substituent in ***syn*-1** simultaneously decreases θ to 38° and increases ϕ to 70°. In ***cis*-17**, both the SF_5 and SO_2Ph groups float above the axis defined by C1 and C3 with $\omega \approx 31°$ and $\phi \approx 37°$, respectively. Additional crystallographic comparisons can be found in the SI.[32]

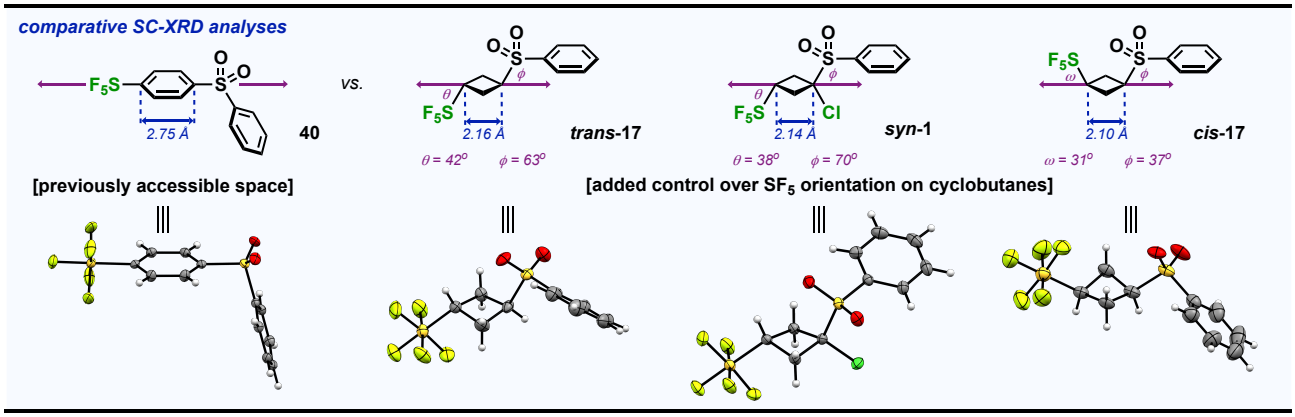
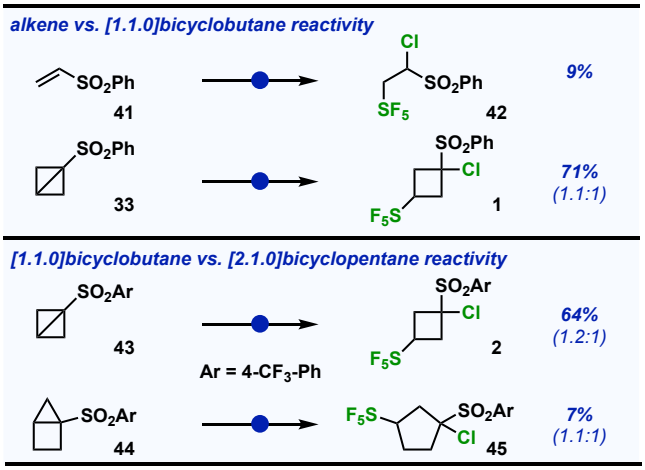


Figure 1. Select structural comparisons. Crystal structures for **40**, ***trans*-17**, ***syn*-1**, and ***cis*-17** determined by SC-XRD (displacement ellipsoids depicted at 50% probability level). The unit cell for **40** contains two symmetry-independent moieties (only one shown).

From a mechanistic standpoint, while both SF_5Cl and BCBs are known to participate in radical chain propagations, the putative addition of electrophilic SF_5 radicals to the 3-position of BCBs substituted with EWGs is notable. That is, nucleophilic radicals are typically employed in radical addition across BCBs substituted with EWGs[33] (and electrophilic radicals pair with more electron-rich BCBs[34]). Also, SF_5 radical addition to analogous alkenes, such as **41** (Scheme 5, *top panel*), is an established limitation due to the apparent radical polarity mismatch (**42** is formed in <10% yield even when other established initiation conditions are employed; see SI). Another comparison between similarly substituted [1.1.0]bicyclobutane and [2.1.0]bicyclopentane, or "housane," substrates (Scheme 5, *bottom panel*) reveals that conversion of **44** to **45** does not proceed as efficiently as pentafluorosulfanylation of **43** to make **2**, despite a similar release in ring strain.[13b]



Scheme 5. (*Top*) BCB reactivity vs. an analogously substituted alkene (Method A). (*Bottom*) BCB reactivity vs. an analogously substituted housane (Method A). ^{19}F NMR yields are reported with isomeric ratios in parentheses.

DFT studies at the PWPB95-D4/def2-QZVPP//PCM(Et_2O)-ωB97X-D/def2-SVP level of theory (See SI for computational details)[35] provide some insight into the observed differences in reactivity among analogously substituted BCBs, housanes, and alkenes (Figure 2). For one, SF_5 radical addition to BCB **33** (to make **IM1**) and housane **46** (to make **IM2**) are both predicted to be exergonic by 13.0 and 22.6 kcal/mol, respectively. On the other hand, SF_5 radical addition to alkene **41** (to make **IM3**) is endergonic (ΔG = +3.6 kcal/mol). In addition, a significantly lower activation energy barrier was determined for pentafluorosulfanylation of **33** ($\Delta G^{\ddagger}$ = +8.3 kcal/mol for **TS1**) vs. **46** ($\Delta G^{\ddagger}$ = +13.3 kcal/mol for **TS2**), consistent with SF_5 radical addition being less likely to occur on housanes vs. BCBs, despite appearing more favorable from a thermodynamic standpoint. Note that a similar barrier was computed for SF_5 radical addition to alkene **41** ($\Delta G^{\ddagger}$ = +13.4 kcal/mol for **TS3**). Thus, C(sp^3)–SF_5 bond formation was determined to be more kinetically favorable for the BCB substrate than either the housane or the alkene. It is important to note, however, that overall reaction barriers will also account for the generation of the SF_5 radical, a complicated process that will be discussed in a subsequent report.

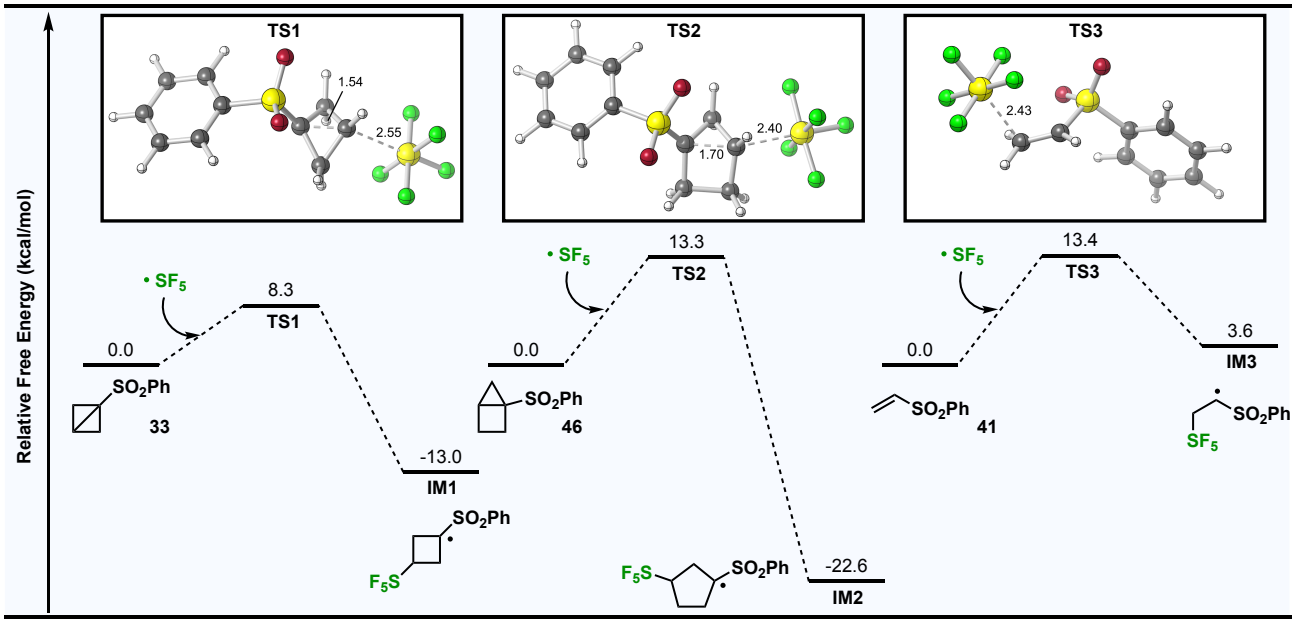


Figure 2. Free energy profiles at the PWPB95-D4/def2-QZVPP//PCM(Et_2O)-ωB97X-D/def2-SVP level of theory comparing SF_5 radical addition across an analogously substituted BCB (**33**), housane (**36**), and alkene (**41**).

Our relative predicted barriers for radical attack are consistent with Duarte's model based on bond delocalization in small rings,[36] including the observation that BCB **33** is still determined to be less susceptible to radical attack than [1.1.1]propellane – the topic of our previous work.[9] Finally, our observations are further corroborated by analysis of radical Fukui functions (Figure 3).[37] Condensed Fukui functions computed for **33**, **41**, and **46** at the PCM(Et2O)-ωB97X-D/def2-SVP level of theory indicate that the BCB has a stronger susceptibility toward radical attack compared to the alkene and housane.

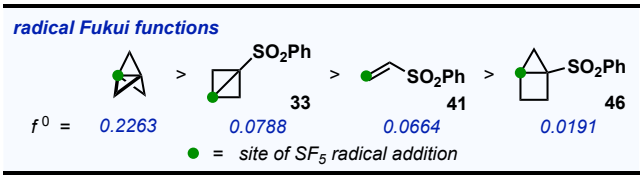


Figure 3. Fukui functions comparing site-susceptibilities to radical attack.

In short, we report on the synthesis, modification, structure,[38] and mechanistic features of pentafluorosulfanylated cyclobutanes (SF_5-CBs), as well as their $ArSF_4$-CB and CF_3SF_4-CB congeners. Future work will expand the scope of pentafluorosulfanylation of [1.1.0]bicyclobutanes, as well as explore applications of SF_5-CBs as "hybrid isostere" building blocks in complex molecule synthesis.

Acknowledgements

C.R.P. thanks the NIH/NIGMS (R35GM150861) and the University of California, Davis for financial support. W.Y.K thanks the Croucher Foundation for financial support through a doctoral scholarship. W.Y.K. and D.J.T. also thank the NSF ACCESS program (CHE030089) for computational support. A. N. R. thanks the NSF Graduate Research Fellowship Program for financial support. The authors also thank the NSF (CHE1531193) for the Dual Source X-ray Diffractometer, as well as the UC Davis core NMR facility.

Keywords: pentafluorosulfanylation • cyclobutanes • strain-release functionalization • hybrid isosteres • radical reactions

References

[1] a) S. Altomonte, M. Zanda, *J. Fluorine Chem.* **2012**, *143*, 57-93; b) P. R. Savoie, J. T. Welch, *Chem. Rev.* **2015**, *115*, 1130-1190; c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315-8359; d) M. Sani, M. Zanda, *Synthesis* **2022**, *54*, 4184-4209; e) M. Magre, S. Ni, J. Cornella, *Angew. Chem. Int. Ed.* **2022**, *61*, e202200904; f) G. Haufe, *Tetrahedron*, **2022**, *109*, 132656-132691.

[2] For recent applications of TCICA/KF in aryl-SF_5 compound synthesis, see: a) C. R. Pitts, D. Bornemann, P. Liebing, N. Santschi, A. Togni, *Angew. Chem. Int. Ed.* **2019**, *58*, 1950-1954; b) L. Wang, J. Cornella, *Angew. Chem. Int. Ed.* **2020**, *59*, 23510-23515; c) L. Wang, S. Ni, J. Cornella, *Synthesis* **2021**, *53*, 4308-4312.

[3] For other recent applications of TCICA/KF in oxidative fluorination of heteroatoms, see: a) D. Bornemann, C. R. Pitts, C. J. Ziegler, E. Pietrasiak, N. Trapp, N. Santschi, A. Togni, *Angew. Chem. Int. Ed.* **2019**, *58*, 12604-12608; b) F. Brüning, C. R. Pitts, J. Kalim, D. Bornemann, C. Ghiazza, J. deMontmillon, N. Trapp, T. Billard, A. Togni, *Angew. Chem. Int. Ed.* **2019**, *58*, 18937-18941; c) J. Häfliger, C. R. Pitts, D. Bornemann, R. Käser, N. Santschi, J. Charpentier, E. Otth, N. Trapp, R. Verel, H. P. Lüthi, A. Togni, *Chem. Sci.* **2019**, *10*, 7251-7259; d) D. Bornemann, F. Brüning, N. Bartalucci, L. Wettstein, C. R. Pitts, *Helv. Chim. Acta* **2021**, *104*, e2000218; e) A. N. Ragan, Y. Kraemer, W.-Y. Kong, S. Prasad, D. J. Tantillo, C. R. Pitts, *Angew. Chem. Int. Ed.* **2022**, *61*, e202208046; f) D. Wegener, K. F. Hoffmann, A. Pérez-Bitrián, I. Bayindir, A. N. Hadi, A. Wiesner, S. Riedel, *Chem. Commun.* **2022**, *58*, 9694-9697.

[4] a) C. R. Pitts, N. Santschi, A. Togni, WO2019/229103, **2019**; b) J.-Y. Shou, X.-H. Xu, F.-L. Qing, *Angew. Chem. Int. Ed.* **2021**, *60*, 15271–15275; c) Y. Kraemer, E. N. Bergman, A. Togni, C. R. Pitts, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205088.

[5] a) T. Umemoto, U.S. Patent US2008/0234520, **2008**; b) T. Umemoto, L. M. Garrick, N. Saito, *Beilstein J. Org. Chem.* **2012**, *8*, 461-471.

[6] a) S. Aït-Mohand, W. R. Dolbier, Jr., *Org. Lett.* **2002**, *4*, 3013-3015; b) D. Rombach, H.-A. Wagenknecht, *Angew. Chem. Int. Ed.* **2020**, *59*, 300-303; c) F.-F. Feng, J.-A. Ma, D. Cahard, *J. Org. Chem.* **2021**, *86*, 13808-13816; d) A. Gilbert, M. Birepinte, J.-F. Paquin, *J. Fluorine Chem.* **2021**, *243*, 109734-109743; e) V. Debrauwer, I. Leito, M. Lõkov, S. Tshepelevitsh, M. Parmentier, N. Blanchard, V. Bizet, *ACS Org. Inorg. Au* **2021**, *1*, 43-50; f) G. Lefebvre, O. Charron, J. Cossy ,C. Meyer, *Org. Lett.* **2021**, *23,* 5491-5495; g) D. Rombach, B. Birenheide, H.-A. Wagenknecht, *Chem. Eur. J.* **2021**, *27*, 8088-8093; h) A. Taponard, T. Jarrosson, L. Khrouz, M. Médebielle, J. Broggi, A. Tlili, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204623; i) L. C. Peyrical, M.-R. Oullet-Du Berger, M. Boucher, M. Birepinte, J.-F. Paquin, A. B. Charette, *Org. Lett.* **2023**, *25*, 2487-2491; j) L. Popek, J. J. Cabrera-Trujillo, V. Debrauwer, N. Blanchard, K. Miqueu, V. Bizet, *Angew. Chem. Int. Ed.* **2023**, *62*, e202300685; k) M.-R. Oullet-Du Berger, M. Boucher, J.-F. Paquin, *J. Fluorine Chem.* **2023**, *268*, 110131.

[7] a) A. Joliton, J.-M. Plancher, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 2113-2117; b) L. Popek, T. M. Nguyen, N. Blanchard, D. Cahard, V. Bizet, *Tetrahedron* **2022**, *117-118*, 132814; c) R. Kordnezhadian, B.-Y. Li, A. Zogu, J. Demaerel, W. M. De Borggraeve, *Chem. Eur. J.* **2022**, *28*, e202201491; d) V. Mastalerz, K. Lam, J.-F. Paquin, *J. Fluorine Chem.* **2023**, *268*, 110113.

[8] a) B. Stump, C. Eberle, W. B. Schweizer, M. Kaiser, R. Brun, R. L. Krauth-Siegel, D. Lentz, F. Diederich, *ChemBioChem* **2009**, *10*, 79–83; b) P. Wipf, T. Mo, S. J. Geib, D. Caridha, G. S. Dow, L. Gerena, N. Roncal, E. E. Milner, *Org. Biomol. Chem.* **2009**, *7*, 4163-4165; c) S. Altomonte, G. L. Baillie, R. A. Ross, J. Riley, M. Zanda, *RSC Adv.* **2014**, *4*, 20164-20176; d) M. V. Westphal, B. T. Wolfstädter, J.-M. Plancher, J. Gatfield, E. M. Carreira, *ChemMedChem* **2015**, *10*, 461-469; e) M. F. Sowaileh, R. A. Hazlitt, D. A. Colby, *ChemMedChem* **2017**, *12*, 1481-1490.

[9] Y. Kraemer, C. Ghiazza, A. N. Ragan, S. Ni, S. Lutz, E. K. Neumann, J. C. Fettinger, N. Nöthling, R. Goddard, J. Cornella, C. R. Pitts, *Angew. Chem. Int. Ed.* **2022**, *61*, e202211892.

[10] a) A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P.

Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O'Donnell, *J. Med. Chem.* **2012**, *55*, 3414−3424; b) G. M. Locke, S. S. R. Bernhard, M. O. Senge, *Chem. Eur. J.* **2019**, *25*, 4590-4647; c) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839-2849; d) E. G. Tse, S. D. Houston, C. M. Williams, G. P. Savage, L. M. Rendina, I. Hallyburton, M. Anderson, R. Sharma, G. S. Walker, R. S. Obach, M. H. Todd, *J. Med. Chem.* **2020**, *63*, 11585-11601.

[11] N. Erdeljac, C. Thiehoff, R. P. Jumde, C. G. Daniliuc, S. Höppner, A. Faust, A. K. H. Hirsch, R. Gilmour, *J. Med. Chem.* **2020**, *63*, 6225-6237.

[12] S. Cuadros, G. Goti, G. Barison, A. Raulli, T. Bortolato, G. Pelosi, P. Costa, L. Dell'Amico, *Angew. Chem. Int. Ed.* **2023**, *62*, e202303585.

[13] For recent reviews on strain-release functionalization of [1.1.0]bicyclobutanes, see: a) A. Fawcett, *Pure Appl. Chem.* **2020**, *92*, 751-765; b) J. Turkowska, J. Durka, D. Gryko, *Chem. Commun.* **2020**, *56*, 5718-5734; c) C. B. Kelley, J. A. Milligan, L. J. Tilley, T. M. Sodano, *Chem. Sci.* **2022**, *13*, 11721-11737; d) M. Golfmann, J. C. L. Walker, *Commun. Chem.* **2023**, *6*, 9.

[14] a) O. P. Demchuk, O. V. Hryshchuk, B. V. Vashchenko, S. A. Trofymchuk, K. P. Melnykov, A. Skreminskiy, D. M. Volochnyuk, O. O. Grygorenko, *Eur. J. Org. Chem.* **2021**, *2021*, 87-95; b) M. R. Bauer, P. Di Fruscia, S. C. C. Lucas, I. N. Michaelides, J. E. Nelson, R. I. Storer, B. C. Whitehurst, *RSC Med. Chem.* **2021**, *12*, 448-471; c) M. R. van der Kolk, M. A. C. H. Janssen, F. P. J. T. Rutjes, D. Blanco-Ania, *ChemMedChem* **2021**, *17*, e202200020; d) C. Hui, Y. Liu, M. Jiang, P. Wu, *Trends Chem.* **2022**, *4*, 677-681.

[15] a) T. T. Wager, B. A. Pettersen, A. W. Schmidt, D. K. Spracklin, S. Mente, T. W. Butler, H. Howard, Jr., D. J. Lettiere, D. M. Rubitski, D. F. Wong, F. M. Nedza, F. R. Nelson, H. Rollema, J. W. Raggon, J. Aubrecht, J. K. Freeman, J. M. Marcek, J. Cianfrogna, K. W. Cook, L. C. James, L. A. Chatman, P. A. Iredale, M. J. Banker, M. L. Homiski, J. B. Munzner, R. Y. Chandrasekaran, *J. Med. Chem.* **2011**, *54*, 7602-7620; b) C. Nowikow, R. Fuerst, M. Kauderer, C. Dank, W. Schmid, M. Hajduch, J. Rehulka, S. Gurska, O. Mokshyna, P. Polishchuk, I. Zupkó, P. Dzubak, U. Rinner, *Bioorg. Med. Chem.* **2019**, *27*, 115032; c) A. Malashchuk, A. V. Chernykh, V. V. Hurmach, M. O. Platonov, O. Onopchenko, S. Zozulya, C. G. Daniliuc, A. V. Dobrydnev, I. S. Kondratov, Y. S. Moroz, O. O. Grygorenko, *J. Mol. Struct.* **2020**, *1210*, 128025.

[16] For rare examples of SF_5-substituted cyclobutanes synthesized via cycloaddition, see: a) R. E. Banks, M. G. Barlow, R. N. Haszeldine, W. D. Morton, *J. Chem. Soc., Perkin Trans.* **1974**, 1266-1271; b) J. Bittner, K. Seppelt, *Chem. Ber.* **1990**, *123*, 2187-2190.

[17] E. Yoshioka, S. Kohtani, K. Sawai, Kentefu, E. Tanaka, H. Miyabe, *J. Org. Chem.* **2012**, *77*, 8588-8604.

[18] a) A. F. Stepan, C. Subramanyam, I. V. Efremov, J. K. Dutra, T. J. O'Sullivan, K. J. DiRico, W. S. McDonald, A. Won, P. H. Dorff, C. E. Nolan, S. L. Becker, L. R. Pustilnik, D. R. Riddell, G. W. Kauffman, B. L. Kormos, L. Zhang, Y. Lu, S. H. Capetta, M. E. Green, K. Karki, E. Sibley, K. P. Atchison, A. J. Hallgren, C. E. Oborski, A. E. Robshaw, B. Sneed, C. J. O'Donnell, *J. Med. Chem.* **2012**, *55*, 3414−3424; b) M. Jung, V. N. G. Lindsay, *J. Am. Chem. Soc.* **2022**, *144*, 4764-4769.

[19] a) X. Wu, W. Hao, K.-Y. Ye, B. Jiang, G. Pombar, Z. Song, S. Lin, *J. Am. Chem. Soc.* **2018**, *140*, 14836-14843; b) C. J. Pratt, R. A. Aycock, M. D. King, N. T. Jui, *Synlett* **2020**, *31*, 51-54; c) X. Yu, M. Lübbesmeyer, A. Studer, *Angew. Chem. Int. Ed.* **2021**, *60*, 675-679; d) P.-F. Chen, D.-S. Li, W.-T. Ou, F. Xue, H.-P. Deng, *Org. Lett.* **2023**, DOI: 10.1021/acs.orglett.3c02332.

[20] M. Birepinte, P. A. Champagne, J.-F. Paquin, *Angew. Chem. Int. Ed.* **2022**, *61*, e202112575.

[21] B. Ganem, J. O. Osby, *Chem. Rev.* **1986**, *86*, 763-780.

[22] a) S.-T. Lin, J. A. Roth, *J. Org. Chem.* **1979**, *44*, 309-310; b) J. M. Khurana, S. Kumar, B. Nand, *Can. J. Chem.* **2008**, *86*, 1052-1054.

[23] J. O. Osby, S. W. Heinzman, B. Ganem, *J. Am. Chem. Soc.* **1986**, *108*, 67-72.

[24] J. C. Sarma, M. Borbaruah, R. P. Sharma, *Tetrahedron Lett.* **1985**, *26*, 4657-4660.

[25] a) L. Zhong, P. R. Savoie, A. S. Filatov, J. T. Welch, *Angew. Chem. Int. Ed.* **2014**, *53*, 526-529; b) L. Zhong, A. S. Filatov, J. T. Welch, *J. Fluorine Chem.* **2014**, *167*, 192-197; c) P. Das, K. Niina, T. Hiromura, E. Tokunaga, N. Saito, N. Shibata, *Chem. Sci.* **2018**, *9*, 4931-4936; d) K. Niina, K. Tanagawa, Y. Sumii, N. Saito, N. Shibata, *Org. Chem. Front.* **2020**, *7*, 1276-1282; e) K. Maruno, K. Niina, O. Nagata, N. Sibata, *Org. Lett.* **2022**, *24*, 1722-1726; f) K. Iwaki, K. Maruno, O. Nagata, N. Shibata, *J. Org. Chem.* **2022**, *87*, 6302-6311; g) K. Iwaki, K. Tanagawa, S. Mori, K. Maruno, Y. Sumii, O. Nagata, N. Shibata, *Org. Lett.* **2022**, *24*, 3347-3352; h) K. Maruno, K. Hada, Y. Sumii, O. Nagata, N. Shibata, *Org. Lett.* **2022**, *24*, 3755-3759; i) T. Aggarwal, K. Hada, Y. Murata, Y. Sumii, K. Tanagawa, K. Niina, S. Mori, J. Escorihuela, N. Shibata, *Angew. Chem. Int. Ed.* **2023**, *62*, e202307090.

[26] a) A. Ikeda, L. Zhong, P. R. Savoie, C. N. von Hahmann, W. Zheng, J. T. Welch, *Eur. J. Org. Chem.* **2018**, *2018*, 772-780; b) A. Ikeda, A. Capellan, J. T. Welch, *Org. Biomol. Chem.* **2019**, *17*, 8079-8082; c) M. Deng, M. Wilde, J. T. Welch, *J. Org. Chem.* **2023**, *88*, 11363-11366.

[27] X. Zhao, J.-Y. Shou, J. J. Newton, F.-L. Qing, *Org. Lett.* **2022**, *24*, 8412-8416.

[28] X. Zhao, J.-Y. Shou, F.-L. Qing, *Sci. China Chem.* **2023**, DOI: 10.1007/s11426-023-1715-2.

[29] J. R. Walker, M. Hall, C. T. Eggers, H. Lazaro, WO2019/232384, **2019**.

[30] D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443-4458.

[31] K. Matsuzaki, K. Okuyama, E. Tokunaga, N. Saito, M. Shiro, N. Shibata, *Org. Lett.* **2015**, *17*, 3038-3041.

[32] P. Liebing, C. R. Pitts, M. Reimann, N. Trapp, D. Rombach, D. Bornemann, M. Kaupp, A. Togni, *Chem. Eur. J.* **2021**, *27*, 6086-6093.

[33] For example: G. Ernouf, E. Chirkin, L. Rhyman, P. Ramasami, J.-C. Cintrat, *Angew. Chem. Int. Ed.* **2020**, *132*, 2640-2644.

[34] For example: M. Silvi, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 9511-9515.

[35] a) J.-D. Chai, M. Head-Gordon. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615-6620; b) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305; c) E. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032–3041; d) L. Goerigk, S. Grimme, *J. Chem. Theory Comput.* **2011**, *7*(2), 291–309; e) E. Caldeweyher, S. Ehlert, A. Hansen, H. Neugebauer, S. Spicher, C. Bannwarth, S. Grimme, *J. Chem. Phys.* **2019**, *150*, 154122; f) F. Neese, *WIREs Comput. Mol. Sci.* 2022, **12**, e1606

[36] A. Sterling, R. Smith, E. Anderson, F. Duarte, *ChemRxiv preprint* **2023**, DOI: https://doi.org/10.26434/chemrxiv-2021-n0xm9-v2.

[37] a) R. G. Parr, W. Yang, *J. Am. Chem. Soc.* **1984**, *106*, 4049-4050; b) P. W. Ayers, M. Levy, *Theor. Chem. Acc.* **2000**, *103*, 353-360; c) P. Geerlings, F. De Proft, W. Langenaeker, *Chem. Rev.* **2003**, *103*, 1793-1874; d) T. Lu, F. Chen, *J. Comput. Chem.* **2012,** *33*(5), 580-92; e)F. L. Hirshfeld, *Theoret. Chim. Acta* **1977,** *44* 129-138.

[38] CCDC 2288249, 2288250, 2288251, and 2288252 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.