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# Minimalistic graphical presentation approach for total syntheses

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ABSTRACT

We report a single image minimalistic presentation format for total syntheses, wherein on the foundation of a color-coded synthetic step/complexity chart are displayed the structure of the target molecule along with five key analysis parameters (total number of steps = **TNS**, longest linear sequence = **LLS**, oxidation reduction steps = **ORS**, protecting group steps = **PGS** and productive steps = **PS** percentage) for the synthetic blueprint. This purpose of this concise communication format is to enable rapid viewing and comparisons of target syntheses for the benefit of teaching, studying, and mastering synthetic organic chemistry.



## 1. Introduction

Like architecture, and other creative design disciplines, the synthesis of organic target molecules leaves the "synthetic architect" infinite room for expressions of creativity, strategic and practical choices as well as personal preferences for designing blueprints. Unlike architecture, even the most well thought out target blueprints in organic chemistry routinely fail or require major adjustments or reorganization of steps before succeeding. This frustrating and exciting reality is the result of many factors, such as a) limitations in predictability and generality of scope of reactions with respect to steric and electronic factors, b) shape and physical property challenges molecules present, c) functional group incompatibilities, d) stereochemical control issues, e) unexpected side reactions to name a few. Consequently, it is not surprising that total syntheses of natural products and pharmaceutical target structures often vary wildly in their approaches, efficiency, creativity and practical applications.

Many transformative and outstanding contributions have been made in the last 100 years toward formulating good design principles to aid synthetic chemists in effectively assembling target structure of interest. In this regard, following early seminal contributions from synthetic trailblazers Robinson [1] and Woodward [2], a number of important strategies focusing on a) retrosynthesis [3], b) useful chiral building blocks [4], c) atom economy [5], d) target function [6], e) ideality and efficiency [7], f) asymmetric catalysis [8] and g) informatics guided synthesis [9] as well as recent important advances in computational synthesis planning [10] all of which are recommended reading to anyone interested in achieving mastery in the exciting field of target-oriented synthesis. Beyond these synthesis planning concepts, the significant contributions of Green Chemistry Principles [11], and best industry practices whose goals are to achieve syntheses that are scalable, efficient, while producing the least amount of waste are parameters today's synthetic chemists should be well versed in.

Ideal syntheses are few and far apart and non-trivial to achieve. One example of ideal synthesis would be target syntheses involving a single step. In our survey of the literature, we were surprised learn how exceedingly rare one step total syntheses are. Shown in Fig. 1 is a recent one step total synthesis example from the Echavarren group [12], which showcases state of the art metal-catalysis cascade, which impressively transforms readily available starting materials geranyl acetone and acetylene, in the form of calcium carbide, into the natural product waitziacuminone employing gold catalysis.

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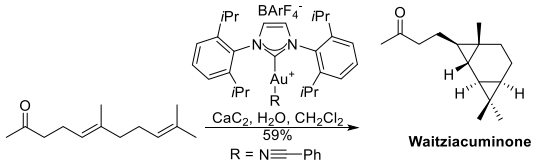


**Fig. 1.** Example of one-step total synthesis.

## 2. Results and discussion

In teaching advanced undergraduate and graduate students how to apply the fundamental concepts and reactions they have learned toward target oriented synthesis, the author(s) have found it instructive to analyze as well as compare multiple published syntheses of a target molecule of interest to convey the impact of synthetic blueprint designs, choices of disconnections and reactions as well as starting materials have on the synthesis. These teaching and training efforts have over time suggested to us a need to convey multiple important parameters simultaneously to enable more rapid and detailed insights and comparisons. This we concluded could be effectively accomplished using some type of image minimalism presentation approach, which is an area our group has been invested in making contributions to for some years [13].

When communicating multivariable content graphically it is easy to overload and present too much in one image resulting in deliverables that are not pleasing to look at or easy to decipher for a non-expert. The question then became what variables and information content should be presented for each synthesis to give the most informative insight and overview. For our teaching mission, we decided on the following five variables and their abbreviations [1]: *Longest linear sequence* (**LLS**) [2], *Total number of steps* (**TNS**) [3], *Oxidation and reduction steps* (**ORS**) [4], *Protecting group steps* (**PGS**), and [5] *Productive steps* (**PS**). Why these variables? We reasoned that the most communicated of these variables is "longest linear sequence" (**LLS**), thus making it essential to include. Since majority of target syntheses are non-linear or branched this parameter does not capture well all the blueprint design decisions, which is why we decided it was important to also capture "total number of steps" (**TNS**) employed. In this regards, for both parameters we count as a step an actual transformation that needs its own reagents, which means that even though some reaction sequences can be "telescoped" we still break them down. There are two reasons for this decision. The first one is pedagogical in that we want students to see the actual breakdown of reactions used. Secondly, even if multiple reactions are done in one-pot if each involves their own reagents there is clearly cost (even effort) involved (of materials/catalysts/reagents), which is why we concluded that to not count these as steps would be a mistake. The selection of the third and fourth variables, which we named "oxidation and reduction steps" (**ORS**) and "protecting group steps" (**PGS**), was inspired by the efforts of Baran and coworkers, who have put forth analyses and reviews highlighting redox [14] and protecting group [15] transformations as the "prime culprits" responsible for inefficiency (high step count) in syntheses. The fifth parameter we decided to include is an assessment of the steps taken in the synthetic journey towards the target structures. We call this parameter "productive steps" (**PS**), and it is displayed as a percentage, which is obtained by dividing the number of productive steps by the total number of steps (**PS%** = (**TNS**/**PS**)*100). We define any step wherein a bond is made, or atom added that can be found in the final structure to be productive. Notably, deprotection steps, where replacement of the protecting group with a hydrogen atom, are not counted as productive steps. This parameter provides the reader with a rough idea of how effective the synthetic blueprint was for a given synthesis. In addition, we concluded that it would be useful to indicate if a synthesis was asymmetric, as it is well known that realizing total syntheses that deliver enantiopure material can be a daunting synthetic challenge. Furthermore, for all asymmetric syntheses we also communicate if the source of chirality is from chiral pool or from asymmetric (catalytic) transformation. Molecular complexity as defined by Bottcher [16] building upon foundation laid by Bertz [17], and Hendrickson [18], and recent display and analysis applications to natural product syntheses by Shenvi [19], captivated us as these provide single image insights into each synthetic journey that complement well the above-mentioned essential parameters along with an image of the target structure. The graphical foundation for our single image presentation we decided would be a graph of molecular complexity vs LLS for each synthesis.

In honor of John L. Wood, who the corresponding author had the great privilege to start his natural product total synthesis journey with as a graduate student in his group, we chose to present all published total syntheses of the Wood group to date [20]. Presented in Table 1 is analysis data for these 27 total syntheses with TNS, LLS, ORS, PGS and PS% numbers for each synthesis. The productive step percentages (PS%), which range from 31 to 91%, serve as a reminder of how difficult it is to achieve high PS% with the total syntheses of hippolachnin A (91%) and hosieine A (89%) getting closest to that elusive goal with. It is important to note that these high scoring total syntheses both produced racemic target material. Current state of art of asymmetric reactions available and chiral pool starting material sources do not always lend them self readily to convert a total synthesis that delivers racemic final products into a minimally modified route that delivers enantiopure final target product. In the hosieine case, it appears that key gold-catalyzed transformation or alkyne addition steps can be modified to realize an asymmetric total synthesis without any loss of productive steps. The highest scoring asymmetric total syntheses are that of staurosporine (**PS** = 76%) and plagiochianin B (**PS** = 72%), which are most impressive synthetic design execution outcomes. Given

**Table 1**
Step analysis of John L. Wood total syntheses (1995–2021).

| Name | Year | TNS | LLS | ORS | PGS | PS% |
|---|---|---|---|---|---|---|
| Hippolachnin A | 2016 | 11 | 10 | 3 | 0 | 91% |
| Hosieine A | 2018 | 9 | 9 | 3 | 1 | 89% |
| Staurosporine | 1996 | 21 | 14 | 7 | 3 | 76% |
| Speradine E | 2018 | 8 | 7 | 1 | 3 | 75% |
| Plagiochianin B | 2021 | 18 | 13 | 5 | 3 | 72% |
| Latifolic Acid | 2001 | 7 | 7 | 5 | 1 | 71% |
| Cyclopiamide A | 2018 | 7 | 6 | 1 | 3 | 71% |
| Phyllantidine | 2020 | 14 | 14 | 5 | 4 | 71% |
| (+)-K252a | 1995 | 14 | 7 | 3 | 2 | 64% |
| Kalihinol C | 2004 | 25 | 25 | 12 | 4 | 64% |
| Securinine | 2012 | 19 | 19 | 6 | 2 | 63% |
| Herquline B | 2019 | 16 | 16 | 6 | 4 | 63% |
| Tetrapetalone C | 2017 | 29 | 25 | 14 | 6 | 62% |
| Tetrapetalone A | 2017 | 28 | 24 | 13 | 6 | 61% |
| Herquline C | 2019 | 15 | 15 | 6 | 4 | 60% |
| Citrinadin B | 2013 | 27 | 27 | 6 | 7 | 59% |
| Luminacin D | 2002 | 19 | 13 | 8 | 8 | 58% |
| Syringolide 1 | 1995 | 9 | 9 | 2 | 3 | 56% |
| Panepoxydone | 2000 | 11 | 11 | 5 | 5 | 55% |
| Phomoidride D | 2018 | 31 | 26 | 7 | 11 | 55% |
| Latifoline | 2001 | 13 | 9 | 6 | 3 | 54% |
| Aspergilline A | 2017 | 17 | 16 | 7 | 5 | 53% |
| Ingenol | 2004 | 38 | 37 | 16 | 10 | 47% |
| Welwitindolinone A | 2006 | 26 | 24 | 7 | 8 | 46% |
| Epoxysorbicillinol | 2001 | 12 | 12 | 2 | 4 | 42% |
| Caesalpinnone A | 2019 | 14 | 12 | 4 | 7 | 36% |
| Caesalpinflavan B | 2019 | 13 | 11 | 3 | 7 | 31% |

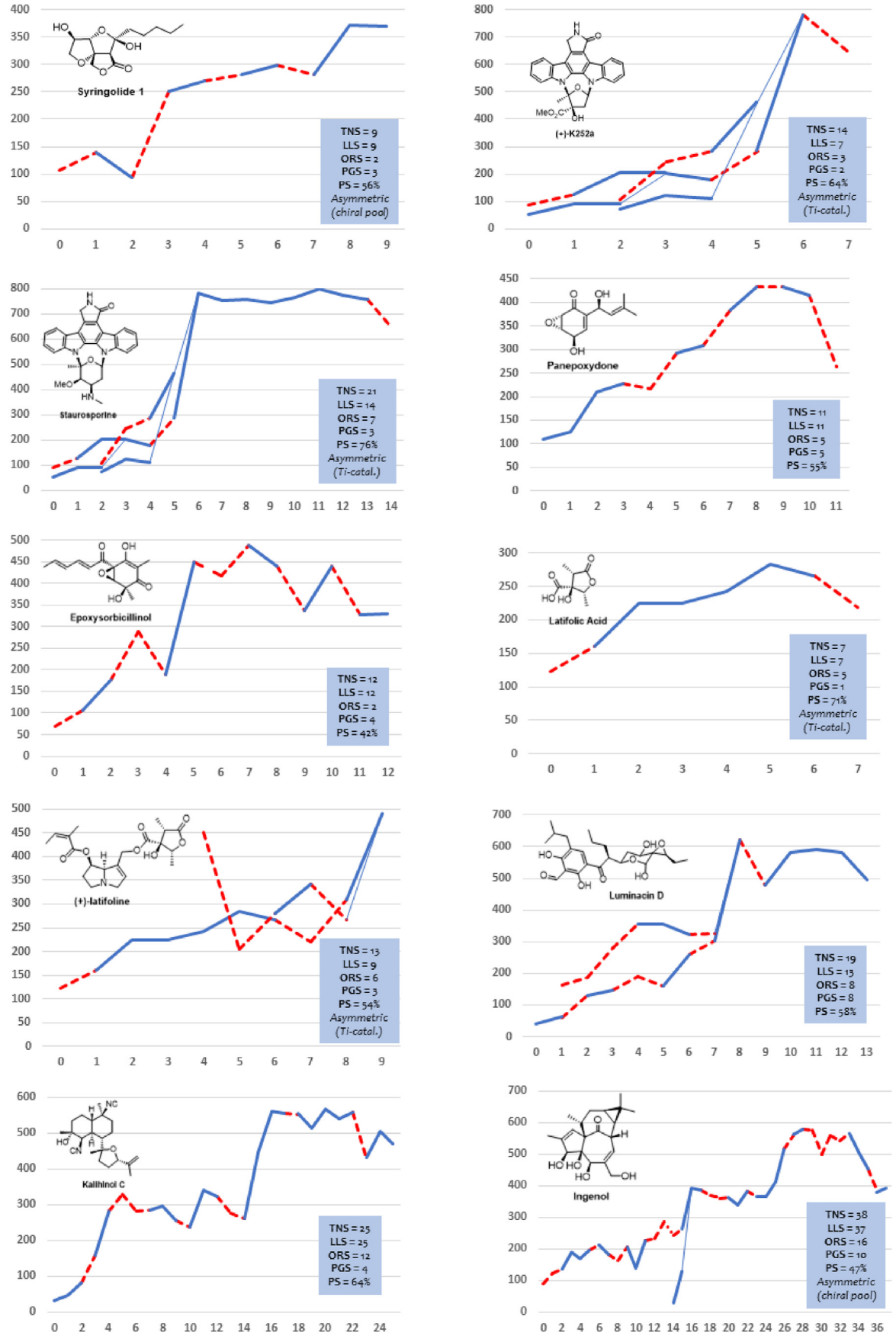


**Fig. 2.** Graphical representation of John L. Wood total syntheses (Part 1).

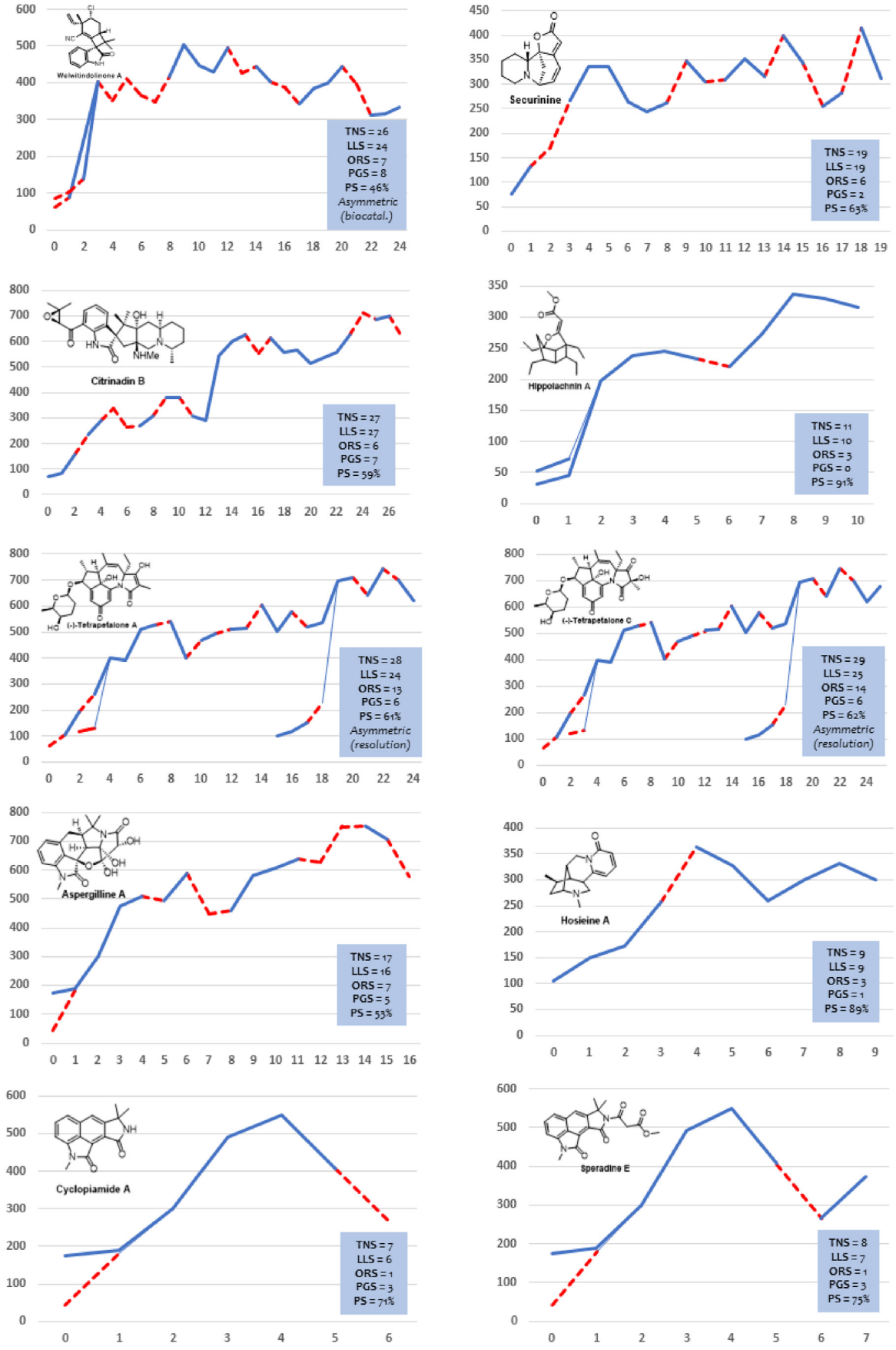


**Fig. 3.** Graphical representation of John L. Wood total syntheses (Part 2).

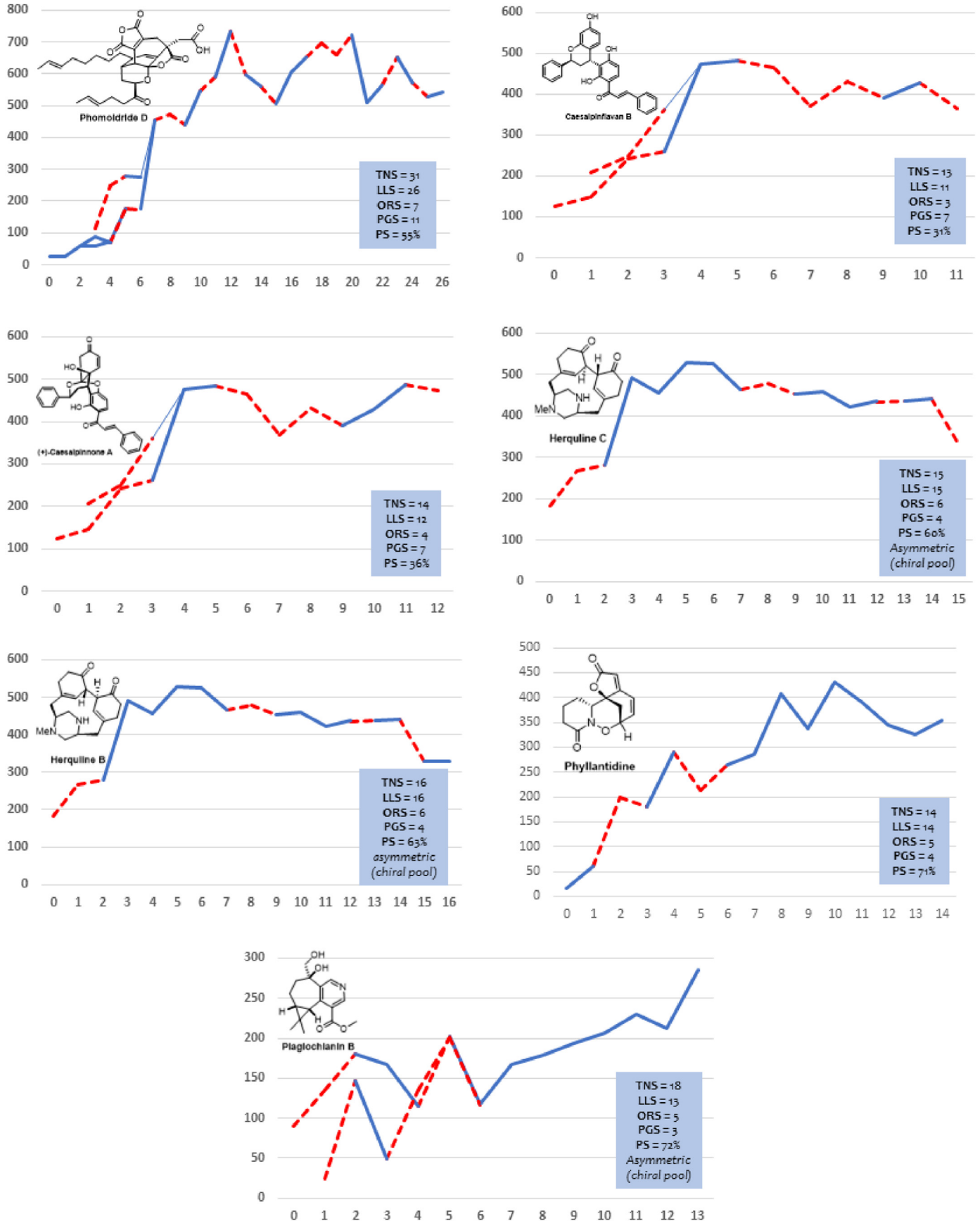


**Fig. 4.** Graphical representation of John L. Wood total syntheses (Part 3).

the difficulty of the target structures, achieving PS% in the 70%s and 60%s should be considered very good with 50%s being laudable in their own right.

We have carefully compiled this analysis data for each of the twenty-seven Wood group synthesis in the following three figures with syntheses presented chronologically (1995–2021). Our new single image graphical minimalism display for total syntheses includes three components [1]: structure of target molecule [2], a graph detailing the synthesis journey of the final synthetic blueprint serves as the graphical foundation with the x-axis representing the number of steps for the longest linear sequence (**LLS**) and the y-axis represents Bottcher's complexity parameter, and [3] a small concise databox displaying **LLS**, **TNS**, **ORS**, **PGS** and **PS**-percentage data for each target as well as information about if a synthesis is asymmetric with minimal insights about if asymmetric origin (chiral pool, asymmetric catalysis or other asymmetric reactions). Importantly, we have made two key changes that differ from earlier complexity/synthesis plots [21] that are aligned with our aspirations to provide maximum information content for a synthesis in a single image, by adding 1) color coding to indicate productive (blue lines) and unproductive steps (red dotes lines) and 2) reaction steps that are not associated with LLS are also displayed as separate lines that intercept (thin blue line is intercept point and not a step) with the core LLS-graph to provide a complete overview of all steps.

Comparisons of total syntheses of the same molecule is an excellent way to "get to know" the target structure and learn about strength and weaknesses of synthetic blueprints and specific design decisions and reaction choices (see Fig. 2, Fig. 3 and Fig. 4). To highlight the use of our minimalistic graphical analysis display for comparing total syntheses we have selected the natural product englerin A. Englerin A is an intriguing [3.2.1] oxabicyclic structure with a fused five membered ring and two ester side chains [22]. Because of its important biological profile and compact oxygenated structure, it has been pursued by many synthetic groups from around the world. We have analyzed 17 formal and total syntheses spanning the years 2010–2019, which represent all published englerin A total syntheses to date [23]. To allow formal syntheses to be compared to completed ones, we have used and analyzed the endgame steps for each formal synthesis from the synthesis their route overlapped with. Thirteen of the englerin A syntheses are asymmetric with the other four syntheses producing racemic englerin a. Given that this popular target represents contributions accomplished in the second decade of the 21st century (2010–2019), it is interesting to analyze the choices these research groups made for installing asymmetry (Fig. 5). Eight of the fourteen syntheses use chiral pool starting materials represented by (R)-citronellal, (R)-carvone, (−)-isopulegol, (R)-limonene and (R)-pantolactone. Asymmetric transformations developed by Sharpless and Noyori are employed to install asymmetry in three englerin A syntheses. Two more recent asymmetric reaction transformations, namely organocatalyzed aldol and rhodium catalyzed cycloaddition were selected by two of the eighteen groups. Hatakeyama's commercially available chiral ketone starting material falls in theory into either category as both chiral pool, and asymmetric transformation were utilized for its assembly. It is clear from these englerin A syntheses that chiral pool starting materials are still important for synthesis, with four of the five shortest asymmetric syntheses selecting such building blocks for their assemblies.

Analysis and graphical minimalistic presentation of the seventeen englerin A syntheses are presented in chronological order in Fig. 6. To enable better visual comparisons the x- and y-axes have been standardized, and the structure of englerin A has been omitted for clarity to avoid redundancies in presentation. Furthermore, our analyses revealed that these syntheses are all mostly linear, wherein LLS is almost equal to TNS and most side-chain steps being near identical, which is why we opted for further clarity to omit displaying these few steps in the comparison image. Our analyses have provided us with a rich and exciting dataset, wherein **TNS** = 10–32, **LLS** = 8–28, **ORS** = 1–13, **PGS** = 0–8, and **PS** = 80-41%. The **PS** percentages in particular highlights how challenging it is still in the year 2022 to achieve highly efficient (ideal) total syntheses. These seventeen research groups tackled this natural product target with the results of one group realizing productive step percentage of 80%, two groups 65%, 2 groups 50%+ with the remaining groups scoring 41–50%. As highlighted and popularized by Baran, oxidation/reduction steps (**ORS**) and protection group steps (**PGS**) are commonly the two reaction categories responsible for holding syntheses back from achieving ideality. This is quite apparent when analyzing englerin A syntheses, wherein the percentage of **ORS** used steps range from 10% to 50%, with the percentage range 0%–38% for PGS steps. It is important to note though that we count all **ORS** steps and do not differentiate between productive (strategic) and non-productive (non-strategic) in the total count, but we do clearly make this distinction in the color coding on the complexity chart and in the final **PS** percentages. Interestingly, the shortest and most efficient of the englerin A syntheses is from Chain (**LLS** = 8 and **TNS** = 10) whose synthetic blueprint masterfully navigated achieving the lowest score for these two troublesome analysis categories, with **PGS** = 0 and **ORS** = 1, which is an incredible achievement and a testament to their synthetic design and judicious choice of starting materials. The complexity plot nicely captures their synthetic journey, which in this exemplary case is a daredevil straight up the cliff climb without much hesitation. The last step represents installation of the last side chain by displacement of a leaving group of greater complexity than the nucleophile thus the drop in complexity.

## 3. Conclusions

In summary, we report a new minimalistic presentation of published total syntheses for the purpose of enabling the reader to rapidly learn about what a given synthetic blueprint accomplished

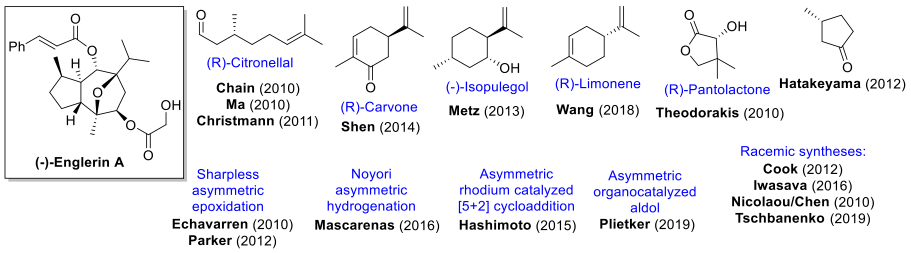


**Fig. 5.** Englerin A – chiral pool starting materials and asymmetric transformations.

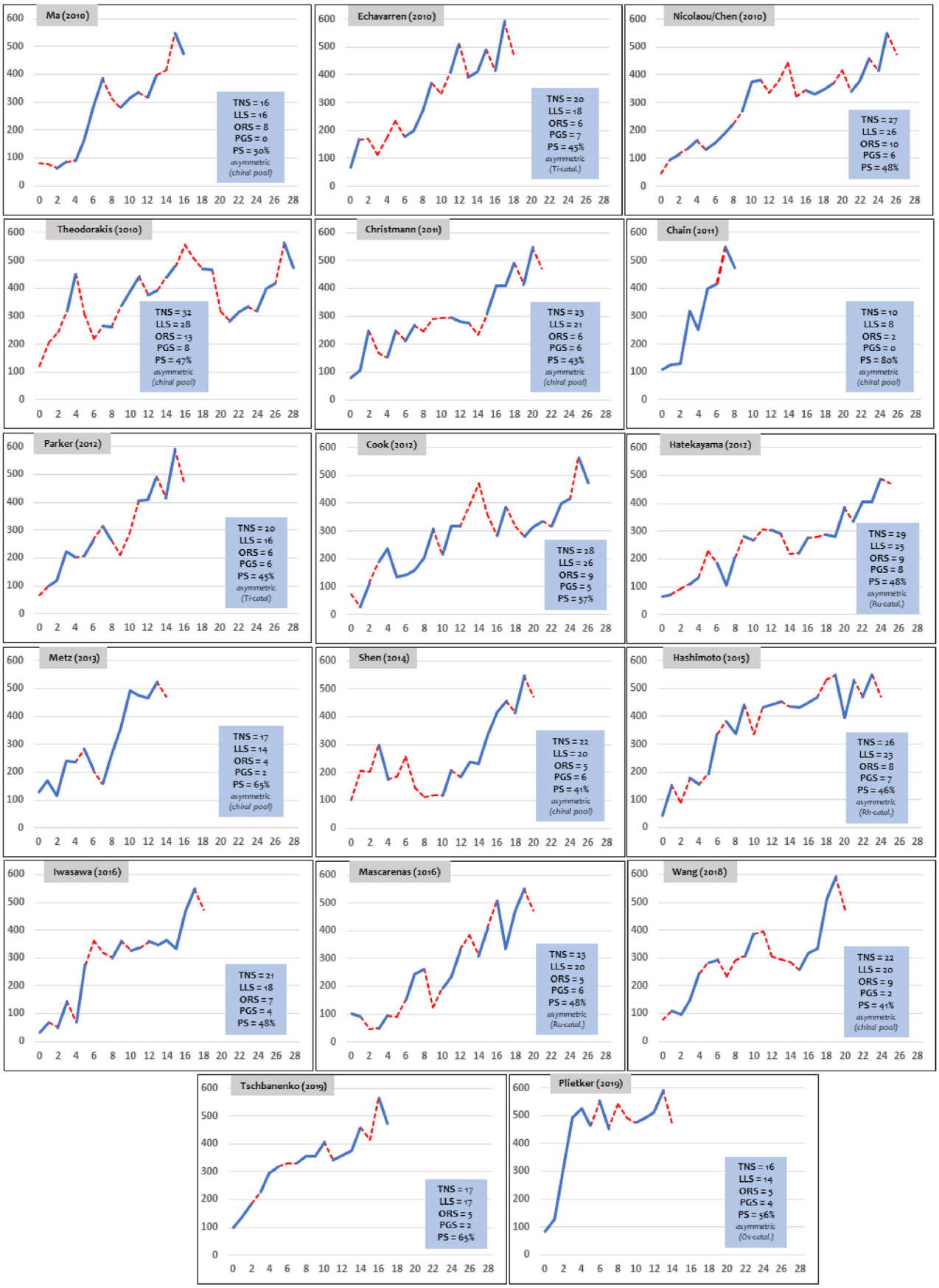


**Fig. 6.** Englerin a total syntheses comparisons.

and allow easy comparisons between total syntheses. This single image format includes a core color-coded graph displaying the steps of a synthesis using complexity parameter as well as structure of the target molecule and key analysis parameters (**LLS**, **TNS**, **ORS**, **PGS** and **PS**%) and if a synthesis is asymmetric. It is our sincere hope that this type of minimalistic presentation approach will find use and applications in teaching synthetic organic chemistry and to highlight how challenging it still is to achieve an outstanding total synthesis, which in turn suggests that field has a long, exciting way to go and is far from maturity and desperately in need of powerful new synthetic reactions, disconnections, and catalytic asymmetric transformations.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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## References

[1] R.A. Robinson, J. Chem. Soc. Trans. 111 (1917) 762–768.
[2] (a) R.B. Woodward, W.E. Doering, J. Am. Chem. Soc. 67 (1945) 860, 774;
(b) R.B. Woodward, F.E. Bader, H. Bickel, A.J. Frey, R.W. Kierstead, J. Am. Chem. Soc. 78 (1956) 2023–2025;
(c) R.B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, H. Vorbruggen, J. Am. Chem. Soc. 88 (1966) 852–853;
(d) R.B. Woodward, Pure Appl. Chem. 33 (1973) 145–178.
[3] (a) E.J. Corey, X. M., Logical of chemical synthesis **1989**, Wiley; E. J. Corey Angew. Chem. Int. Ed. 30 (1991) 455–465.
[4] (a) S. Hanessian, Acc. Chem. Res. 12 (1979) 159–165;
(b) S. Hanessian, Total Synthesis of Natural Products: the Chiron Approach, Pergamon Press, 1983.
[5] (a) B.M. Trost, Science 254 (1991) 1471–1477;
(b) B.M. Trost, B.M. Angew, Chem. Int. Ed. 34 (1995) 259–281.
[6] (a) P.A. Wender, V.A. Verma, T.J. Paxton, T.H. Pillow, Acc. Chem. Res. 41 (2008) 40–49;
(b) P.A. Wender, B.L. Miller, Nature 460 (2009) 197–201;
(c) P.A. Wender, Tetrahedron 69 (2013) 7529–7550.
[7] (a) T. Newhouse, P.S. Baran, R.W. Hoffmann, Chem. Soc. Rev. 38 (2009) 3010–3021;
(b) T. Gaich, P.S. Baran, J. Org. Chem. 75 (2010) 4657–4673;
(c) D.S. Peters, C.R. Pitts, K.S. McClymont, T.P. Stratton, C. Bi, P.S. Baran, Acc. Chem. Res. 54 (2021) 605–617.
[8] A.M. Walji, D. W. C., MacMillan Synlett (2007) 1477–1489.
[9] S. Woo, R.A. Shenvi, Acc. Chem. Res. 54 (2021) 1157–1167.
[10] (a) C.W. Coley, L. Rogers, W.H. Green, K.F. Jensen, ACS Cent. Sci. 3 (2017) 1237–1245.
[11] P.T. Anastas, J.C. Warner, Green Chemistry: Theory and Practice, Oxford University Press, New York, 1998.
[12] D. Scharnagel, I. Escofet, H. Armengol-Relats, M.E. Orbe, J.N. Korber, A.M. Echavarren, Angew. Chem. Int. Ed. 59 (2020) 4888–4891.
[13] a) N.A. McGrath, M. Brichacek, J.T. Njardarson, J. Chem. Educ. 87 (2010) 1348–1349;
(b) C. Draghici, J.T. Njardarson, J. Chem. Educ. 89 (2012) 1080–1082;
(c) E.A. Ilardi, E. Vitaku, J. T. Njardarson J. Chem. Ed. 90 (2013) 1403–1405;
(d) E.A. Ilardi, E. Vitaku, J.T. Njardarson, J. Med. Chem. 57 (2014) 2832–2842;
(e) B.R. Smith, C.M. Eastman, J.T. Njardarson, J. Med. Chem. 57 (2014) 9764–9773;
(f) E. Vitaku, D.T. Smith, J.T. Njardarson, J. Med. Chem. 57 (2014) 10257–10274;
(g) M.D. Delost, D.T. Smith, B.J. Anderson, J.T. Njardarson, J. Med. Chem. 61 (2018) 10996–11020;
(h) K.A. Scott, J.T. Njardarson, Top. Curr. Chem. 376 (2018) 1–34;
(i) P. Das, M.D. Delost, M.H. Qureshi, D.T. Smith, J.T. Njardarson, J. Med. Chem. 62 (2019) 4265–4311;
(j) K.A. Scott, M.H. Qureshi, P.B. Cox, C.M. Marshall, B.C. Bellaire, M. Wilcox, B.A.R. Stuart, J.T. Njardarson, J. Med. Chem. 63 (2020) 15449–15482;
(k) K.A. Scott, P.B. Cox, J.T. Njardarson, J. Med. Chem. 65 (2022) 7044–7072.
[14] N.Z. Burns, P.S. Baran, R.W. Hoffmann, Angew. Chem. Int. Ed. 48 (2009) 2854–2867.
[15] I.S. Young, P.S. Baran, Nat. Chem. 1 (2009) 193–205.
[16] T. Bottcher, J. Chem. Inf. Model. 56 (2016) 462–470.
[17] (a) S.H. Bertz, J. Am. Chem. Soc. 103 (1981) 3599–3601;
(b) S.H. Bertz, New J. Chem. 27 (2003) 860–869.
[18] (a) J.B. Hendrickson, J. Am. Chem. Soc. 97 (1975) 5784–5800;
(b) J.B. Hendrickson, P. Huang, G. Toczko, J. Chem. Inf. Comput. Sci. 27 (1987) 63–67.
[19] R.M. Demoret, M.A. Baker, M. Ohtawa, S. Chen, C.C. Lam, S. Khom, M. Roberto, S. Forli, K.N. Houk, R. Shenvi, J. Am. Chem. Soc. 142 (2020) 18599–18618.
[20] (a) J.L. Wood, S. Jeong, A. Salcedo, J. Jenkins, J. Org. Chem. 60 (1995) 286–287;
(b) J.L. Wood, B.M. Stoltz, H.-J., Dietrich J. Am. Chem. Soc. 117 (1995) 10413–10414;
(c) J.L. Wood, B.M. Stoltz, S.N. Goodman, J. Am. Chem. Soc. 118 (1996) 10656–10657;
(d) J.B. Shotwell, S. Hu, E. Medina, M. Abe, R. Cole, C.M. Crews, J.L. Wood, Tetrahedron Lett. 41 (2000) 9639–9643;
(e) J.L. Wood, B.D. Thompson, N. Yusuff, D.A. Pflum, M.S. Matthaus, J. Am. Chem. Soc. 123 (2001) 2097–2098;
(f) I. Drutu, E.S. Krygowski, J.L. Wood, J. Org. Chem. 66 (2001) 7025–7029;
(g) J.B. Shotwell, E.S. Krygowski, J. Hines, E. Koh, E.W.D. Huntsman, H.W. Choi, J.S. Schneekloth, J.L. Wood, C.M. Crews, Org. Lett. 4 (2002) 3087–3089;
(h) R. White, G.F. Keaney, C.D. Slown, J.L. Wood, Org. Lett. 6 (2004) 1123–1126;
(i) A. Nickel, T. Maruyama, H. Tang, P.D. Murphy, B. Greene, N. Yusuff, J.L. Wood, J. Am. Chem. Soc. 126 (2004) 16300–16301;
(j) S.E. Reisman, J.M. Ready, A. Hasuoka, C.J. Smith, J.L. Wood, J. Am. Chem. Soc. 128 (2006) 1448, 1448;
(k) J.-H. Chen, S.R. Levine, J.F. Buergler, T.C. McMahon, M.R. Medeiros, J.L. Wood, Org. Lett. 14 (2012) 4531–4533;
(l) K. Kong, J.A. Enquist, M.E. McCallum, G.M. Smith, T. Matsumaru, E. Menhaji-Klotz, J. L. Wood J. Am. Chem. Soc. 135 (2013) 10890–10893;
(m) M.E. McCallum, C.M. Rasik, J.L. Wood, M.K. Brown, J. Am. Chem. Soc. 138 (2016) 2437–2442;
(n) H.H. Dhanjee, Y. Kobayashi, J.F. Buergler, T. McMahon, M.W. Haley, J.M. Howell, K. Fujiwara, J.L. Wood, J. Am. Chem. Soc. 139 (2017) 14901–14904;
(o) M.C. Nakhla, J.L. Wood, J. Am. Chem. Soc. 139 (2017) 18504–18507;
(p) Y.-W. Huang, K. Kong, J.L. Wood, Angew. Chem. Int. Ed. 57 (2018) 7664–7667;
(q) M.C. Nakhla, K.N. Weeks, M.N. Villalobos, J.L. Wood, Tetrahedron 74 (2018) 5085–5088;
(r) J.C. Leung, A.A. Bedermann, J.T. Njardarson, D.A. Spiegel, G.K. Murphy, N. Hama, B.M. Twenter, P. Dong, T. Shirahata, I.M. McDonald, M. Inoue, N. Taniguchi, T.C. McMahon, C.M. Schneider, N. Tao, B.M. Stoltz, J. L. Wood Angew. Chem. Int. Ed. 57 (2018) 1991–1994;
(s) J.C. Timmerman, N.J. Sims, J. L. Wood J. Am. Chem. Soc. 141 (2019) 10082–10090;
(t) J.B. Cox, A. Kimishima, J.L. Wood, J. Am. Chem. Soc. 141 (2019) 25–28;
(u) K.M. Lambert, J.B. Cox, L. Liu, A.C. Jackson, S. Yruegas, K.B. Wiberg, J.L. Wood, Angew. Chem. Int. Ed. 59 (2020) 9757–9766;
(v) R.K. Jackson III., J.L. Wood, Org. Lett. 23 (2021) 1243–1246.
[21] (a) H.W. Whitlock, J. Org. Chem. 63 (1998) 7982–7989;
(b) M. Chanon, R. Barone, C. Baralotto, M. Julliard, J. B. Hendrickson Synthesis (1998) 1559–1583;
(c) R. Barone, M. Chanon 41 J. Chem. Inf. Comput. Sci. 41 (2001) 269–272;
(d) J.R. Proudfoot, J. Chem. Inf. Model. 53 (2013) 1035–1042.
[22] R. Ratnayke, D. Covell, T.T. Ransom, K.R. Gustafson, J.A. Beutler, Org. Lett. 11 (2009) 57–60.
[23] (a) K. Molawi, N. Delpont, A.M. Echavarren, Angew. Chem. Int. Ed. 49 (2010) 3517–3519;
(b) Q. Zhou, X. Chen, D. Ma, D., Angew. Chem. Int. Ed. 49 (2010) 3513–3516;
(c) K.C. Nicolaou, Q. Kang, S.Y. Ng, D.Y.-K. Chen, J. Am. Chem. Soc. 132 (2010) 8219–8222;
(d) J. Xu, J.E. Caro-Diaz, E.A. Theodorakis, Org. Lett. 12 (2010) 3708–3711;
(e) Z. Li, M. Nakashige, W.J. Chain, J. Am. Chem. Soc. 133 (2011) 6553–6556;
(f) L. Radtke, M. Willot, H. Sun, S. Ziegler, S. Sauerland, C. Strohmann, R. Frohlich, P. Habenberger, H. Waldmann, M. Christmann, Angew. Chem. Int. Ed. 50 (2011) 3998–4002;
(g) P. Gao, S.P. Cook, Org. Lett. 14 (2012) 3340–3343;
(h) K. Takahashi, K. Komine, Y. Yokoi, J. Ishihara, S. Hatakeyama, J. Org. Chem. 77 (2012) 7364–7370;
(i) J. Lee, K.A. Parker, Org. Lett. 14 (2012) 2682–2685;
(j) M. Zachel, A. Kesberg, P. Metz, Angew. Chem. Int. Ed. 52 (2013) 5390–5392;
(k) J. Zhang, S. Zheng, W. Peng, Z. Shen, Tetrahedron Lett. 55 (2014)

1339–1341;
(l) T. Hanari, N. Shimada, Y. Kurosaki, N. Thrimurtulul, H. Nambu, M. Anada, S. Hashimoto, Chem. Eur J. 21 (2015) 11671–11676;
(m) H. Kusama, A. Taqzawa, K. Ishida, N. Iwasawa, Chem. Asian J. 11 (2016) 64–67;
(n) R. Nelson, M. Gulias, J. Mascarenas, F. Lopez, Angew. Chem. Int. Ed. 55 (2016) 14359–14363;
(o) P. Liu, Y. Cui, K. Chen, X. Zhou, W. Pan, J. Ren, Z. Wang, Org. Lett. 20 (2018) 2517–2521;
(p) L. Guo, B. Plietker, Angew. Chem. Int. Ed. 58 (2019) 8346–8350;
(q) C. Reagan, G. Trevitt, K. Tchabanenko, Eur. J. Org. Chem. (2019) 1027–1037.