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Radical Retrosynthesis

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Abstract

In *The Logic of Chemical Synthesis*, E. J. Corey stated that the key to retrosynthetic analysis was a "wise choice of appropriate simplifying transforms" (Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York, 1989). Through the lens of "ideality", chemists can identify opportunities that can lead to more practical, scalable, and sustainable synthesis. The percent ideality of a synthesis is defined as [(no. of construction rxns) + (no. of strategic redox rxns)]/(total no. of steps) × 100. A direct consequence of designing "wise" or "ideal" plans is that new transformations often need invention. For example, if functional group interconversions are to be avoided, one is faced with the prospect of directly functionalizing C—H bonds (Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976; Brückl, T.; et al. *Acc. Chem. Res.* **2012**, *45*, 826). If protecting groups are minimized, methods testing the limits of chemoselectivity require invention (Baran, P. S.; et al. *Nature* **2007**, *446*, 404; Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193). Finally, if extraneous redox manipulations are to be eliminated, methods directly generating key skeletal bonds result (Burns, N. Z.; et al. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854). Such analyses applied to total synthesis have seen an explosion of interest in recent years. Thus, it is the interplay of aspirational strategic demands with the limits of available methods that can influence and inspire ingenuity. E. J. Corey's sage advice holds true when endeavoring in complex molecule synthesis, but together with the tenets of the "ideal" synthesis, avoiding concession steps leads to the most strategically and tactically optimal route (Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784; Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, 75, 4657).

Polar disconnections are intuitive and underlie much of retrosynthetic logic. Undergraduates exposed to multistep synthesis are often taught to assemble organic molecules through the combination of positively and negatively charged synthons because, after all, opposites attract. Indeed, the most employed two-electron C—C bond forming reactions today are those based upon either classical cross-coupling reactions (e.g., Suzuki, Negishi, or Heck) or polar additions (aldol, Michael, or Grignard). These reactions are the mainstay of modern synthesis and have revolutionized the way molecules are constructed due to their robust and predictable nature. In contrast, radical chemistry is sparsely covered beyond the basic principles of radical chain processes (i.e., radical halogenation). The historical perception of radicals as somewhat uncontrollable species does not help the situation. As a result, synthetic chemists are not prone to make radical-based strategic bond disconnections during first-pass retrosynthetic analyses.

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Notes

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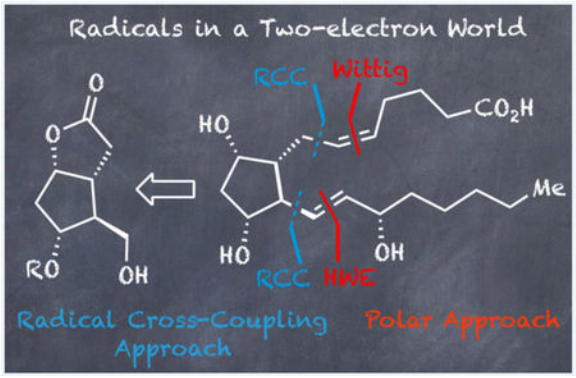
Recent interest in the use of one-electron radical cross-coupling (RCC) methods has been fueled by the realization of their uniquely chemoselective profiles and the opportunities they uncover for dramatically simplifying synthesis. In general, such couplings can proceed by relying on the innate preferences of a substrate (innate RCC) or through interception with a mediator (usually a transition metal) to achieve programmed RCC. This Account presents a series of case studies illustrating the inherent strategic and tactical advantages of employing both types of radical-based cross-couplings in a variety of disparate settings. Thematically, it is clear that one-electron disconnections, while not considered to be intuitive, can serve to enable syntheses that are more direct and feature a minimal use of protecting group chemistry, functional group interconversions, and nonstrategic redox fluctuations.

Graphical Abstract:



1. INTRODUCTION: TACTICS AND STRATEGIES IN RETROSYNTHETIC ANALYSIS

For the purposes of this Account, and to contextualize the role that a powerful reactivity platform has in retrosynthetic analysis, it is important to define and contrast *strategies* and *tactics*. Generally, a synthetic *strategy* is characterized by the specific bonds that are disconnected in retrosynthetic analysis. On the other hand, a synthetic *tactic* is specified as the reactivity mode by which a particular transform is accomplished. An example of this distinction is illustrated in Figure 1A through three completely different approaches to the natural product hapalindole Q(**1**). First, in 1993, Albizati disclosed an elegant synthesis of **1** utilizing a key Pd-catalyzed coupling between 3-bromoindole **2** and vinyl acetate **3**. This strategy maximizes convergence by forging a key sp^2–sp^3 bond (shown in green) through a two-electron enolate/aryl tactical manifold that was certainly bold for its era.[1] In retrospect, one caveat of this two-electron tactic is the requirement for the prefunctionalization or protection of both coupling partners (acylation or bromination) to achieve the desired chemo- and regioselectivity. To eliminate these concession steps (schematically highlighted in red hereafter), our lab enlisted a tactically different approach to **1** by exploiting the native reactivity of indole (**4**) and (*R*)- (–)-carvone (**5**).[2] The deprotonation of these two coupling partners, followed by oxidation with a Cu^{II} salt, allowed for their oxidative radical coupling. While strategically identical to the Albizati synthesis (same green bond forged), the single electron oxidation tactic enabled the minimization of concession steps toward **1**. Lastly, the

Kerr group demonstrated a strategic alternative from the former two examples. A Diels–Alder reaction between enal **6** and diene **7** afforded bicyclic indole **8**, which was later elaborated to hapalindole Q(**1**) through various functional group interconversions.[3] Kerr's retrosynthetic analysis constituted a stereoelectronically programmed strategy differing greatly from the one- or two-electron cross-coupling strategies. Thus, the advantages of a one-electron disconnection manifested in the form of increased ideality and diminished step count.

As exemplified by the prior case study, the power of radical cross-coupling (RCC) to minimize prefunctionalizations while retaining convergency and modularity was an early clue that it could be both a strategic and tactical asset.[4] From a broader perspective and by analogy to innate and guided C—H functionalization,[5b] two general categories of RCC can be identified (Figure 1B): *innate* and *programmed*. *Innate RCC* involves the generation of a radical (transient or persistent) and its subsequent addition to a radical acceptor. For instance, the Minisci reaction traditionally employs a carboxylic acid (**10**) as a radical precursor, and when combined with an activated heteroarene (**13**), the bond formation innately occurs at either the 2 or 4 position or both due to the electronics of the arene acceptor.[6] Similarly, radical addition to a *β*-substituted electron-deficient alkene (**12**) results in either a mixture of olefin isomers or predominantly the *E* isomer following extrusion of the X-group. The key aspect to note is that in either case, the regio- and stereochemical outcome is dictated by the innate bias of the radical acceptor component (see **16** or **17**).[7] *Programmed* RCC involves the generation of a radical (transient or persistent), which is intercepted by a mediator (for instance, a metal catalyst) that guides bond formation with a suitably functionalized partner. For example, a radical generated from a viable precursor (**9**–**11**) can be selectively coupled to a premetalated pyridine (**15**) heterocycle in the presence of a Ni- or Fe-based catalyst to deliver the product with substitution at the 3 position (**19**).[8] Similarly, Ni-catalyzed RCC can take place with the geometrically defined olefin **14** to give exclusively the *Z* olefinic product **18**.[9] Under programmed RCC, the stereo- and regiochemical outcomes (**18**–**19**), dictated by the organo-metallic species, are steadfast to their coupling partners and can result in selectivity orthogonal to their innately functionalized counterparts. The general mechanisms of two of these kinds of processes (HAT olefin functionalization and the coupling of a redox-active species) are depicted in Figure 1C. It is worth noting that one might consider homolytic aromatic substitution (Minisci) type processes to be outside the realm of a "cross-coupling" since the canonical definition holds that a transition metal is involved in the bond-forming step.[10] We note, however, that the area of "transition metal-free cross-coupling" (which encompasses many homolytic processes) has garnered main-stream acceptance in recent years.[11] Thus, to augment the way one considers how a radical can react with a substrate, we believe this classification is useful.

This Account explores the definitive strategic and tactical benefits that can result in the application of RCC in synthesis, regardless of the target. While many academic groups tend to focus on simplifying natural product synthesis, RCC applies to both traditional settings and ones with more translational impact (medicines, materials, agrochemicals, etc.). The

case studies outlined below call attention to the many interesting opportunities that exist to improve organic synthesis employing RCC versus conventional two-electron pathways.

2. TACTICAL APPLICATIONS OF RADICAL CROSS-COUPLING

2.1. Hydrogen Atom Transfer Radical Cross-Coupling

Hydrogen atom transfer (HAT) has emerged as a powerful way to tactically construct C—X and C—C bonds from olefin starting materials.[12] However, only in recent years has the latter type of bond been forged so as to access highly functionalized or congested systems. As olefins are among the most versatile, inexpensive, and ubiquitous functional groups, this approach has inherent pragmatic advantages.

Figure 2 illustrates several examples of HAT-mediated C—C bond construction. The two-electron based synthesis of glycoside derivative **20** (Figure 2A) required an arduous preparation of lithiated precursor **21** from olefin **25** prior to its coupling with Michael acceptor **22**.[13] Conversely, the one-electron tactic planned for the radical combination of synthons **23** and **24**. In practice, olefin **25** was used as a one-electron precursor in an innate radical coupling event with **22** under Fe catalysis with $PhSiH_3$ as a stoichiometric hydride source.[14] Similarly, ketone **26** was envisioned to arise from the RCC of a benzylic radical **27** with acceptor synthon **28** (Figure 2B). The coupling of olefins **29** and **30** proceeded smoothly under Fe catalysis to provide access to **26**, an important intermediate for drug discovery at Astra Zeneca. The two-electron pathway, theoretically arising from anion **31** and cation **32**, was not synthetically viable. Following a Michael addition between ketone **33** and enone **30**, chemoselective monoreduction of a single carbonyl was unsuccessful.[15] The superior chemoselectivity achieved through the radical pathway is another reminder of the orthogonality of one-electron chemistry over harsher polar alternatives.

Beyond enabling C—C bond formation, HAT RCC has also aided the construction of C—N bonds. Figure 3 depicts two examples that illustrate the power radical amination has over existing protocols. The synthesis of benzopyrazole **34**, an intermediate en route to a glucorticoid receptor modulator, was previously accessed through the coupling of an anionic amine **35** to a requisite tertiary carbocation (**36**). In practice, nitroarene **37** first had to be reduced to afford an intermediate aniline, which was coupled with aziridinyl electrophile **38**.[16] Comparatively, it was envisioned the concessional reduction could be avoided by combining radical synthons **39** and **40**. Tactically, the identical nitroarene (**37**) could be used in combination with the simple allylic amine **41**. The *in situ* formation of the tertiary radical with concomitant nitro-reduction of **37** promoted a smooth cross-coupling to afford **34** in one step. The same radical coupling tactic was also employed to synthesize diaminopyridine **42**, central to the synthesis of a reverse transcriptase inhibitor. The one-electron synthons **43** and **44** were envisaged to derive from the coupling of nitropyridine **45** and 2-methyl-2-butene (**46**), which, under Fe catalysis, were efficiently cross-coupled.[17] This process is favorable, as prior access to **42** from **45** and **47** suffered from two additional reduction steps and also demanded the use of the more expensive **47**.[18]

2.2. Redox-Active Ester Radical Cross-Coupling

While the utilization of olefins as radical precursors allowed for efficient access to valuable chemical space, the exploitation of carboxylic acids as RCC partners can also confer tactical benefits.[19] Generally, it was found that upon conversion of feedstock carboxylic acid starting materials to redox-active esters (RAEs, see Figure 4A for a representative list) through standard peptide coupling conditions, they were rendered competent RCC partners. It is notable that HOAt and HOBt esters, utilized for decades as activated esters for two-electron amide bond formation can be employed in these one-electron processes. By analogy to the widely employed HATU and HBTU reagents, HITU[20] and CITU[21] were introduced for the rapid installation of NHPI and TCNHPI groups, respectively. Additionally, other groups have reported utilizing native carboxylic acids in similar yet complementary RCC methodology featuring an electro-philic (rather than nucleophilic) coupling partner [22]. In a tactical sense, the combination of these RAEs with premetalated nucleophiles and a transition metal catalyst allowed them to participate in programmed, decarboxylative RCC reactions with inherent chemo- and regioselectivity advantages (Figure 4A).

For example, even the preparation of simple arenes such as 48 became facile via this one-electron pathway (Figure 4B). Prior synthesis of **48** required an Fe-catalyzed Friedel–Crafts event between bromobenzene (**50**) and cyclohexanol (**49**).[23] This affords a mixture of regioisomers and also requires nearly 0.5 equiv of Ag additive, while the decarboxylative cross-coupling between acid **51** and 4-bromophenylboronic acid (**52**) provided **48** as the sole product. Following *in situ* preparation of the RAE, the chemoselective Suzuki–Miyaura-type cross-coupling occurs while retaining the aryl bromide.[8] The orthogonality of the one-electron pathway is important, as selective reactivity of the Ni catalyst system provides sp^2–sp^3 coupling over a potential sp^2–sp^2 pathway involving the pendant aryl bromide.

Cubane, a rigid structural motif that is becoming more popular in medicinal chemistry, was also tactically functionalized through programmed RCC (Figure 4C). The planned coupling of radical **54** and aryl radical **55** allowed for the utilization of cubane monoester **56** and aryl zinc **57** as coupling partners under Fe catalysis. Hydrolysis of the cross-coupled product provided access to **53**, which could be used in further downstream RCC events.[24] In comparison, the prior route proceeded through a diiodide intermediate (not shown, derived from diacid **58**), subsequent arylation with **59**, and further lithiation/carboxylation with CO_2.[25] It is worth noting that a careful study of cubane cross-coupling concluded that two-electron (Pd-based) tactics were futile.[26]

Decarboxylative RCC has also allowed for the direct synthesis of unnatural amino acid derivatives (Figure 4D) such as **60**, which previously required a four-step sequence from aspartic acid derivative **61**. Ultimately, this two-electron sequence can be traced back to the coupling of alkynyl unit **62** and its requisite amino acid partner **61**, but nonstrategic manipulations detract from its conciseness and scalability.[27] By exploiting the radical synthon **63**, accessed from glutamic acid derivative **64**, **60** was synthesized in one step following its direct coupling to the alkynyl zinc **65**. This alkynylation reaction also proceeds on one-mole scale with little change in yield.[28] The ability to access unnatural amino acids

from their natural derivatives allows for near-ideal access to enantiopure building blocks with enabling applications in medicine and chemical biology.

2.3. Desulfonylative Radical Cross-Coupling

The sulfone functional group has been often associated with two-electron chemistry. For example, it serves as a useful handle for a variety of nucleophilic substitution reactions, with fluorination being one of the most prominent. Unfortunately, after efficient incorporation of the fluorine atom, a reductive radical desulfonation reaction is usually an ensuing concession step.[29] The invention of redox-active sulfones was premised on turning that concession step into a skeleton-building step through a productive RCC. The identification of *N*-phenyl sulfonyl tetrazoles as viable partners for RCC is a powerful tactic toward enabling the efficient incorporation of fluorine atoms into valuable synthetic intermediates.[30]

Figure 5 contains two examples where desulfonylative RCC provided a tactical advantage over existing syntheses. Recently, the synthesis of naphthalene **66** was reported using a Cu-catalyzed two-electron approach retrosynthetically exploiting synthons **67** and **68**.[26] A drawback to this approach was the preparation of a highly active nucleophile from **69** that required two concession steps to access **66**. In comparison, using sulfone **72** exploited radical synthon **71**, which was subsequently coupled under Ni catalysis with arylzinc **73**. This direct tactical approach obviates the necessity for toxic Sn reagents and prefunctionalization, providing a facile, programmable installation of the fluoromethyl moiety.[27]

Fluorinated intermediates like **74** (Figure 5B) can be deceptively difficult to synthesize using two-electron tactics. With no difluorinated synthetic precursor available, circuitous access to **74** required many concession steps from **75**, and the use of organostannane **76** as a carbonyl surrogate.[31] In stark contrast, RCC of synthons **77** and **78** is simple and direct starting from acetal **80** and difluorosulfone **79**. Following the sp^2–sp^3 RCC, a simple Pinnick oxidation provided **74** in two steps instead of eight.[26]

2.4. Tactical Combinations Exemplified with Pyrone-Terpenoids

Subglutinol B (**81**, Figure 6) is a representative member of a group of bioactive natural products wherein a pyrone is appended to a terpene framework.[32] This terpene family has attracted significant interest from the community, and all previous approaches featured two-electron based retrosyntheses. For example, Hong and co-workers' elegant synthesis of **81** proceeded from ester **82** in four steps. This intermediate was assembled through the two-electron incorporation of the side chains affording synthons **83** and **84**, experimentally realized through the union of fragments **85**–**87**, which in turn was derived from the Wieland–Miescher ketone. Installation of the vinyl tetrahydrofuran ring required two steps from tricyclic ketone **88**, and a further ten steps (7 concessional) were needed to access key intermediate **82**.[33] The one-electron approach allows access to **82** in a much more direct fashion in which synthons **89**–**91** logically allowed for the construction of **82** through RCC of the bicyclic alcohol **92**. This alcohol first underwent a series of oxidation reactions (one strategic) to construct acid **95**. Innate RCC of the carboxylic acid with **93** allowed for diastereoselective incorporation of the first side chain, while cleavage and oxidation of the

triethylsilyl ether unveiled another acid for functionalization. Decarboxylative alkenylation installed the isopropenyl group with high diastereocontrol. A final olefination provided **82**, which allowed for 15-step access to subglutinol B with 73% ideality. The tactical use of RCC solved a number of stereochemical issues and allowed for modular access to several other members of this terpene family.[34]

3. STRATEGIC APPLICATIONS OF RADICAL CROSS-COUPLING

The previous section outlined how existing plans can be streamlined and rendered more efficient by simply changing from a two-electron to a one-electron reactivity mode. This paradigm shift can also be applied to problems of a more strategic nature, where a new bond disconnection opens up a completely different retrosynthetic opportunity. As discussed below, the following case studies demonstrate the compelling advantages to be had in terms of efficiency, ideality, selectivity, and modularity.

3.1. Radical Cross–Coupling of Sulfinates

The use of sulfinate salts as radical precursors has found widespread utility in medicinal chemistry due to their predictable reactivity and easy handling.[6,35] Furthermore, they also provide retrosynthetic short-cuts and enable rapid scaffold diversification. For example, bipyridine **96** (Figure 7), an important compound in a Novartis drug-discovery program, was synthesized previously using a two-electron strategy. First, 2,5-dibromopyridine (**97**) was lithiated and acylated with **98**. This resultant trifluoromethylketone was then converted to a cyclopropane over a three-step bis-homologation sequence followed by a final Pd-catalyzed cross-coupling to deliver **96** in 3% yield.[36] The RCC strategy harnessed the power of sulfinates as radical precursors to perform a regioselective innate functionalization of pyridine **100**. Thus, direct radical trifluoromethylcyclopropanation with **101** gave an intermediate pyridyl boronic ester, which was then cross-coupled with **102** in the same pot to afford **96**. This is yet another striking example of one- and two-electron cross-coupling orthogonality as the Bpin functionality was perfectly compatible with the RCC step.[37]

3.2. Redox-Active Ester Radical Cross-Coupling

In nearly all discovery endeavors, a chemist’s ability to make modifications on an existing complex scaffold can be enabling and cost-effective.[38] Carboxylic acids are unique due to their ubiquity and stability, and functionalization beyond classic amide bond construction would prove useful. One such opportunity presented itself in the rapid late-stage incorporation of boronic acids (Figure 8). For example, **103** was previously synthesized through unifying synthons **104** and **105**, requiring the preparation of a “designer” borono-amino acid (**106**, Figure 8A).[39] From a practicality standpoint, the need to design several derivatives of **103** is arduous and time-consuming from a medicinal chemist’s perspective. In contrast, an RCC strategy exploits a late-stage modification through the coupling of boryl radical **107** with radical **108**. The acylated peptide **109** can then be directly converted to its borylated analog **103** in one step. Two other examples that demonstrate the power of this “acid swap” are shown in Figure 8B through the successful synthesis of a borono-vancomycin derivative and a novel elastase inhibitor.[40]

One of the most frustrating maneuvers in multistep synthesis involves the “retooling” of a carboxylic acid to an olefin, as it generally requires an oxidation state adjustment and the ensuing olefin formation often lacks chemoselectivity or complete stereocontrol. It is generally true that when accessed from a carbonyl (through Wittig or related processes) or another olefin (through cross metathesis), the mechanism of alkene incorporation onto a core scaffold dictates both of those factors. The next several case studies illustrate the strategic advantages of using a RCC-based approach to address this challenge (Figure 9). In Figure 9A, synthesis of the steroid derivative **110** under the conventional two-electron manifold required seven steps, two of which were strategic.[41] The RCC disconnection instead invokes an sp^2–sp^3 bond formation between **112** and **113** in which the olefin itself is a preformed alkenyl-zinc species (generated with complete geometric purity through stereospecific alkyne metalation). In practice, the RCC strategy has the same starting material as the Wittig approach but only involves two essential steps: acylation followed by decarboxylative alkenylation. Decarboxylative alkenylation also enabled a direct and convergent synthesis of α-tocotrienol (**114**) via the coupling of radical **115** with radical **116** (Figure 9B). Acid **117** (synthesized in 2 steps) was efficiently coupled under Ni catalysis with alkenyl zinc reagent **118** followed acetate cleavage to deliver **114**.[9] In contrast, the two-electron approach proceeded through a linear sequence involving Wittig olefination of aldehyde **119** followed by downstream alkylation with sulfone **121**. Notably, the stereoselectivity of the olefination is not complete (10:1 *E/Z*) compared with the RCC approach (>20:1 *E/Z*), and the needed concession steps detract from the ideality and efficiency of the two-electron strategy.[42]

Decarboxylative RCC has also been effective synthesizing biologically important classes of natural products (Figure 9C,D). In Corey’s landmark prostaglandin synthesis, a Horner–Wadsworth–Emmons reaction between phosphonate **124** and aldehyde **123** followed by a downstream Wittig olefination constituted key reactions for appending on the side chains (Figure 9C). Ultimately, though, intermediary concession steps detracted from the overall efficiency.[43] By employing synthon **126** in an RCC approach, it was imagined that the sequential coupling of radicals **127** and **128** would proceed with high *E/Z* stereospecificity thus allowing for rapid access to unnatural prostaglandin analogs. In practice, the decarboxylative coupling of **129** with organozinc **130** followed by subsequent lactone opening and a second alkenylation delivered intermediate **131** in only 3 steps. It is worth noting that even though the radical decarboxylation event is stereoablative, the innate bias of the substrate allows for a highly diastereoselective coupling of **129** and **130**.[9]

Diastereoselective RCC can also change the way one might consider the construction of recurring structural motifs. For example, installation of the 1,2-diol moiety has largely been associated with olefin oxidation or use of the chiral pool, which was employed in a two-electron approach to cladospolide C (**132**, Figure 9D) wherein the diol moiety was mapped onto a tartaric acid derivative **133**. Utilizing synthons such as **134**–**136** resulted in the need for multiple olefination reactions and nonstrategic redox manipulations to access **133**.[44] The use of RCC on tartaric acid significantly streamlines such a plan. Thus, sequential coupling of organozincs **140** and **141** to tartartic acid derivative **139** provided a concise formal synthesis, which proceeds in half the number of steps, in an order of magnitude higher yield, and with complete diastereocontrol.[9]

RCC-based logic can also be used to bring the celebrated modularity of cross-coupling to classic cycloaddition reactions whose scope is intimately tied to the idiosyncratic properties of the reaction partners. This was recently demonstrated with representative members of the canonical cycloaddition modes (2 + 1, 2 + 2, 3 + 2, and 4 + 2) wherein maleic anhydride essentially served as a surrogate for an ethylene diradical synthon **142** (Figure 10A). Thus, an almost limitless variety of enantiopure scaffolds (**143**) could be accessed from sequential cycloaddition, desymmetrization, and RCC.

Aside from accessing new chemical space, this strategy could be applied to simplify a number of existing routes in the literature. For example, while exploring epothilone derivatives, the Nicolaou group targeted cyclobutane fragment **144** (Figure 10B). A polar retrosynthesis yielded the nucleophilic partners **146** and **147** as synthons and the chiral cyclobutane **145**. Aldehyde **148** was prepared in three steps from a bis-protected *cis*-diol and subsequently functionalized by sequential Wittig reactions with **149** and **150** to install the alkyl chain. Next, a series of concession steps resulted in an intermediate aldehyde that was homologated with **149** giving **144** after hydrolysis and acylation. Thus, the two-electron analysis provides this fragment in ten total steps from **148** with six concession steps.[45] A one-electron analysis of the problem leads to a cyclobutane diradical synthon **151** whose equivalent can be accessed using a [2 + 2]-cycloaddition with maleic anhydride to furnish **152**. Starting from cycloadduct **152**, desymmetrization provided an enantiopure *trans*-cyclobutane. The first carbon–carbon bond was formed via activation and Fe-catalyzed RCC with Grignard **153**. Ester hydrolysis and activation of the resulting acid followed by Ni-catalyzed RCC with organozinc **154** provided the fragment core in only 4 steps. Deprotection of the silyl ether, acylation, and hydroboration and oxidation of the alkyne yielded epothilone intermediate **144** in six steps, two being two nonstrategic. The modular nature of RCC provides a concise approach to the desired enantiomer by employing convergence and minimizing concession steps.[46]

Saphris (asenapine, **155**, Figure 11) is an FDA-approved antipsychotic currently marketed as a racemate despite the (+)-enantiomer exhibiting more favorable pharmacokinetics. This near-symmetric molecule is a challenge to rapidly procure with two-electron disconnections (*vide infra*) but straightforward using a cycloaddition–RCC strategy employing symmetrical diradical synthon **157**. The adduct of maleic anhydride with the simplest azomethine ylide (**158**) could be enantiose-lectively methanolyzed, activated, and subjected to RCC with organozinc **159** to install the first aryl ring. Ester hydrolysis, activation, and a second RCC event with organozinc **160** delivered **156** after N-methylation. The use of this RCC strategy exploited the modular nature of cross-couplings to install similarly functionalized arenes where selectivity issues could be mitigated.[43] It is instructive to compare the radical-based route to a more conventional polar analysis as was reported by Chandrasekhar in 2016.[47] Initially, allylic alcohol **161** (synthesized in 10 steps) was esterified with acid **162** under Mitsunobu conditions, thereby setting the stage for an Ireland–Claisen rearrangement, which proceeded with 9:1 selectivity. The resultant acid was methylated, and oxidative cleavage of the intermediate olefin provided an aldehyde. Global reduction using DIBAL-H, tosylation of the diol, and substitution with methylamine provided tricycle **156**.

3.3. Redox-Active Sulfone Radical Cross-Coupling

Just as carboxylic acids, olefins, and halides have earned a strategic role in programmed RCC reactions, the sulfone group has also emerged as an important functional handle for rapid molecular diversification. Through using various two-carbon linchpin reagents bearing a sulfone, the strategic simplification of complex targets can be achieved through successive RCC transformations (Figure 12). For example, a hybrid one- and two-electron approach had previously provided access to building block **163** (Figure 12A). Although the key aryl–alkyl bond was made through a Ni-mediated cross-coupling with an alkyl iodofluoride, its incorporation required the multistep homologation of **165** with malonate **164** followed by two decarboxylations. Thus, the synthesis of **163** took place in six steps, three of which were functional group interconversions.[48]

In comparison, the RCC pathway to **163** exploited the use of radical synthons **167**–**169**. Decarboxylative Giese addition of **170** to sulfone **171** allowed for facile incorporation of the fluoroethyl unit. RCC of arylzinc **172** with the intermediate redox-active sulfone provided **163** in only two steps.[26] In contrast to diethylmalonate (**164**), whose sole purpose was to serve as a halide surrogate, vinyl sulfone **171** enabled both bis-homologation and direct functionalization. The synthesis of difluoride **173** (Figure 12B) was also efficiently accomplished through the use of a different linchpin sulfone (**176**, exemplified by diradical synthon **174**). Using piperidine **175**, an initial decarboxylative radical addition to **176** resulted in an intermediate sulfone that was subsequently difluorinated under basic conditions with NFSI. Finally, desulfonylative RCC concluded the concise one-electron access to **173**.[26] The two-electron route to this same compound required eight steps, only three of which were strategic. Furthermore, the crucial fluorination step utilized HF and provided no opportunity for synthetic modularity (i.e., variable F incorporation), a vital aspect of expedited discovery campaigns. While the two-electron synthons from polar retrosynthetic analysis seem straightforward because they originate from carbonyl chemistry, the lack of chemoselectivity limits its overall efficiency.[49] Whereas incorporation of F atoms usually dictates the focus of a retrosynthetic analysis, RCC simplifies and modularizes the approach as it treats such functionality no differently than any other substituent (such as a methyl group).

4. CONCLUSION

Pursuing ideality in synthesis is essentially a forcing function for invention, imploring chemists to design more selective, efficient, and *wise* transformations. To this end, RCC has proven to enable the concise synthesis of natural products, pharmaceutically relevant intermediates, and exotic architectures such as cubanes and boronic acids. One key feature of the RCC transforms is the exploitation of both feedstock chemicals (olefins, carboxylic acids) and designed functionality (sulfones) as handles for controlled bond formation. In contrast to two-electron based cross-coupling platforms, RCC is especially useful for the construction of sp^3–sp^x bonds in a manner that is mild, chemoselective, and orthogonal. Although polar disconnections permeate the fabric of retrosynthetic analysis, the incorporation of radical and homolytic disconnections can often provide an exciting opportunity to maximize ideality. For the reasons outlined above and illustrated throughout

this Account, one can anticipate the broad adoption of one-electron based coupling transforms having a net positive effect on the logic of chemical synthesis.

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Biographies

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Stephen Harwood was born in California in 1995 and received his undergraduate education from University of California, Berkeley, in 2017 conducting research under Professor Thomas Maimone. Currently, he is a graduate student in Professor Baran's research group investigating radical cross-coupling strategies in the total synthesis of terpene natural products.

Phil S. Baran was born in New Jersey in 1977 and received his undergraduate, graduate, and postdoctoral education from NYU, Scripps, and Harvard, respectively. Since returning to Scripps in 2003, his laboratory has been dedicated to the study of fundamental organic chemistry.

ABBREVIATIONS

CITU	tetrachloro-*N*-hydroxyphthalimide tetramethyluronium hexafluorophosphate
HAT	hydrogen atom transfer
HATU	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxide hexafluorophosphate
HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HITU	*N*-hydroxyphthalimide tetramethyluronium hexafluorophosphate
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	hydroxybenzotriazole
NFSI	*N*-fluorobenzenesulfonimide
NHPI	N-hydroxyphthalimide

RAE	redox-active ester
RCC	radical cross-coupling
TCNHPI	*N*-hydroxytetrachlor-ophthalimide

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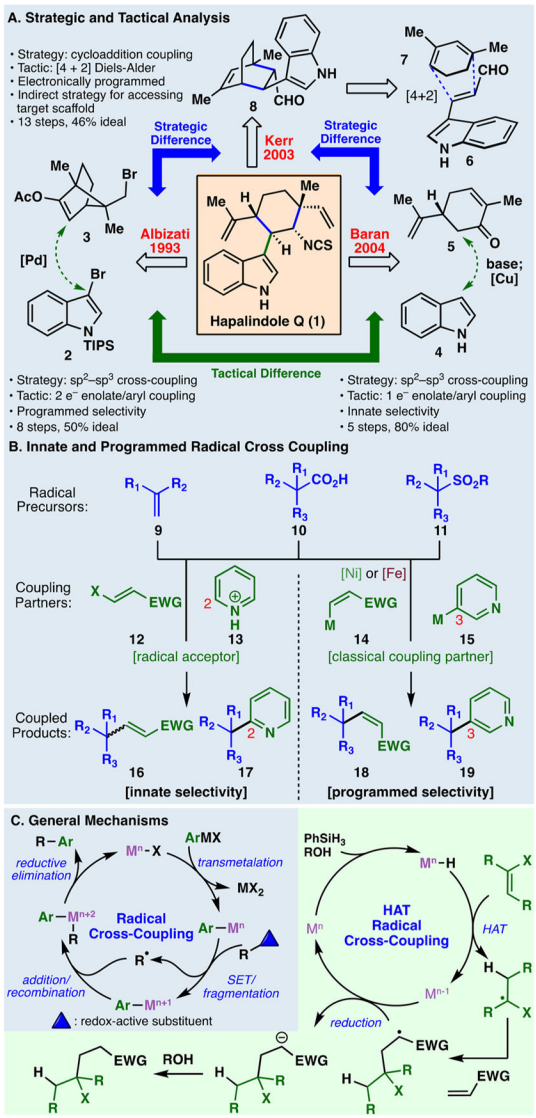

Figure 1.

(A) Tactical and strategic retrosynthesis, (B) types of radical cross-coupling, (C) RCC mechanisms.

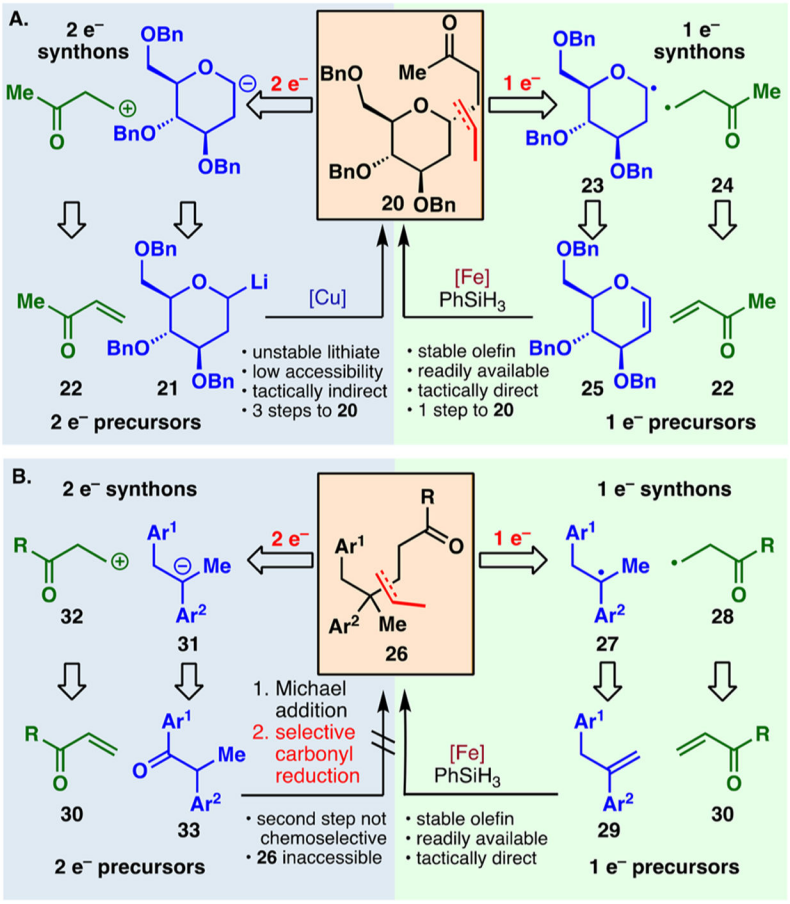

Figure 2.
Tactical approaches to (A) glycan **20** and (B) ketone **26**.

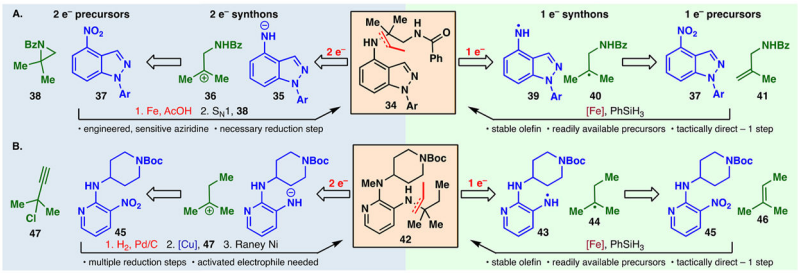

Figure 3.
Tactical approaches to (A) benzopyrazole **34** and (B) pyridine **42**.

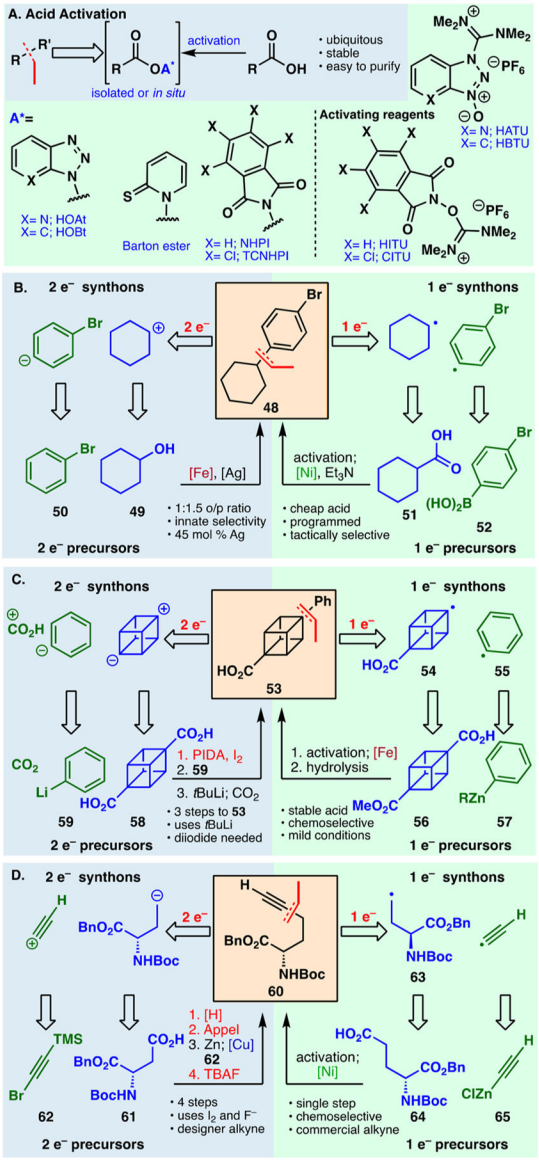

Figure 4.

RAE formation (A) and tactical approaches to (B) bromide **48**, (C) cubane **53**, and (D) alkyne **60**.

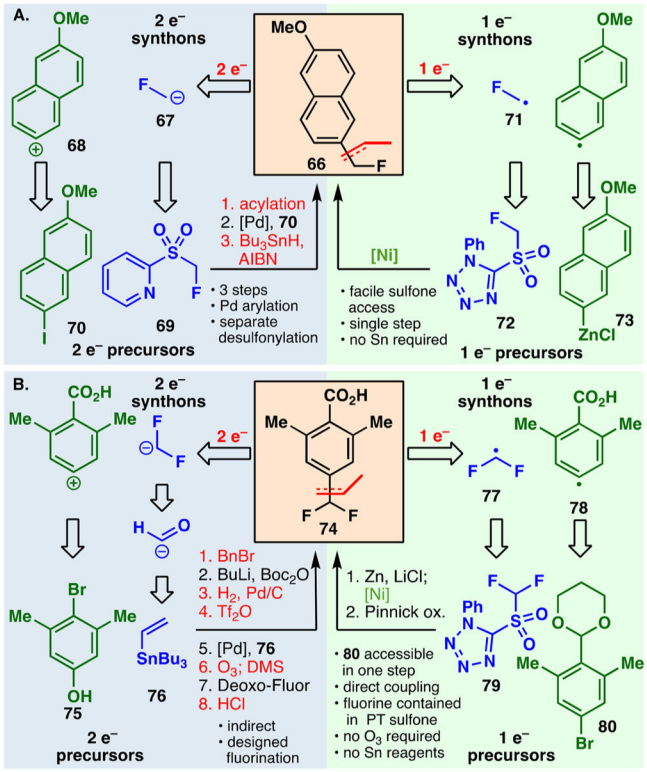

Figure 5.

Tactical approaches to (A) naphthalene **66** and (B) difluoride **74**.

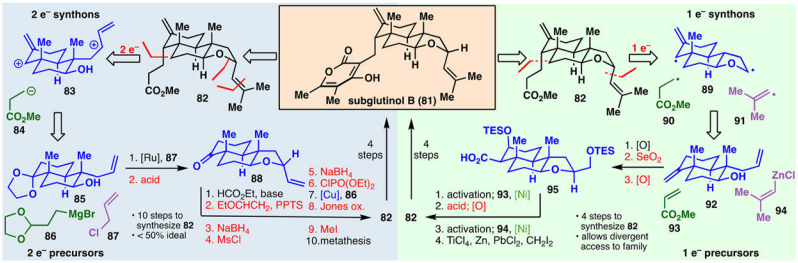

Figure 6.
Tactical approaches to subglutinol B (**81**).

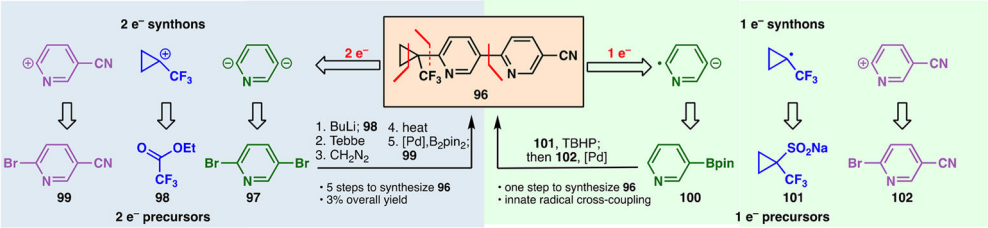

Figure 7.
Strategic approaches to bipyridine **96**.

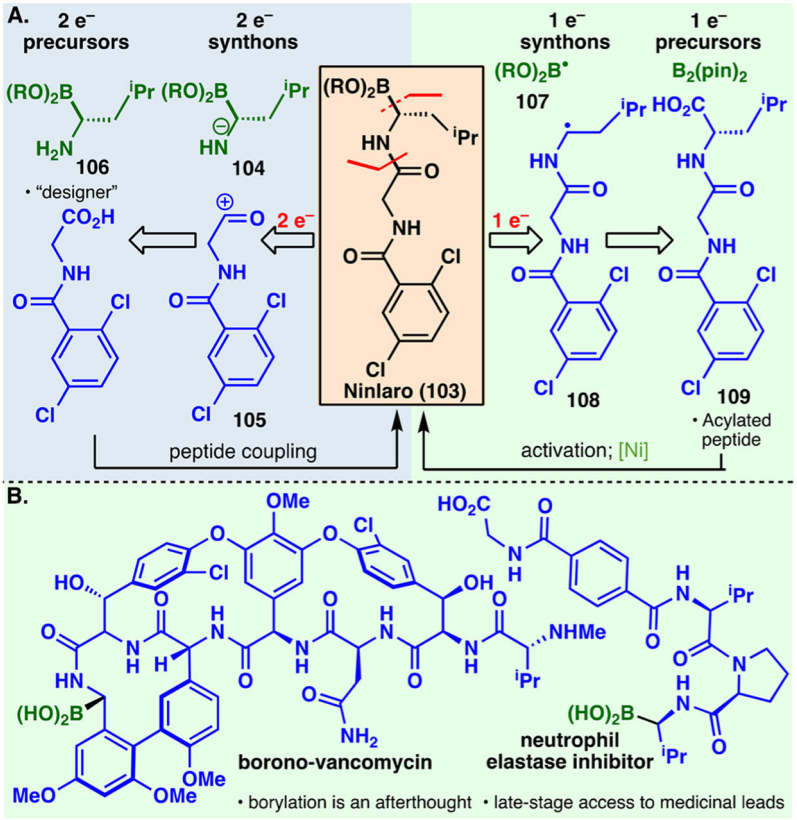

Figure 8.

(A) Strategic approaches to Ninlaro (**103**) and (B) representative boronic acids accessed by decarboxylative RCC.

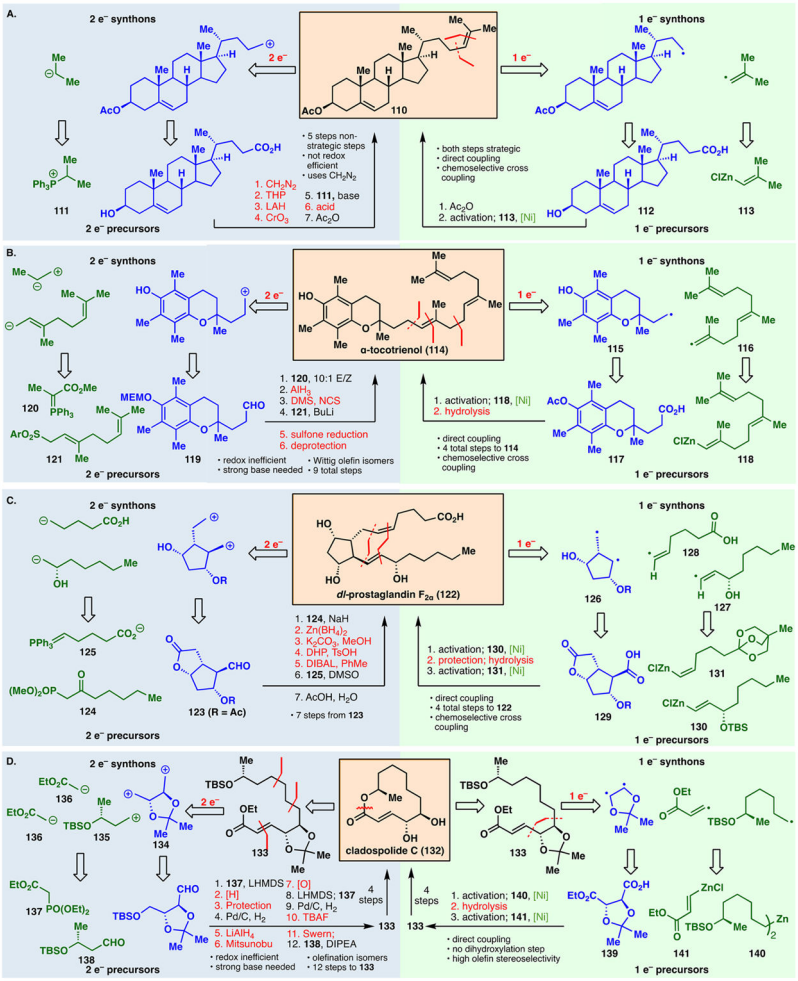

Figure 9.

Strategic approaches to (A) steroid **110**, (B) α-tocotrienol (**114**), (C) $PGF_{2\alpha}$ (**122**), and (D) cladospolide C (**132**).

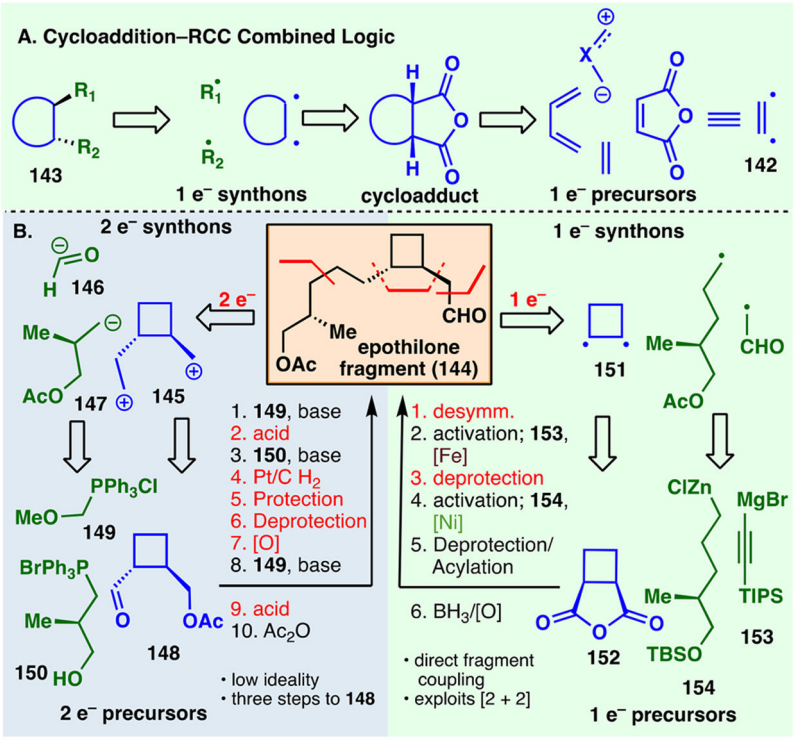

Figure 10.

(A) Combined cycloaddition–RCC retrosynthetic logic and (B) strategic approaches to aldehyde **144**.

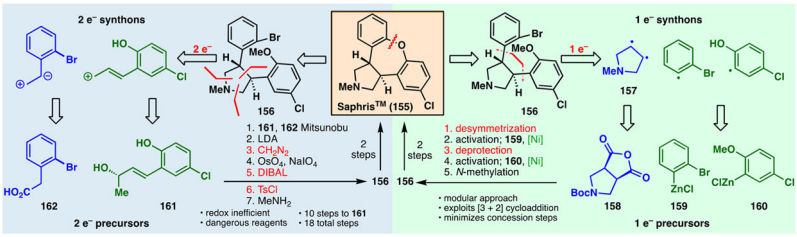

Figure 11.
Strategic approaches to Saphris (asenapine, **155**).

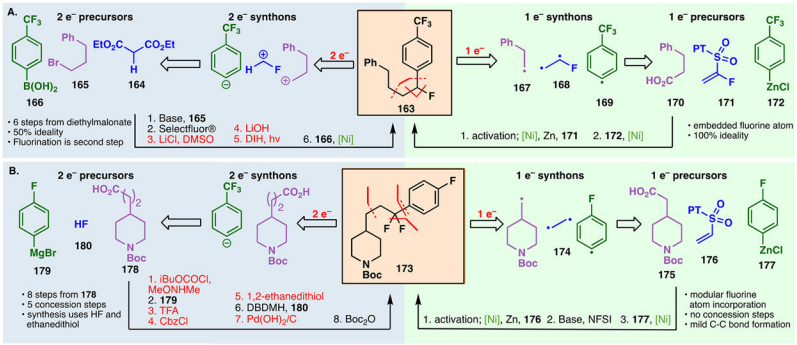

Figure 12.

Strategic approaches to (A) fluoride **163** and (B) difluoride (**173**).