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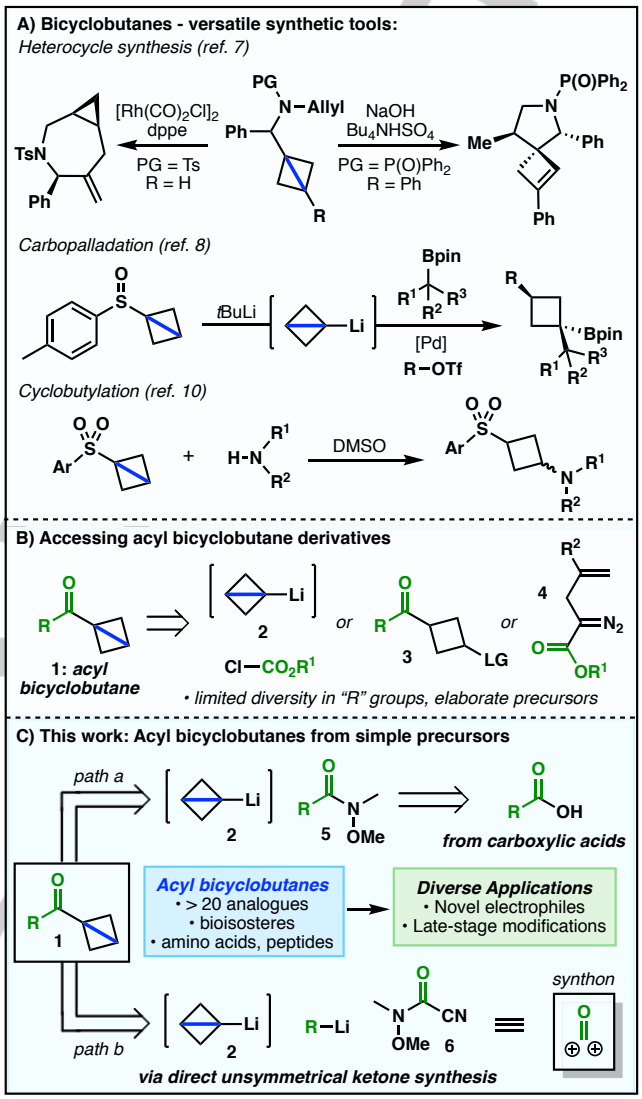
Structurally Diverse Acyl Bicyclobutanes: Valuable Strained Electrophiles

Brett D. Schwartz,[+] Meng Yao Zhang,[+] Riley H. Attard, Michael G. Gardiner and Lara R. Malins*

Abstract: Bicyclo[1.1.0]butanes (BCBs) are highly strained carbocycles that have emerged as versatile synthetic tools, particularly for the construction of functionalized small molecules. Herein, we disclose two efficient pathways for the rapid preparation of over 20 structurally diverse BCB ketones, encompassing simple alkyl and aryl derivatives, as well as unprecedented amino acid, dipeptide, bioisostere, and bifunctional linchpin reagents currently inaccessible using literature methods. Analogues are readily forged in two steps and in high yields from simple carboxylic acids or *via* unsymmetrical ketone synthesis beginning with a convenient carbonyl dication equivalent. The utility of this novel toolbox of strained electrophiles for the selective modification of proteinogenic nucleophiles is highlighted.

Chemists have long been fascinated by strained cyclic molecules. Our understanding of ring strain has evolved considerably since Adolf von Baeyer's seminal publication on strain theory in 1885,[1] as has our ability to harness strain energy for the development of powerful new bond-forming reactions.[2] As the simplest of bicyclic hydrocarbons, bicyclo[1.1.0]butanes (BCBs) have captured the imagination of chemists since Wiberg and Ciula's first synthesis was reported in 1959.[3] The potential energy stored in the bridging bond (~66 kcal/mol) has been exploited for applications in synthesis and studies of fundamental reactivity.[4] The last several years, in particular, have been marked by renewed and sustained interest in the BCB motif, leading to innovative pathways for enzymatic BCB synthesis[5] and new, enabling transformations[6] (see representative examples, Scheme 1A). The Wipf group, for example, has extensively explored BCBs as precursors to valuable heterocyclic motifs.[7] Aggarwal and coworkers have leveraged the reactivity of BCBs and their inherent ring-strain to facilitate carbopalladation[8] and radical addition[9] at the central C–C σ-bond. Baran and coworkers have disclosed a convenient approach to the late-stage cyclobutylation of pharmaceutically-relevant amines,[10] capitalizing on the electrophilicity of BCBs with bridgehead electron-withdrawing groups (e.g. aryl sulfones, explored in pioneering work by Gaoni[11]). This wealth of emerging chemistry underpins the importance of efficient approaches to structurally diverse BCB analogues.

Our initial interest in the BCB motif stemmed from the prospect of harnessing the electrophilicity of BCBs activated by bridgehead EWG groups[12] for the late-stage, Click-type[13] modification of proteinogenic nucleophiles. In this context, BCBs



Scheme 1. A) Diverse applications of bicyclobutanes (BCBs); B) Common approaches to acyl BCBs; C) This work: acyl BCBs from versatile precursors.

are underexplored, despite a broad appreciation for the value of strained carbocycles in bioconjugation chemistry[14] (e.g. cyclooctynes,[15] trans-cyclooctenes[16]). Notably, Baran and coworkers have employed BCB aryl sulfones for highly-selective cysteine functionalization;[10, 17] however, the initial reagent synthesis, a 6-step protocol from the aryl sulfonyl chloride, limits expeditious access to BCB analogues, including bifunctional reagents amenable to further diversification. Acyl BCBs (e.g. **1**, Scheme 1B), bearing bridgehead carbonyl substituents, are attractive alternatives. These BCB derivatives exhibit enhanced electrophilicity[12] over the corresponding sulfones; moreover, the carbonyl motif offers additional opportunities for diversification, particularly in the context of bioconjugation chemistry.[18] "Parent" acyl BCBs such as **1**, bearing a single bridgehead carbonyl substituent, have traditionally been accessible *via* three primary pathways (Scheme 1B): 1) direct carboxylation of

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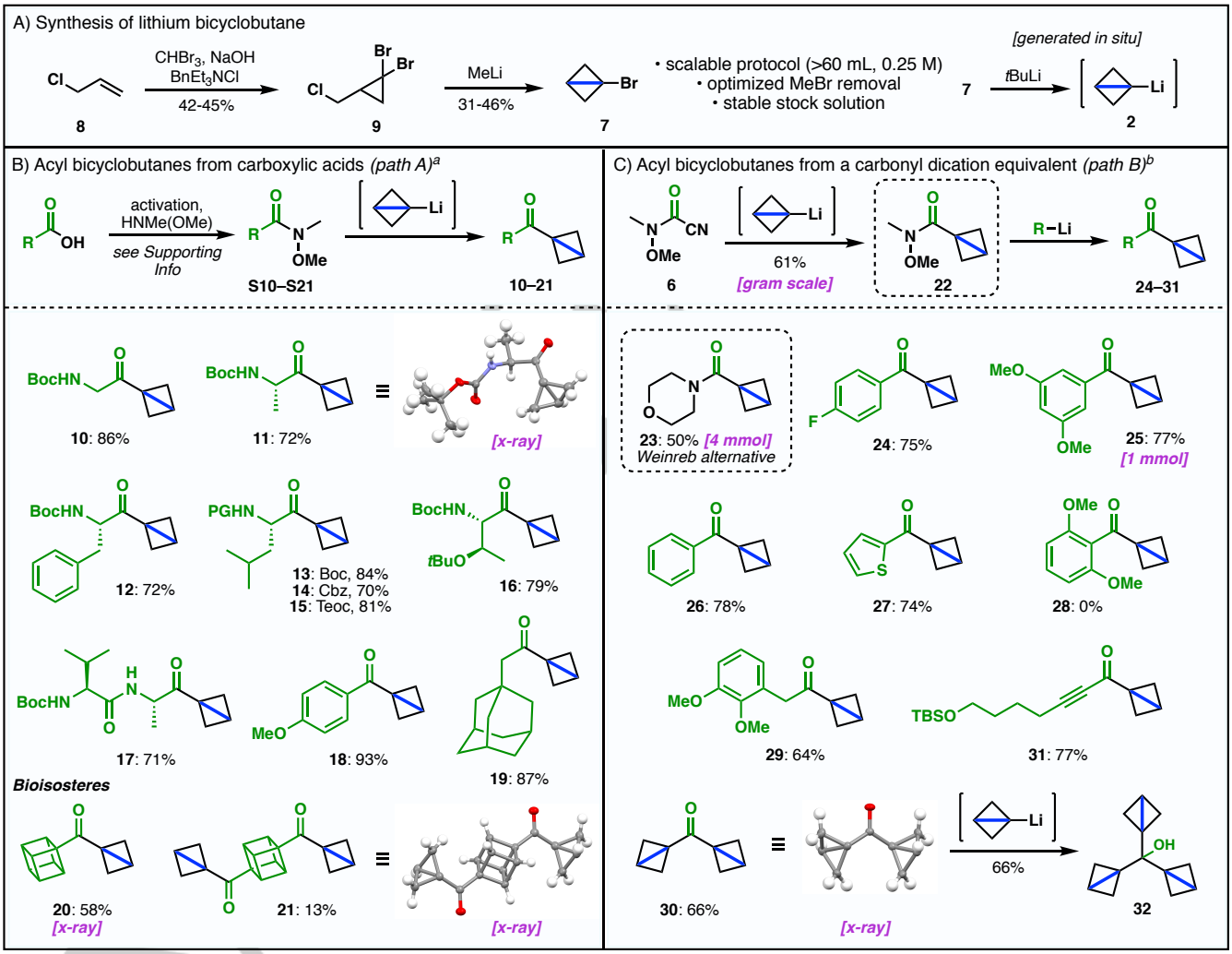
lithiated BCB **2**[19] (e.g. using alkyl chloroformates[19-20]); 2) transannular cyclization of cyclobutanes such as **3** *via* deprotonation and 1,3-elimination[3, 4b, 21]; and 3) intramolecular cyclopropanation of diazo precursors (e.g. **4**).[22] The latter approach has been rendered enantioselective[23] and has been judiciously exploited in a recent total synthesis.[24] Nevertheless, conventional approaches have not enabled access to a broad diversity of "parent" acyl BCBs bearing complex or densely functionalized R groups (see **1**); in many cases, such derivatives would require highly elaborate or intractable synthetic precursors. Examples of BCB ketones are particularly scarce with only a handful (e.g. R = phenyl[21b]; methyl[21c, 25]; isopropyl[25a]) reported to date.

In an effort to expand the scope of high-value BCB ketone analogues for synthetic applications, we identified carboxylic acids as ideal synthetic precursors—both abundant and readily available—with the rationale that acyl BCBs should be accessible from Weinreb amides **5** *via* treatment with lithiated BCB **2** (*path a*, Scheme 1C). We likewise envisaged that reagent **6**,[26] a powerful carbonyl dication equivalent, would serve as an inherently diversifiable precursor to acyl BCBs *via* unsymmetrical ketone synthesis[27] (*path B*, Scheme 1C). Remarkably, these nucleophilic acyl substitution pathways have not been explored in the literature. Herein, we report the realization of these endeavors, and disclose the preparation of over 20 structurally unique BCB ketones, encompassing aryl and alkyl derivatives, amino acids and dipeptides, high-value bioisosteres and bifunctional linchpin reagents. We additionally highlight the promising utility of these molecules for the functionalization of proteinogenic nucleophiles, underpinning future applications in selective peptide and protein modification.

We began to probe the feasibility of the proposed pathways through careful optimization of literature approaches to lithium BCB **2**[19, 28] *via* 1-bromo BCB **7**[29] (see Scheme 2A and the Supporting Information for details). To this end, cyclopropanation of allyl chloride **8**, followed by treatment of the resulting dibromocyclopropane **9** with MeLi readily afforded bromo BCB **7** on decagram scale. Removal of the equivalent



[a]Conditions for addition of Li-BCB **2** to Weinreb amides: Weinreb amide (1.0 equiv.), Li-BCB **2** (1.1 equiv. + 1.0 equiv. per N–H bond), THF, –78 °C, 5 min.
[b]Reaction conditions for sequential organometallic addition: **22** (1.0 equiv.), **R–Li** (1.0–1.6 equiv.), THF, –78 °C, 5 min.

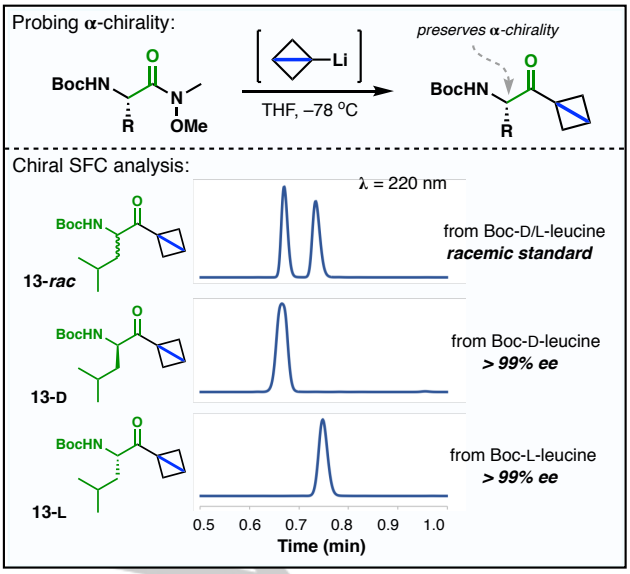
Scheme 2. A) Scalable approach to Li-BCB **2**; B) Synthesis of acyl bicyclobutanes from carboxylic acids; C) Acyl bicyclobutanes from linchpin reagent **22**.

of MeBr produced *via* Li-halogen exchange with MeLi was critical to the subsequent formation and application of lithium BCB **2** in nucleophilic acyl substitution chemistry. However, the thermal instability of 1-bromo BCB **7** and its structural similarities to MeBr complicated conventional purification by short-path distillation. In our hands, sparging and sonicating under a nitrogen atmosphere proved an optimal approach for removal of MeBr (see Supporting Information), affording stock solutions of bromo BCB **7** which were stable at low temperatures for several months. Generation of lithium BCB **2** by treatment with *t*BuLi[28] was carried out as required for immediate use *in situ*.

Initially, a set of alkyl Weinreb amides derived from protected amino acids—readily available in our laboratory—were prepared (see Scheme 2B and the Supporting Information). Reaction of Weinreb precursors with lithium BCB reagent **2** in THF at –78 °C afforded the expected acyl BCB derivatives of Boc-glycine (**10**), Boc-alanine (**11**), Boc-phenylalanine (**12**), and Boc-leucine (**13**) in 5 minutes and in excellent yields (> 70% in all cases). A diverse array of common α-amine protecting groups (e.g. Boc-leucine **13**, Cbz-leucine **14** and Teoc-leucine **15**) were well-tolerated, as was side-chain *tert*-butyl protection of threonine (**16**). In order to evaluate the consequences of BCB ketone synthesis on amino acid α-chirality, ketones derived from both L- (**13-L**) and D-Boc-leucine (**13-D**) were analyzed using chiral supercritical fluid chromatography (SFC) (see Scheme 3 and the Supporting Information). No erosion of α-chirality was observed, providing an important precedent for the generation of complex α-chiral BCB ketones. Dipeptide substrates were likewise suitable, with **17** isolated in 71% yield as a single diastereomer from the corresponding Weinreb amide. Importantly, all amino acid-derived acyl BCBs were stable to aqueous workup and column chromatography on silica gel. Several of the amino acid derivatives were isolated as crystalline solids (e.g. **11**) and structures confirmed by X-ray crystallography. Given the acid sensitivity of the bicyclobutane motif,[4b] however, particular care was taken to avoid exposure to acid (see Supporting Information).

In addition to novel amino acid electrophiles and chiral pool-derived acyl BCBs, we adapted the protocol to provide rapid access to aryl (**18**) and alkyl (**19**–**21**) ketones. A suite of unprecedented "Clickable" reagents, including for the installation of valuable bioisosteres (e.g. **19**, **20**, and **21**),[30] was accessible in two steps from the readily available carboxylic acid precursors. Notably, cubyl-BCB **20** and bifunctional, bis-BCB cubane **21** were isolated as crystalline solids and the structures confirmed by X-ray crystallography; these compounds were also stable to long-term storage (–25 °C) as solutions in benzene.

Encouraged by the proof-of-principle results with functionalized Weinreb derivatives, we were next interested in exploring the direct synthesis of BCB ketones *via* sequential organometallic addition to a carbonyl dication equivalent (*path b*, Scheme 1C). Reaction of lithium BCB **2** with Mander-type reagent **6**,[26] readily available in-house, afforded Weinreb intermediate **22**, resulting from initial substitution at the acyl cyanide. We envisioned **22** could serve as a valuable dielectrophile linchpin reagent and suitable precursor to diverse BCB analogues (see Scheme 2C).

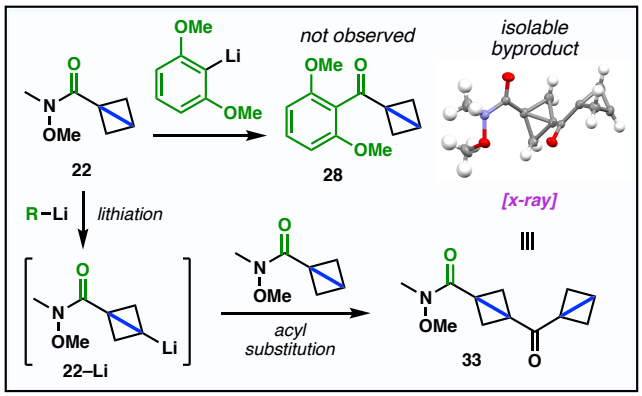


Scheme 3. Retention of amino acid α-chirality during acyl BCB synthesis.

Importantly, key intermediate **22** was accessible in 61% yield on gram-scale and was stable to long-term storage. Morpholino-amide **23** was also accessible using a similar strategy. Gratifyingly, treatment of Weinreb intermediate **22** with organolithium reagents enabled the divergent preparation of aryl (**24**–**26**), heteroaryl (**27**) alkyl (**29**, **30**), and alkynyl (**31**) BCB ketones. Reactions were carried out at –78 °C and were generally complete in 5 minutes (see Supporting Information for details). Interestingly, despite the electrophilicity of the BCB bridgehead carbon and the substantial p-character of the central bond,[31] organometallic reagents resulted exclusively in acyl substitution products rather than Michael-type additions[12] to afford ring-opened cyclobutanes. Products were stable to aqueous workup and column chromatography, although in some cases decomposition or polymerization (particularly of the highly activated aryl ketone derivatives) was observed when stored neat, even at low temperature. This process could be inhibited by the addition of a radical inhibitor (e.g. BHT).[3, 7c]

The reaction was notably responsive to steric bulk of the organometallic reagent, with synthesis of 3,5-dimethoxyphenyl ketone **25** proceeding in 77% yield (1 mmol scale), while the corresponding 2,6-dimethoxy product **28** was not observed. In the latter case, we observed formation of an intriguing self-condensation product **33** (see Scheme 4), which we postulate arises from lithiation of the ring junction to afford **22–Li** followed by acyl substitution with Weinreb reagent **22**.[32] While a deleterious pathway for the formation of aryl BCB **28**, facile bridgehead lithiation suggests that further diversification of BCB ketones (e.g. through trapping with suitable electrophiles[20]) may be feasible. Reaction of linchpin reagent **6** with excess lithium BCB **2** led to the one-pot formation of bis-BCB ketone **30**, a novel tri-electrophile, in 66% yield as a crystalline solid (Scheme 2C). Treatment of **30** with an additional equivalent of **2** afforded tertiary alcohol **32**, bearing an unprecedented arrangement of three BCB motifs. Such derivatives open new vistas for the study of strained hydrocarbons and highlight the versatility of

this approach for the synthesis of novel BCB analogues currently inaccessible using literature methods (see Scheme 1B).



Scheme 4. Bridgehead lithiation by bulky organometallic reagents.

With a toolbox of new acyl BCB derivatives in hand, our attention finally turned to probing the reactivity of these compounds with proteinogenic nucleophiles—an area of fundamental interest to our laboratory. Preliminary studies exploited aryl BCB ketone **25,** the synthesis of which was readily scalable. Compound **25** was predicted to be highly reactive on the basis of prior work by Azran and Hoz, which examined the effect of bridgehead EWGs on the reactivity of BCBs toward nucleophilic attack with NaOMe.[12] The authors of this study found that rate constants for the methanolysis of phenyl BCB ketone were over two orders of magnitude greater than the corresponding sulfonyl, ester, and cyano-substituted BCBs. Nevertheless, we observed that BCB derivative **25** maintained remarkable selectivity for cysteine over other potential nucleophilic residues (e.g. tyrosine, serine and lysine). Upon treatment with BCB **25** in the presence of Et_3N and THF, Boc-Cys-OEt reacted to form **34** as a mixture of diastereomers in 68% yield (Scheme 5A). The reaction was quenched at 45 minutes but proceeded nearly to completion in under 10 minutes. Prolonged reaction times (t = 51 h) led to eventual functionalization of Boc-Tyr-OMe (**35**, 73%), while no reaction occurred with Boc-Ser-OMe or Boc-Lys-OMe. Selectivity for cysteine was extended to dipeptide model Cbz-Lys-Cys-OMe **38**, bearing a free lysine amine. Reaction with the parent linchpin Weinreb-BCB reagent **22** afforded Cys alkylation product **39** in 69% yield, demonstrating the utility of BCB toolbox molecules for the late-stage installation of functional handles. The observed thiol reactivity of **22** was extended to *p*-methoxybenzyl thiol derivative **40**, which was accessible in 75% yield. Thiophenol derivatives bearing both electron-donating (**41**) and electron-withdrawing (**42** and **43**) substituents were likewise amenable to strain-release alkylation. Notably, the high-yielding synthesis of cubyl-thiophenol derivative **43** leverages BCB reagent **20** for rapid and efficient bioisostere incorporation. Further studies to evaluate the feasibility of employing acyl BCBs for the functionalization of bioactive small molecules, peptides, and proteins are currently underway in our laboratory and will be reported in due course.

In summary, we have developed two enabling strategies for the synthesis of high-value acyl BCBs from readily available precursors. Structurally novel strained carbocycles including amino acid, dipeptide, and bioisostere-derived BCB ketones are accessed for the first time, affording an unprecedented toolbox of "Clickable" electrophiles. We have demonstrated proof-of-principle for the application of these reagents in the selective modification of cysteine residues, laying the groundwork for future applications in peptide and protein modification and the design of covalent inhibitors. Given the rich chemistry of BCBs as versatile synthetic tools, we likewise envisage that the compounds reported herein will find broad application in organic synthesis and will serve as intriguing substrates for the continued study of strained cyclic motifs.

Acknowledgements

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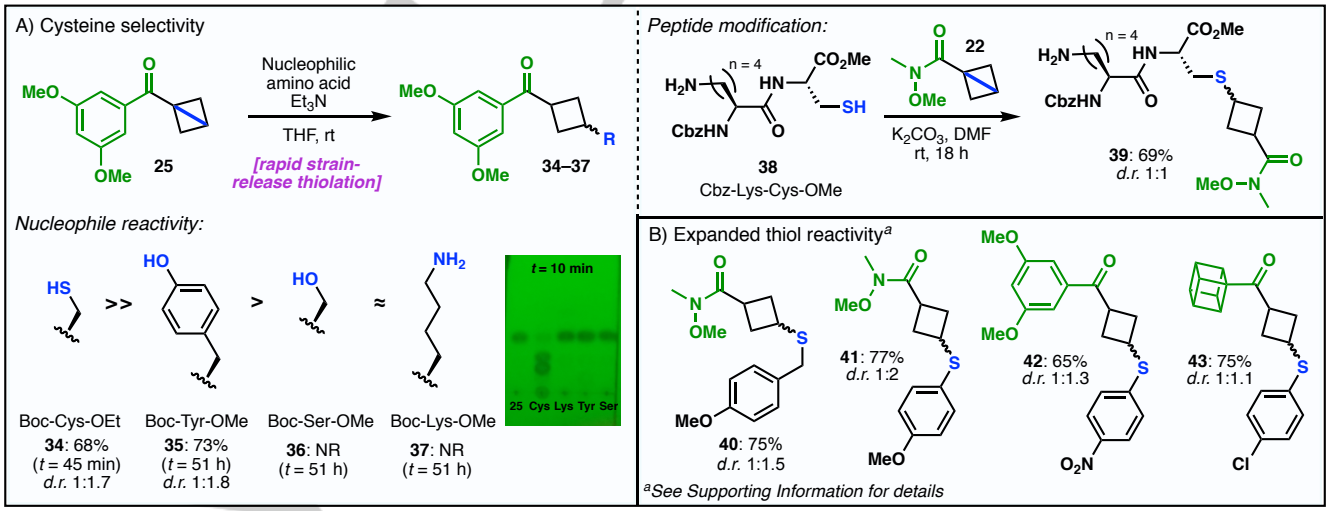

Scheme 5. A) Cysteine selectivity with BCB **25**; B) Strain-release thiolation.

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Keywords: amino acids • bicyclobutane • hydrocarbons • peptide modification • strained electrophiles

[1] A. von Baeyer, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2278.

[2] K. B. Wiberg, *Angew. Chem. Int. Ed.* **1986**, *25*, 312-322.

[3] K. B. Wiberg, R. P. Ciula, *J. Am. Chem. Soc.* **1959**, *81*, 5261-5262.

[4] a) A. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* **2006**, *106*, 4926-4996; b) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Schertler, J. Lavanish, *Tetrahedron* **1965**, *21*, 2749-2769; c) H. K. Hall Jr, A. B. Padias, *J. Polym. Sci. Pol. Chem.* **2003**, *41*, 625-635; d) I. R. Ramazanov, A. V. Yaroslavova, U. M. Dzhemilev, *Russ. Chem. Rev.* **2012**, *81*, 700-728.

[5] K. Chen, X. Huang, S. B. J. Kan, R. K. Zhang, F. H. Arnold, *Science* **2018**, *360*, 71.

[6] a) G. Ernouf, E. Chirkin, L. Rhyman, P. Ramasami, J. C. Cintrat, *Angew. Chem. Int. Ed.* **2019**, doi: 10.1002/anie.201908951; b) X. Ma, D. L. Sloman, Y. Han, D. J. Bennett, *Org. Lett.* **2019**, *21*, 7199-7203; c) R. M. Bychek, V. Hutskalova, Y. P. Bas, O. A. Zaporozhets, S. Zozulya, V. V. Levterov, P. K. Mykhailiuk, *J. Org. Chem.* **2019**, doi: 10.1021/acs.joc.1029b01947.

[7] a) P. Wipf, M. A. Walczak, *Angew. Chem. Int. Ed.* **2006**, *45*, 4172-4175; b) M. A. Walczak, P. Wipf, *J. Am. Chem. Soc.* **2008**, *130*, 6924-6925; c) M. A. Walczak, T. Krainz, P. Wipf, *Acc. Chem. Res.* **2015**, *48*, 1149-1158.

[8] A. Fawcett, T. Biberger, V. K. Aggarwal, *Nature Chem.* **2019**, *11*, 117-122.

[9] M. Silvi, V. K. Aggarwal, *J. Am. Chem. Soc.* **2019**, *141*, 9511-9515.

[10] a) R. Gianatassio, J. M. Lopchuk, J. Wang, C. M. Pan, L. R. Malins, L. Prieto, T. A. Brandt, M. R. Collins, G. M. Gallego, N. W. Sach, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *Science* **2016**, *351*, 241-246; b) J. M. Lopchuk, K. Fjelbye, Y. Kawamata, L. R. Malins, C. M. Pan, R. Gianatassio, J. Wang, L. Prieto, J. Bradow, T. A. Brandt, M. R. Collins, J. Elleraas, J. Ewanicki, W. Farrell, O. O. Fadeyi, G. M. Gallego, J. J. Mousseau, R. Oliver, N. W. Sach, J. K. Smith, J. E. Spangler, H. Zhu, J. Zhu, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 3209-3226.

[11] a) Y. Gaoni, *Tetrahedron Lett.* **1981**, *22*, 4339-4340; b) Y. Gaoni, *J. Org. Chem.* **1982**, *47*, 2564-2571.

[12] C. Azran, S. Hoz, *Tetrahedron* **1995**, *51*, 11421-11430.

[13] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.

[14] M. F. Debets, S. S. van Berkel, J. Dommerholt, A. T. Dirks, F. P. Rutjes, F. L. van Delft, *Acc. Chem. Res.* **2011**, *44*, 805-815.

[15] N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126*, 15046-15047.

[16] M. L. Blackman, M. Royzen, J. M. Fox, *J. Am. Chem. Soc.* **2008**, *130*, 13518-13519.

[17] Following initial studies by Baran and coworkers, a strain-release approach to peptide radioiodination was reported: P. Zhang, R. Zhuang, X. Wang, H. Liu, J. Li, X. Su, X. Chen, X. Zhang, *Bioconjug. Chem.* **2018**, *29*, 467-472.

[18] Ketones have found broad utility in both oxime and hydrazone ligation chemistry: D. K. Kölmel, E. T. Kool, *Chem. Rev.* **2017**, *117*, 10358-10376.

[19] J. Weber, U. Haslinger, U. H. Brinker, *J. Org. Chem.* **1999**, *64*, 6085-6086.

[20] a) Y. Gaoni, A. Tomazic, *J. Org. Chem.* **1985**, *50*, 2948-2957; b) Y. Gaoni, *Tetrahedron* **1989**, *45*, 2819-2840.

[21] a) V. V. Razin, N. V. Ulin, *Russ. J. Org. Chem.* **2003**, *39*, 33-39; b) S. Hoz, M. Livneh, *J. Am. Chem. Soc.* **1987**, *109*, 7483-7488; c) H. K. Hall, Jr., C. D. Smith, E. P. Blanchard, Jr., S. C. Cherkofsky, J. B. Sieja, *J. Am. Chem. Soc.* **1971**, *93*, 121-130.

[22] N. Ikota, N. Takamura, S. D. Young, B. Ganem, *Tetrahedron Lett.* **1981**, *22*, 4163-4166.

[23] a) C. Qin, H. M. Davies, *Org. Lett.* **2013**, *15*, 310-313; b) R. Panish, S. R. Chintala, D. T. Boruta, Y. Fang, M. T. Taylor, J. M. Fox, *J. Am. Chem. Soc.* **2013**, *135*, 9283-9286.

[24] R. A. Panish, S. R. Chintala, J. M. Fox, *Angew. Chem. Int. Ed.* **2016**, *55*, 4983-4987.

[25] a) L. Sydnes, L. Skattebøl, *Tetrahedron Lett.* **1975**, *16*, 4603-4606; b) W. Shi, F. Xiao, J. Wang, *J. Org. Chem.* **2005**, *70*, 4318-4322.

[26] a) J. Nugent, B. D. Schwartz, *Org. Lett.* **2016**, *18*, 3834-3837; b) J. Nugent, B. D. Schwartz, *Org. Synth.* **2017**, *94*, 184-197.

[27] The Sarpong group has recently published a pyrrole-derived carbonyl linchpin reagent for unsymmetrical ketone synthesis: S. T. Heller, J. N. Newton, T. Fu, R. Sarpong, *Angew. Chem. Int. Ed.* **2015**, *54*, 9839-9843.

[28] M. Kenndoff, A. Singer, G. Szeimies, *J. Prakt. Chem.* **1997**, *339*, 217-232.

[29] A. Düker, G. Szeimies, *Tetrahedron Lett.* **1985**, *26*, 3555-3558.

[30] a) T. A. Reekie, C. M. Williams, L. M. Rendina, M. Kassiou, *J. Med. Chem.* **2019**, *62*, 1078-1095; b) B. A. Chalmers, H. Xing, S. Houston, C. Clark, S. Ghassabian, A. Kuo, B. Cao, A. Reitsma, C. E. Murray, J. E. Stok, G. M. Boyle, C. J. Pierce, S. W. Littler, D. A. Winkler, P. V. Bernhardt, C. Pasay, J. J. De Voss, J. McCarthy, P. G. Parsons, G. H. Walter, M. T. Smith, H. M. Cooper, S. K. Nilsson, J. Tsanaktsidis, G. P. Savage, C. M. Williams, *Angew. Chem. Int. Ed.* **2016**, *55*, 3580-3585.

[31] a) M. D. Newton, J. M. Schulman, *J. Am. Chem. Soc.* **1972**, *94*, 767-773; b) D. R. Whitman, J. F. Chiang, *J. Am. Chem. Soc.* **1972**, *94*, 1126-1129.

[32] We were able to replicate the self-condensation reaction upon treatment of **22** with *t*BuLi as an alternative approach to the generation of **22–Li**. Presumably, *t*BuLi is too sterically encumbered to undergo direct nucleophilic acyl substitution. The observed bridgehead lithiation is reminiscent of Gaoni's work on the direct modification of BCB sulfones (see ref. 20).

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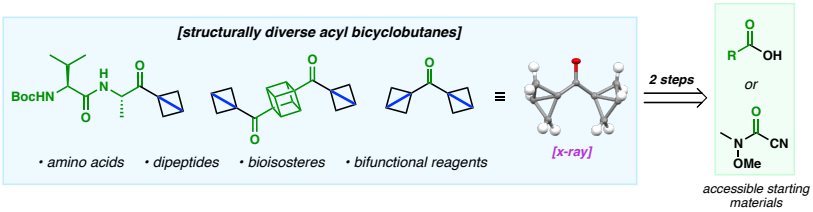

The preparation of an unprecedented toolbox of strained acyl bicyclobutane electrophiles—encompassing amino acids, dipeptides, bioisosteres, and bifunctional linchpin reagents—is reported from simple and readily available precursors.

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